Neurological Complications of Rheumatic Disorders: Updates and Future Directions

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No Relevant Financial Relationships with Commercial Interests

I will not reference an unlabeled or unapproved use of a drug or product in my presentation.

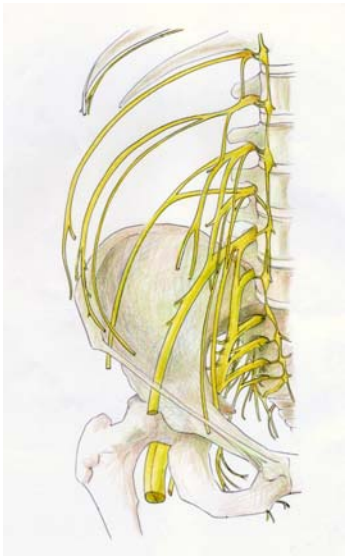
Foot drops---how to distinguish between peripheral neuropathies, radiculopathies, and myelopathies

Case I

A 64 year old gentleman, in the context of weight-lifting, developed “electric bolts” of pain, radiating down outer part of distal left leg, as well as dorsum of foot, and developed partial left foot drop

Six months later, developed chills and anorexia, localized pain between the web of right first and second toe, and then acutely developed right foot drop

Quick differential: No increased tone or reflexes, so dealing with disorder of the peripheral nervous system (PNS)



How can I localize a lesion in the peripheral nervous system without being overwhelmed by complex lumbar plexus anatomy?

Answer: Forget about most of "cross-wiring" between spinal cord and peripheral nerves (i.e. ***"plexopathies"*)---**concentrate on distinguishing whether lesion is likely due to a ***radiculopathy,*** versus a terminal ***peripheral nerve injury***

Points to consider when obtaining a nerve biopsy in suspicion of vasculitic neuropathy

Nerve biopsy ***diagnostic in*** 45% of clinically suspected cases, with muscle biopsy diagnostic in additional 28% of cases

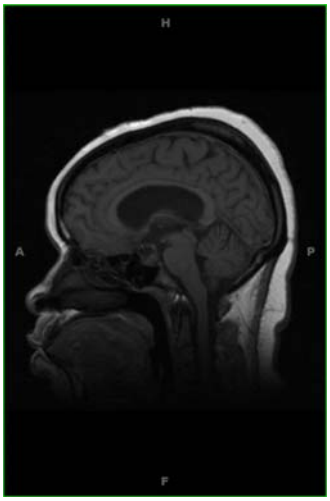
Biopsy an electrodiagnostically “affected but not a dead nerve”

Summary: EMG/NCV and biopsy need to be interpreted in context of clinical syndrome, emphasizing the worth and importance of a careful neurological examination!

(***Said et al, J Neurol, 2005)***

Characterization of distinct CNS manifestations of NPSLE

A simple, 3-step approach for diagnosis and treatment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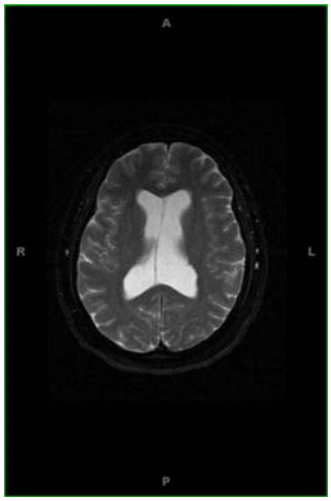
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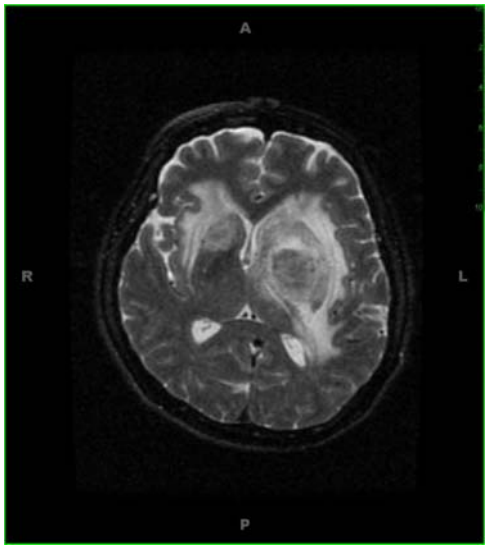
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Step 1: Broadly consider non-SLE causes of an underlying CNS disorder

Vast differential diagnosis of competing non-SLE causes of neuropsychiatric syndromes is simplified and winnowed down using VITAMIN mnemonic

None of these causes reflect disease damage warranting immunosuppressive therapy!

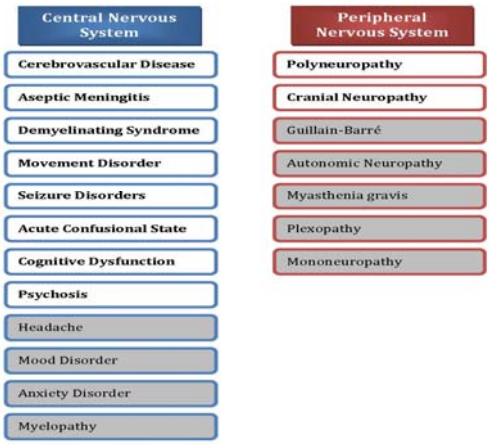
Step 2: Consider the specificity of a particular CNS syndrome for NPSLE

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

Implications of diagnostic step 2:

Various neuropsychiatric syndromes included in the ACR NSPLE nomenclature and case-definitions do not represent the more limited spectrum of NPSLE.

Will almost never start immunosuppressive therapy for headaches, mild cognitive impairment, and affective disorders.

Step 3: Characterization of distinct NPSLE syndromes

Always use VITAMIN mnemonic:

To distinguish SLE versus non-SLE causes
To identify causes of NPSLE syndrome due to damage

Cerebrovascular disease

Prevalence of 5 to 15 percent of SLE patients.

Small-vessel lacunar strokes>embolic strokes>hemorrhagic strokes

For embolic strokes, need to particularly consider Liebman-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.

Mikdashi et al, Stroke, 2007

Use of the VITAMIN mnemonic to detect causes of strokes mediated by disease damage

Vascular/Infections: Septic emboli, subarachnoid hemorrhage from mycotic aneurysms, septic thrombophlebitis, atherosclerosis
Traumatic: N/A
Metabolic: Uncommon. Hyperhomocysteinemia
Autoimmune: Other autoimmune or inflammatory syndromes.
Iatrogenic complications: Metabolic (corticosteroids), infections (immunosuppressive) therapy
Neoplastic: Leptomeningeal disease or lymphomatous infiltration of vasculature

NONE OF THESE DISORDERS WARRANT IMMUNOSUPPRESSIVE THERAPY

Summary of the CNS neurological complications of SLE

- Always suspect a non-SLE cause
- Usually CNS syndromes are not an isolated reason to start immunosuppressive therapy
- At end of this handout, I've included an addendum which defines spectrum, evaluation, and treatment of other CNS syndromes
- How are these features highly salient for neurological evaluation of CNS Sjogren's Syndrome (SS)?

Neurological Complications of Sjogren's Syndrome

Most “diffuse” and focal CNS syndromes in SS do not display phenotype-specificity for SS

The following CNS syndromes are phenotypically non-specific, and are seen with similar frequency in non-SS controls, and in ***most*** cases can be evaluated and treated as if a SS patient did not have SS

Headache (~60%)

Mood disorder and anxiety disorder (~33%)

Strokes and seizures (<5 percent)

Harboe et al, Ann Rheum Disease, 2009
Tjensvoli et al, European Journal of Neurology, 2013

Implications

In a SS patient with headache, anxiety disorder, mood disorder, strokes, and seizures the diagnostic evaluation should proceed as if the patient did not have SS!

Patients with these syndromes should not be subjected to immunosuppressive therapy

Unlike SLE, studies have not conclusively demonstrated that a CNS vasculopathy exists in SS patients

MECHANISMS	SLE patients	SS
Associated with aPL antibodies	Yes, 40 percent aPL antibodies	No, <=10 percent with aPL antibodies
Endothelial activation or arterial stiffness	Yes	Mild, limited surrogate studies
Accelerated atherosclerosis	Yes	Mild, limited surrogate studies

Haga et al, Scand J Rheumatol, 2008
Sabio et al, Arthritis Care & Research, 2014
Vaudo et al, Arthritis & Rheumatism, 2005

Cognitive Impairment

Cognitive impairment: Evaluate for impaired subcortical domains

"Brain fog": A very incisive and illustrative metaphor used by our SS patients

Similar to MS, the pattern of cognitive impairment in SS is characterized by impaired ***subcortical*** domains

These cognitive domains are entirely different than "***A"*** pattern of cortical domains affected in cortical dementia: ***A***lexia, ***A***graphia, ***A***calculia, ***A***phasia

No studies which suggest that cognitive impairment is progressive

Blanc et al, ISRN Neurology, 2013

When should I institute immunosuppressive therapy in SS patients with CNS disease?

Very infrequently!

Demyelinating disorders in SS

In the 1980s and 1990s, literature proposed that MS and “CNS Sjogren’s” could be indistinguishable.

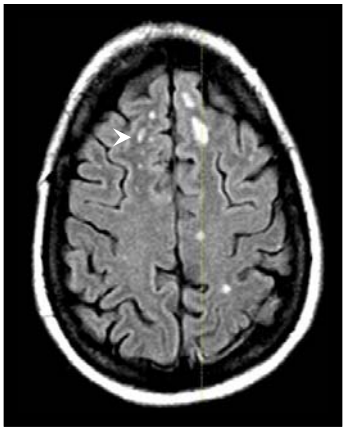
This engendered mass panic!

This largely stemmed from under-appreciation about limits of MRI studies.

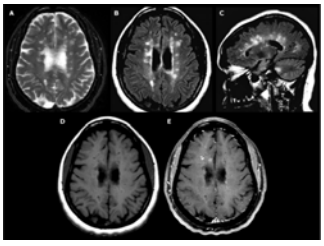
Can we distinguish between brain lesions in SS versus MS?

Most of the time!

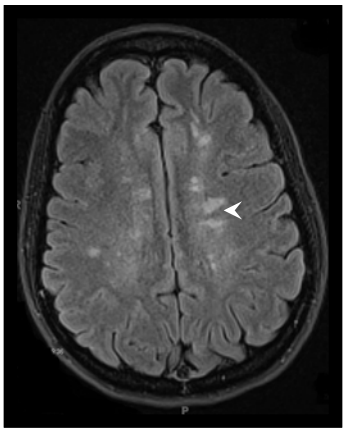
This pattern of T2 hyperintense, ovoid frontal lesions could *potentially* be consistent with MS



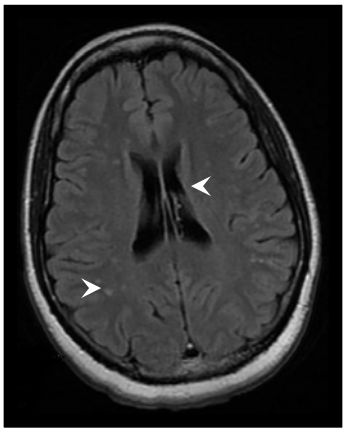
Brain MRI Multiple Sclerosis



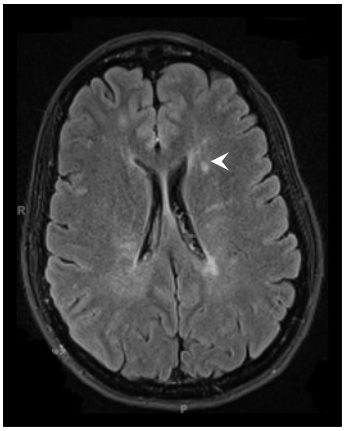
Periventricular lesions which radiate perpendicularly from the ventricular surface: "Dawson's Fingers"



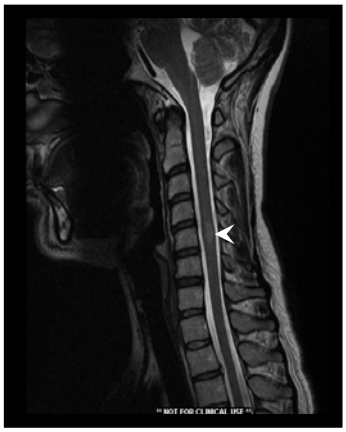
But in MS, you wouldn't see this pattern of periventricular sparing

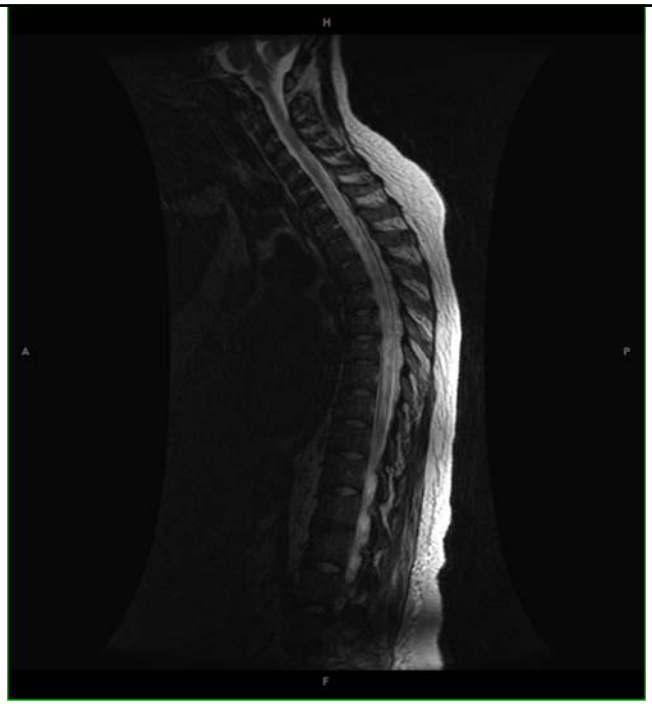


“Non-specific” periventricular lesions: Seen commonly in Sjogren’s patients, but unfortunately including MS as part of the differential diagnosis.



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





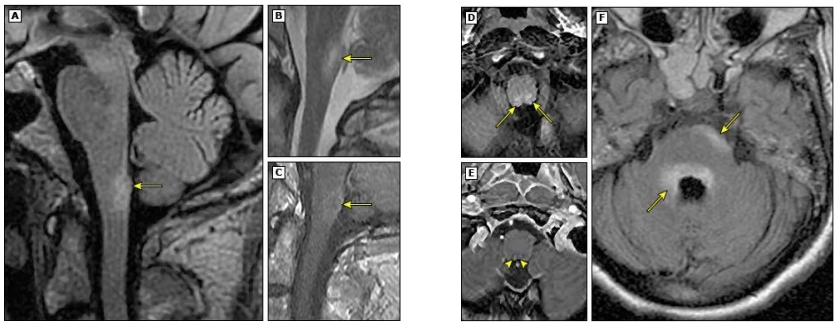
Devic's Syndrome/Neuromyelitis Optica (NMO)

Clinically defined by demyelinating attacks restricted to optic nerve and spinal cord

2006 diagnostic criteria of Devic's syndrome: Attacks of optic neuritis and myelitis, along with two of the following three features:

(1) Myelitis which is "longitudinally extensive" (LETM), spanning three or more vertebral segments
(2) Brain MRI which is nondiagnostic of MS
(3) Anti-aquaporin antibody positivity (70% sensitive, 94% specific)

Dorsal medulla, area postrema, and other brainstem lesions in Neuromyelitis Optica Spectrum Disorders (NMOSD)
(Wingerchuk et al, Neurology, 2015)



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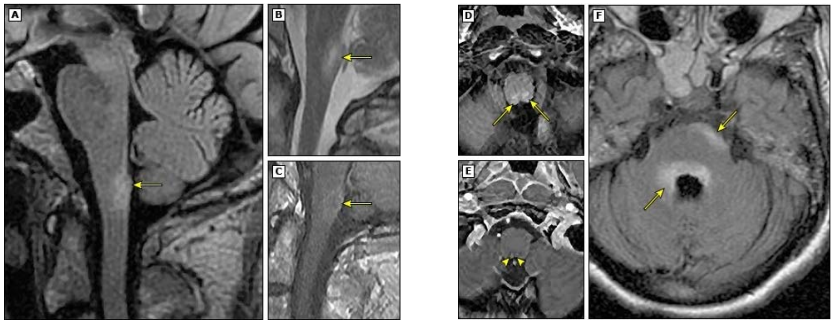
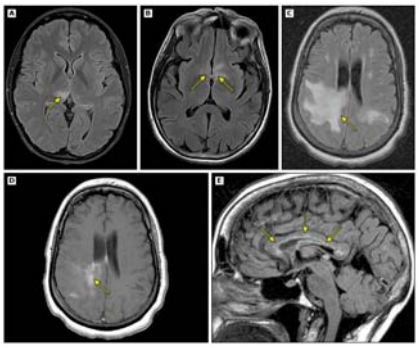


Diencephalic and cerebral lesions in NMOSD



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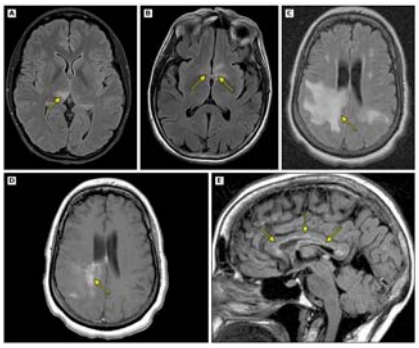


What is relationship between NMOSD is not a CNS manifestation of SS (Birnbaum et al, Arthritis Care Research 2016)

Anti-AQP4 is restricted only to SS NMOSD patients, and not seen in any SS patients without NMOSD

Such 100 percent syndrome-specificity indicates that NMOSD is a coincidental disorder in SS patients

Similar to other CNS neurological disorders, demyelinating syndromes are not a neurological complication of SS

Leads to the following provocative but instructive question

Another CNS neurological complication falls by the wayside in SS

Similar to other CNS neurological disorders, demyelinating syndromes are not a neurological complication of SS

Leads to the following provocative but instructive question

Does CNS Sjogren's actually exist?

Small-fiber neuropathies in SS and SLE

Clinical presentation

A 44-year old female with SLE complains of the following symptoms:

“Caterpillars with sharp claws are crawling on my arms and marching up my neck”

“Hot vats of oil being poured on my thighs.”

“My arms and legs ache when I put on any clothes”

History of a tachy-brady syndrome requiring pacemaker, along with chronic complaints of constipation.

What are clinical features suggestive of a small-fiber neuropathy?

A painful neuropathy which targets thinly-myelinated A-delta or unmyelinated C-fiber nerves

Quality of pain: Burning, paroxysmal, and allodynic

"Small-fiber" deficits on physical examination

Electrodiagnostic studies are normal!

Require further diagnostic studies

Differential diagnosis of potential small-fiber neuropathies VITAMIN mnemonic

Vasculitis

Infection: HIV, hepatitis B, hepatitis C, mycobacterial, fungal

Autoimmune/Inflammatory Disorders: Celiac disease, sarcoidosis,

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

Neoplastic Disorders: Paraneoplastic disorders

Structural "mimics": Syringomyelia, myeloradiculopathies

Punch skin biopsy as a diagnostic marker of SFN

Decreased intra-epidermal nerve-fiber density (IENFD) of unmyelinated nerves

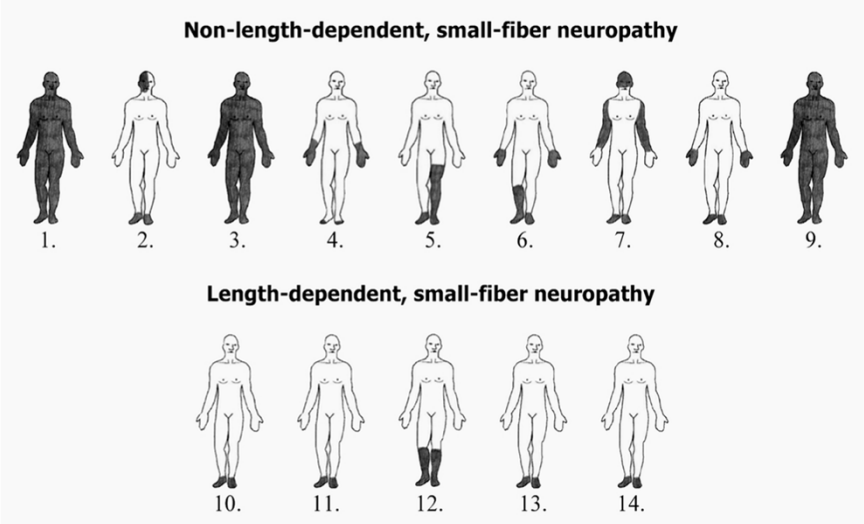
Easy and quick to perform (Sommer et al, Lancet Neurol, 2007)

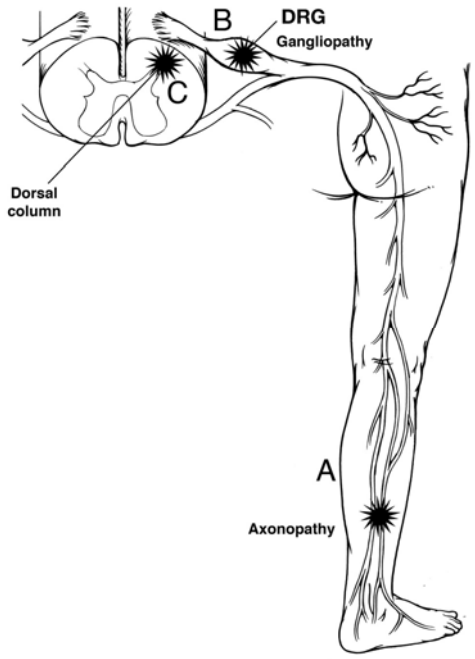
Taken from two standardized sites (proximal thigh and distal leg)

Highly diagnostic, efficient and reliable ~90 percent

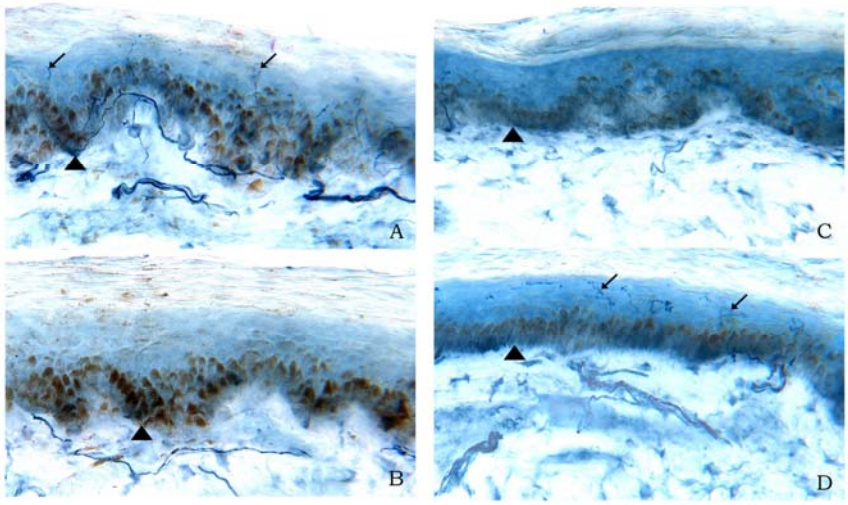
Can identify clinico-pathological subsets that can highlight mechanisms

There are two subtypes of small-fiber neuropathies in SLE





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



"Length-dependent (LD)" versus "non-length-dependent (NLD)" small-fiber neuropathies

(Chai et al, *Medicine*, Sept 2005)

Discriminating features	LD-small-fiber neuropathies	NLD-small-fiber neuropathies
Distribution of pain	***Distal***	***Proximal***
Intra-epidermal nerve fiber density (IENFD)	***Distal<Proximal***	***Proximal≤Distal***
Anatomic target	***Distal***-most axons	***Proximal***-most dorsal root ganglia (DRG)
Mechanisms	Diverse	CD8 T-cell toxicity

Small-fiber neuropathies are an under-recognized PNS disorder of many different inflammatory disorders

Rheumatoid arthritis (Gemignani et al, J Periph Nerv Syst, 2012)

TNF-inhibitors (Birnbaum et al, Semin Arthritis Rheum, 2014)

Inflammatory bowel disease (Gondim et al, Inflamm Bowel Dis, 2015)

MPA (Birnbaum et al, Arthritis Care Res, 2009)

Scleroderma (neuropathic itch)

Treatment of SFN in rheumatic diseases

Aggressive poly-symptomatic approaches

Small case-series suggest a role for IVIG in refractory disease

Larger studies are definitely warranted

IVIG may have preferential efficacy because it turns off pain pathways as well as autoimmunity

Oaklander, Neurotherapeutics, 2016

On the horizon: Autoimmune pain

Several autoantibodies have been identified as a biomarker of chronic pain, even in the absence of tissue or peripheral nerve injury

Nascent appreciation that in certain contexts, pain itself may be an autoimmune disease

Further studies should evaluate in rheumatic disease the applicability of these as well as novel antibodies.

For example, can we identify antibodies in patients having neuropathic-type pain without a neuropathy?

Conclusions

A neurological evaluation and boldly and powerfully disclose diagnostic strategies, mechanisms and treatment

The spectrum of CNS disease directly attributable to SLE and SS is considerably narrower than expected

Use the VITAMIN mnemonic to formulate a differential diagnosis

SFN is an overlooked PNS manifestation of rheumatic diseases

Addendum slides on other CNS manifestations of SLE

Seizures

- Occurs in 5 to 20 percent of patients.
- Seizures are attributable to SLE in approximately 85 percent of cases
- However, it is particularly important to consider vascular, infectious, metabolic, and structural causes in the VITAMIN mnemonic!

Use of the VITAMIN mnemonic to detect causes of seizures mediated by disease damage

Vascular/Infections: Septic emboli, subarachnoid hemorrhage from mycotic aneurysms, septic thrombophlebitis: reflects "cortical irritation."

Traumatic: Rare, subdural or intraparenchymal hemorrhage from a coagulopathy

Metabolic (multiplicity): Hypo/hyernatremia, hyper/hypocalcemia, uremia, PRES

Autoimmune: Other autoimmune or inflammatory syndromes

Iatrogenic complications: infections (immunosuppressive) therapy

Neoplastic: Leptomeningeal disease, paraneoplastic syndromes (causative antibodies can also be seen in non-paraneoplastic syndromes)

MOST THESE DISORDERS WARRANT IMMUNOSUPPRESSIVE THERAPY

Characteristics of seizures in SLE

Clinical characteristics: 70 percent generalized, 30 percent focal, long-term anti-epileptic therapy in only 1/3 of patients [1]

Demographic: Younger age [2] , African-Americans [1,2], and presents ***early***, in less than 1.5 to 5 years of disease onset [1,2]

SLE: Increased with disease activity [1,2,3], disease damage [1,3], aPL,[3] presence of other NPSLE syndromes [2,-4], but lower risk with plaquenil [1,2]

[1]Hanly et al,
[2]Andrade et al, Ann Rheum Dis, 2008
[3]Mikdashi et al, Neurology 2005
[4]Petri et al, J Rheumatol, 2016

Defining patients who are at higher risk of developing seizures and requiring anti-epileptic therapy

- Neuroimaging: Patients with macroscopic lesions involving the cortex
- EEG: Focal electrophysiological lesions

Cognitive impairment in SLE

- Screen for potentially modifiable causes, including hypothyroidism, mood disorders, sleep disorders, and pain syndromes
- However, SLE cognitive impairment is not associated with disease activity
- Emerging theme: Similar to strokes and seizure, there is no role for sustained immunosuppressive therapy

Mechanisms and treatment of focal CNS NPSLE

Vasculopathy stems from many causes, including endothelial upregulation, accelerated atherosclerosis, and antiphospholipid antibodies (Seltzer F, et al, Arthritis Rheum, 2004)

In most cases, this reflects chronic injury to the vasculature, and in focal NPSLE does not usually warrant sustained therapy with immunosuppressive therapy.

For demyelinating syndromes, review slides on spectrum of demyelinating disease in Sjogren's syndrome