Neuro-Rheumatology

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Does this patient have neuropsychiatric lupus?
Systemic Lupus Erythematosus

- Chronic, multi-systemic, inflammatory disorder
- Disproportionately affects women (80-90%) during early adulthood
- More frequent in African-Americans, Hispanics, and Asians
- Relatively common – 50/100,000 people in the US

Diagnosing Lupus

<table>
<thead>
<tr>
<th>Malar rash</th>
<th>Erythema over malar regions of the face sparing the nasolabial folds</th>
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</thead>
<tbody>
<tr>
<td>Discoid rash</td>
<td>Raised erythematous patches with keratotic scaling and follicular plugging</td>
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<tr>
<td>Photosensitivity</td>
<td>Skin reaction from sunlight (many types)</td>
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<tr>
<td>Oral ulcers</td>
<td>Usually painless in oral cavity or nasopharynx</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Nonerosive with tenderness or swelling</td>
</tr>
<tr>
<td>Pleuritis or pericarditis</td>
<td>Either by history or evidence of pleural/periocardial effusion</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>Proteinuria of 0.5 grams daily or cellular casts</td>
</tr>
<tr>
<td>Neurologic disorder</td>
<td>Seizures or psychosis without clear secondary provocative factor</td>
</tr>
<tr>
<td>Hematologic abnormality</td>
<td>Hemolytic anemia or leukopenia or lymphopenia or thrombocytopenia</td>
</tr>
</tbody>
</table>
Diagnosing Lupus

<table>
<thead>
<tr>
<th>Positive anti-nuclear antibody</th>
<th>Generally high-titer</th>
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<tbody>
<tr>
<td>Serology</td>
<td>Positive anti-dsDNA (double strand DNA), anti-Sm (Sm nuclear antigen), or positive antiphospholipid antibodies</td>
</tr>
</tbody>
</table>

Four out of eleven required for diagnosis.

Breadth of criteria reflect clinical heterogeneity of disease.

Systemic Lupus Erythematosus

• Unclear pathogenesis
  – Genetic susceptibility
  – Environmental factors (such as EBV exposure)
  – Hormonal factors (women of childbearing age)

• Associated with autoantibodies against intracellular antigens
  – ANA: present in 95% but not specific
  – Anti-dsDNA: can correlate with disease activity
  – At least another >100 antibodies described
Neurology in SLE

• In 1875, Hebra and Kaposi reported stupor associated with clinical symptom of SLE

• Osler speculated on CNS vasospastic disease similar to Raynaud’s
  – “It seems not improbable that these transient attacks were due to vascular changes in the brain, the counterpart of those occurring in the skin.”

• Others proposed “lupus vasculitis” as cause of symptoms continuing to this day

Osler W. Am J of the Med Sci (1904); 127: 629

Endocarditis

Libman E and Sacks B. Arch Intern Med (1924); 33:701
Pathology in NPSLE

• In 1968, Johnson and EP Richardson described 24 autopsy neuropathological studies from patients with SLE:
  – Most common finding in 80% was micoinfarcts with microglial nodules
  – No cases of generalized arteritis found
• Other autopsy series have also not shown vasculitis as a frequent cause of neurological symptoms

Pathophysiology in NPSLE

• H&E studies not sensitive to disorders affecting neuronal function (such as by signaling changes)
• What about autoantibodies? Some relevant/speculative ones for NPSLE
  – Anti-phospholipid antibodies
  – Anti-NMDAR NR2 subunit
  – Anti-Ribosomal P
  – Anti-Aquaporin 4
  – Anti-MOG
Nomenclature

- Historically, many terms associated with SLE affecting the nervous system
  - Lupus cerebritis
  - Neurolupus
  - CNS lupus
  - Lupoid sclerosis
- Current preferred term is: **Neuropsychiatric SLE (NPSLE)**

### Table 2. Neuropsychiatric syndromes observed in systemic lupus erythematosus

<table>
<thead>
<tr>
<th>Central nervous system</th>
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<tbody>
<tr>
<td>Aseptic meningitis</td>
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<tr>
<td>Cerebrovascular disease</td>
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<tr>
<td>Demyelinating syndrome</td>
<td></td>
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<tr>
<td>Headache (including migraine and benign intracranial hypertension)</td>
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<tr>
<td>Movement disorder (chorea)</td>
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<tr>
<td>Myelopathy</td>
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<tr>
<td>Seizure disorders</td>
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<tr>
<td>Acute confusional state</td>
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<tr>
<td>Anxiety disorder</td>
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<tr>
<td>Cognitive dysfunction</td>
<td></td>
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<tr>
<td>Mood disorder</td>
<td></td>
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<tr>
<td>Psychosis</td>
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</tbody>
</table>

| Peripheral nervous system |          |
| Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome) | |
| Autonomic disorder       |          |
| Mononeuropathy, single/multiplex |         |
| Myasthenia gravis        |          |
| Neuropathy, cranial      |          |
| Plexopathy               |          |
| Polineuropathy           |          |

19 syndromes named to provide standardized nomenclature - does not imply causation by SLE. Other syndromes not named but have been observed like Posterior Reversible Encephalopathy Syndrome (PRES).

ACR. Arthritis & Rheumatism (1999); 42:599
NPSLE

• Prevalence of NPSLE syndromes in SLE: 56% (range from 12-95%)
  – 28% have a neurological complaint at time of diagnosis
• Prevalence of syndromes:
  – Headache: 28-57%
  – Mood disorder: 20-40%
  – Cognitive disorder: 20-80%
  – Cerebrovascular disease: 50-60%
  – Seizure: 10%

Headache

Frequency of headache is similar to studies in general population

Mitsikostas DD, Sfikakis PP, Goadsby PJ. Brain (2004); 127: 1200-1209
Headache and SLE Activity

- Majority of studies do not find relation between headache and SLE activity (out of 6 studies, 4 have been negative)
- No relation between serum anti-cardiolipin Abs and headache

“Lupus headache” in isolation is likely not a marker of disease activity. Treat headache in SLE symptomatically

Depression

- Prevalence of major depression in 20-47%
  - Many methodological flaws (type of interviewing, criteria used, etc.)
- Unclear whether increased prevalence related to disease or chronic illness with disability
- Elevated disease activity increases the odds of major depression modestly by 10%

Possibly related to SLE but many confounders

Psychosis

• In a cohort of 537 patients, psychosis prevalence: **17%**
  – Psychosis at disease onset: 21%
  – Psychosis during course of SLE: 45%
  – Corticosteroid psychosis: 31%
  – Unrelated: 2%
• Psychosis correlates with elevated disease activity

Appenzeller S, Cendes F, Costallat LTL. *Rheumatol Int* (2008); 28:237

Psychosis

• Often with prominent visual hallucinations. Auditory hallucinations more common with steroids.
• CSF usually normal but can show elevated protein/mild pleocytosis
• MRI often normal but can show non-specific lesions
• Antiphospholipid Abs risk factor for psychosis
• Anti-Ribosomal P Ab: Low sen, limited specificity

*Often related to disease activity. First, check for steroid psychosis. Otherwise, treat SLE including with steroids and antipsychotics.*
Stroke

• Stroke account for 10% of deaths in SLE
• Second leading individual cause of death after bacterial sepsis
• Increased risk of stroke (eg. 21 fold increased risk in 30-39 age group)

Mok CC, Ho LV, To CH. Scand J Rheumatol (2009); 38:362

Small Vessel Disease

• Reported early in neuropathological series
• Seen now as T2 hyperintense lesions on MRI
• Not explained by conventional risk factors like hypertension or diabetes
• Correlates with cognitive dysfunction
Small Vessel Disease

Hypercoagulability

• Independent of other variables, SLE itself is a risk factor for thrombotic events
• Risk is higher for venous thromboembolic disease
• Less robust epidemiologic data on arterial thrombotic risk

Embolic Infarcts

- From Libman-Sacks or infectious endocarditis or paradoxical emboli or artery-to-artery
- Microembolic signals can be seen on TCD
  - 9-15% of patients with SLE will have microembolic signals when monitored for an hour over MCA
  - Associated with ischemic infarcts
  - Prevalence is not explained by presence of carotid stenosis or entirely by antiphospholipid antibodies
Anti-phospholipid Antibodies

- **Anti-phospholipid antibodies** are predictive of ischemic stroke – present in 65% of patients with SLE and ischemic stroke.
- Can cause territorial strokes or small infarcts

Atherosclerosis

- Accelerated atherosclerosis in SLE
- Increased prevalence of conventional risk factors such as hypertension, diabetes, dyslipidemia
- These factors do not entirely explain the elevated risk of atherosclerosis in SLE such as carotid stenosis
Vasculitis

• Does it exist?
• yes but very rare
• Individual cases exist in the literature


Stroke

- Check for anti-phospholipid Abs (lupus anticoagulant, anti-cardiolipin IgG/IgM isotype, anti-β2-glycoprotein I IgG/IgM)
- Screen for infective/Libman-Sacks endocarditis (if imaging and syndrome suggestive, proceed to TEE; TTE sensitivity about 11% for LS)
- SLE NOT a contraindication for IV tPA for acute stroke
- Control of modifiable risk factors
- Secondary prevention with anti-platelets or anticoagulation if anti-phospholipid syndrome
Nausea/Vomiting

• 14 year old girl with diagnosis of SLE
  – Arthralgias, pleuritis, ANA 1:10240, serology positive for anti-dsDNA, anti-Ro, anti-cardiolipin IgG
  – Controlled with Plaquenil and methotrexate
• Presented with intractable nausea/vomiting
  – No identifiable source found
  – In pediatric ICU for weeks

Area postrema (circled) lesion that is enhancing
Area Postrema Lesion

- Intractable nausea/vomiting or hiccuping with area postrema lesion is a core clinical syndrome of neuromyelitis optica
- Tested for NMO-IgG against Aquaporin-4 and found to be positive

Longitudinal enhancing spinal cord lesions
SLE Myelitis

NMO negative paraplegia with SLE

SLE - PRES

28 year old woman with SLE with new onset headache and seizures

Jonsson AH and Bhattacharyya S. *Rheumatologist* (2015), March
34 year old woman with SLE and unexplained hyponatremia

Yang N, Bhattacharyya S, Weinblatt M. J of Rheumatology (2017); epub

Does this patient have neurological complications of Sjögren syndrome?
Sjögren Syndrome

- Sicca syndrome: Dry mouth and dry eyes
- Focal lymphocytic infiltration of exocrine glands particularly salivary and lacrimal glands
- 20 fold predominance of women
- Average age of diagnosis is 55 years
- Affects 2-4 million people in US

Diagnosis

- Dry ocular symptoms for at least three months
- Dry oral symptoms for at least three months
- Ocular exocrine dysfunction sign – Positive Schirmer Test or Rose Bengal stain
- Salivary gland dysfunction sign – Decreased salivary flow or abnormal parotid sialography or abnormal salivary scintigraphy
- Histopathology of salivary gland showing lymphocytic foci
- Positive serology for anti-Ro/SSA or anti-La/SSB

4 out of the six criteria required
Either histopathology or positive serology required for diagnosis
In primary SS, sensitivity for anti-Ro 52% and anti-La 34%
Often occurs in context of other autoimmune diseases such as RA and SLE
Sjögren Syndrome

- Classification criteria focus exclusively on dry eyes and dry mouth
- Extra-glandular signs are common and disabling in SS
  - Thyroid dysfunction, 45% of patients
  - Diffuse arthralgias
  - Dry skin, dry respiratory system (chronic cough)
  - Tubulointerstitial renal dysfunction
  - Increased risk of lymphoma

Neurology in SS

- Wide spectrum of involvement. Prevalence depends on definition
- **Most common:** Extreme debilitating fatigue
  - Occurs in 50%
  - Cause is usually undetermined
  - Major contributor to decreased functional status
  - Often diagnosed initially with fibromyalgia or chronic fatigue
Neurology in SS

- Common complaints of attention and memory difficulty
  - Neuropsychology testing often shows frontal executive and verbal memory dysfunction
- Unclear whether from SS, psychological reaction to it, or effect of treatment
- MRI often shows increased burden of white matter T2 hyperintensities

SS Myelitis

- Often presents as longitudinally extensive lesion
- ~90% are seropositive for AQP4 antibody
- At present, should be treated like neuromyelitis optica
SS Encephalitis – Not all NMO

- Recurrent asceptic meningoencephalitis
- Syndrome complex:
  - Fever
  - Myalgia, headache
  - Meningismus
  - Confusion
- Significant pleocytosis in CSF
- Imaging can be normal or leptomeningeal enhancement or focal lesions
- Can spontaneously remit or responds to steroids

SS Limbic Encephalitis
Peripheral Neuropathy

• Many patterns of neuropathy in SS
  – Pure sensory
    • Non-length dependent ganglionopathy (best known)
    • Painful distal neuropathy
  – Symmetric sensorimotor axonal neuropathy
  – Others:
    • Demyelinating neuropathy
    • Cranial neuropathy (such as trigeminal neuropathy)

Testing

• Sensitivity for serology is poor:
  – Anti-Ro: 40-50%
  – Anti-La: 10-20%
• Schirmer test may be positive in majority
• Lip biopsy for salivary gland pathology is also positive in majority
Management

• Generally hard to treat
• Symptomatically treated with neuropathic agents
• Unclear which immunomodulatory regimen to use:
  – Corticosteroids: 30-40% response rate
  – IVlg: 30-40% response
  – Rituximab
  – Infliximab

Is this neurological syndrome from rheumatoid arthritis?
Rheumatoid Arthritis

- Chronic inflammatory disorder marked by synovitis and erosive arthritis
- Present in 0.5-1.0% of adults
- Associated with autoantibodies:
  - Rheumatoid factor
  - Anti-citrullinated peptide autoantibodies
- Symmetric polyarthritis of the hands with morning stiffness

Rheumatoid Meningitis

- Can present with headache and focal neurological deficits
- RF may be present in the CSF
- On MRI, pachymeningeal thickening and enhancement

Yuh WTC, Drew JM, Rizzo M, et al. AJNR (1990); 11: 1247-1248
Rheumatoid Cerebral Vasculitis

- Pathologically, similar to polyarteritis nodosa
- Generally a rare and late feature of rheumatoid arthritis.

Ramos M and Mandybur T. Arch Neurol (1975); 32: 271-275

RA and Spine

- Associated with inflammation in synovial joints of the spine
- C1-C2 joint is synovial and often severely affected
- Inflammation leads to:
  - Bony erosion
  - Ligamentous destruction
  - Pannus formation

Progression of cervical spine disease correlates with peripheral disease (such as in hands). Patients with minimal peripheral disease are unlikely to have advanced cervical spine disease.
Atlanto-Axial Instability

Normal value is < 3 mm. Using axis as reference, atlas can move:
• Anterior-posterior (most common)
• Vertically


Atlanto-Axial Instability

Instability can be occult on single view imaging. Flexion-extension x-rays or MRI should be obtained with clinical suspicion (cervical pain or C2 nerve root compression).

Joaquim AF, Ghizoni E, Tedeschi H, et al. Neurosurg Focus (2015); 38: E4
Superior Migration of Dens

Superior migration of odontoid process can compress brainstem or vertebro-basilar arteries


Superior Migration of Dens

Also known as cranial settling
Subaxial Subluxation

Pannus Formation

Pannus is T1 and T2 hypointense

Rheumatoid Arthritis

• C-spine disease highly prevalent depending on technique
  – 40% if screened by x-ray
  – 70% if screened by MRI (most sensitive)

• **Majority** with radiographic disease will be:
  – Non-progressive/asymptomatic
  – Not require surgical intervention

• Frequency of surveillance imaging for those with radiographic disease is unclear

Is this antiphospholipid syndrome?
Antiphospholipid Syndrome

• Prothrombotic state associated with autoantibodies
• For diagnosis of syndrome, currently require a clinical event and laboratory criteria
• Can occur in the context of other autoimmune diseases such as SLE or be primary

Laboratory Criteria

• Lupus anticoagulant positivity
• Anti-cardiolipin IgG or IgM present in high titres (>40 GPL/MPL or >99th percentile)
• Anti-β2-glycoprotein I IgG or IgM present in greater than 99th percentile titer

Measurements need to be repeated at least 12 weeks apart to be considered definite. Transient positive results are not specific.
Clinical Criteria

- Arterial or venous thrombotic event in any tissue or organ
- Pregnancy complication:
  - One or more unexplained death of a healthy fetus beyond 10th week of gestation
  - One or more premature birth of normal fetus before 34th week from eclampsia or severe pre-eclampsia
  - Three or more consecutive unexplained spontaneous abortions before 10th week

Two Hit Hypothesis

Neurological Complication

• Arterial ischemic stroke
  – Associated with thrombosis affecting large or small caliber arteries
  – Cardioembolism from Libman-Sacks endocarditis
  – Paradoxical embolism from deep venous thrombosis

• Cerebral venous sinus thrombosis

Rare Associations

• Epilepsy
• Headache
• Chorea
• Cognitive Dysfunction
• Psychiatric disorders

Unclear whether causative from autoantibodies or from vascular injury or associated with comorbid autoimmune diseases
Catastrophic APS

- Subset of APS with widespread thrombosis
  - Presence of antiphospholipid antibodies
- Three or more thrombotic events in a week
- Biopsy confirmation of microthrombotic event

What INR goal?

No overall benefit or harm with higher INR goal (difference not significant)

Crowther MA, Ginsberg JS, Julian J, et al. NEJM (2003); 349:1133-1138
Management

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic carrier</td>
<td>Unclear, no therapy or aspirin</td>
</tr>
<tr>
<td>APS and venous event</td>
<td>Anticoagulation with INR 2-3</td>
</tr>
<tr>
<td>APS with arterial event</td>
<td>Area of controversy; INR 2-3 versus INR 2-3 with aspirin versus higher INR target</td>
</tr>
<tr>
<td>Arterial event with low-titre antiphospholipid antibodies</td>
<td>Usual treatment</td>
</tr>
</tbody>
</table>

Insufficient data on newer direct antithrombotic agents

Is this neurological syndrome from mixed connective tissue disorder?
Mixed Connective Tissue Disorder

• A syndrome with features overlapping with other disorders (hence “mixed”).
• Many consensus criteria developed:
  – High titer anti-RNP antibody
  – Raynaud’s phenomenon
  – Swollen/puffy hands
  – Myositis
  – Peripheral sclerosis

Myositis

• High prevalence
• Generally presents later in the course of the disease
• Non-specific with proximal weakness in pelvic and shoulder girdle
• No specific pathology but show features of dermatomyositis and in some cases polymyositis
• Responds to corticosteroids
Trigeminal Sensory Neuropathy

• Unilateral or bilateral numbness in the trigeminal distribution
• Gradual onset most often in maxillary distribution
• Associated pain, paresthesia, or altered chewing
• Unclear treatment and often unresponsive to steroids

Conclusions

• Majority of the rheumatological diseases can cause neurological symptoms via a variety of mechanisms
• Treatment needs to be tailored to the mechanism (ie. no generic treatment for lupus cerebritis)
• We are still learning about how many of the systemic autoimmune diseases cause neurological symptoms