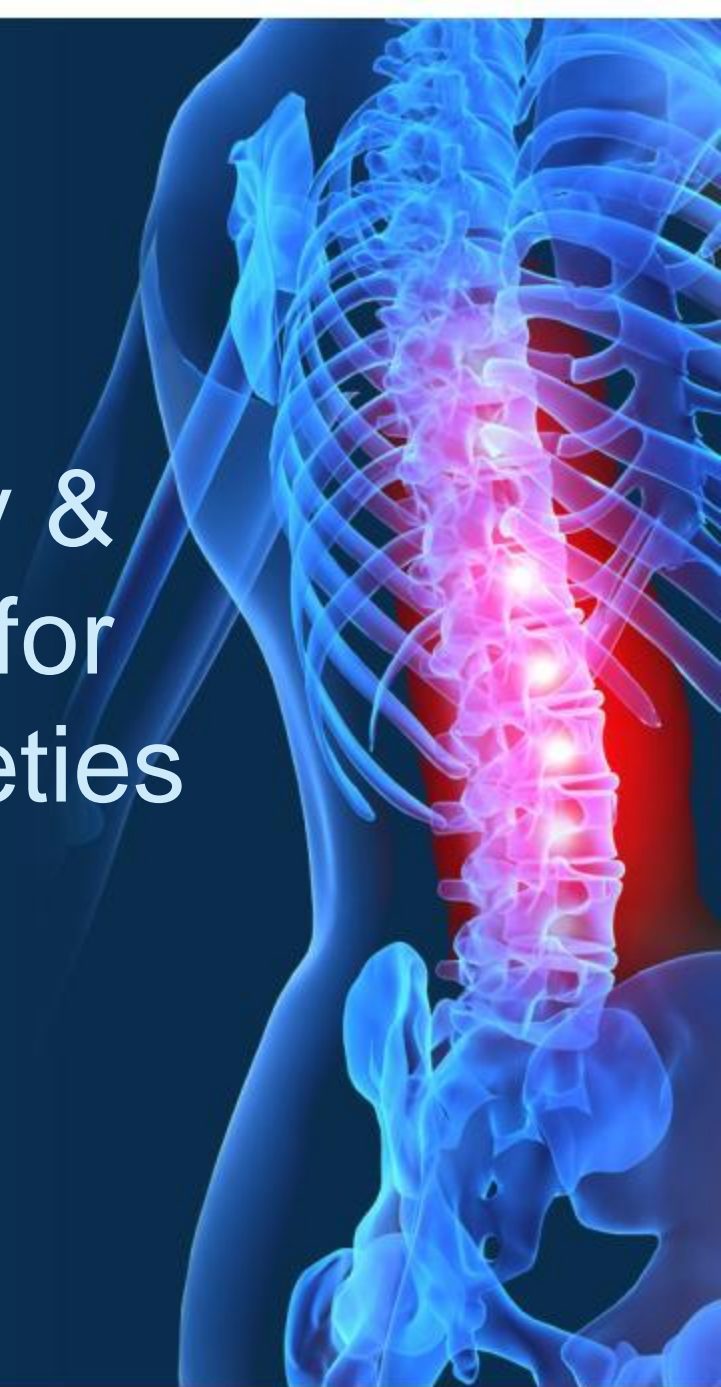


# Annual Rheumatology & Therapeutics Review for Organizations & Societies



# Approach to Lupus Nephritis and Neurological Disease



# Case

- A 23 yo AA female is referred for recent onset lupus manifested by arthritis, discoid lesions, mouth sores, and nephritis. Her PCP started her on prednisone 10mg a day.
- Physical exam shows BP= 150/100 mmHg. She has two discoid lesions on her face, three oral ulcers, synovitis of several MCP and PIP joints and both wrists, and 2+ pedal edema.
- Laboratories show Hct 32%, WBC 3400/microL, plts 146,000/uL. Chemistries are normal except for creatinine 1.4 mg/dL and albumin 2.9 mg/dL. Urinalysis shows 4+ protein, large blood, and 1-2 RBC casts/HPF. Spot urine protein/creatinine ratio is 6.
- Serologies show a positive ANA, anti-dsDNA > 300 units, low C3 52 mg/dL, low C4 <8 mg/dL, and the presence of a lupus anticoagulant.



# Case

- Questions
  - Should a kidney biopsy be done? When and why?
  - Does the kidney biopsy help determine initial therapy?
  - What clinical parameters determine choice of induction therapy?
  - What are the goals of induction therapy?
  - What clinical parameters determine choice of maintenance therapy?
  - What is the best maintenance therapy?
  - What adjunctive therapies should be used in this patient?
  - How is response to therapy monitored? When should therapy be changed?
  - What responses predict prognosis?

# Lupus Nephritis

- Approximately 50% of SLE patients develop significant lupus nephritis.
- Poor prognostic factors
  - Young (age < 26yo) and African-American
  - Elevated creatinine (> 30% over baseline) and/or nephrotic range proteinuria (> 3 gm/day)
  - Biopsy: crescents, fibrinoid necrosis (> 25% of glomeruli), and microvascular clots. Class III or IV with significant activity (index >10) and/or chronicity (index > 3-4) .
  - Poor initial response to therapy
  - Renal relapse
  - Noncompliance with medications

# ACR/EULAR Guidelines for Renal Biopsy

## Renal biopsy indications

Increased creatinine

Urine protein >1 g/d

Urine protein >0.5 g/d + active sed

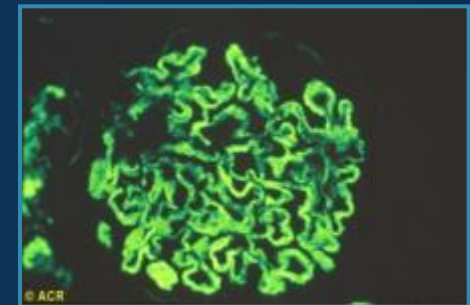
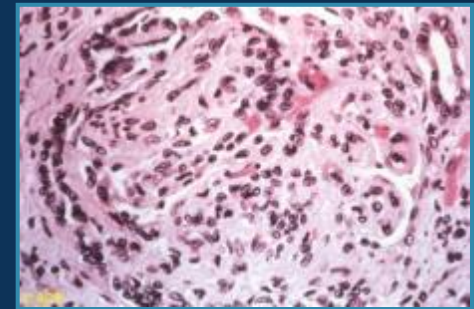
Active urine sediment=cellular casts and/or  $\geq 5$  RBCs/HPF.

Level of evidence (LOE): 2C

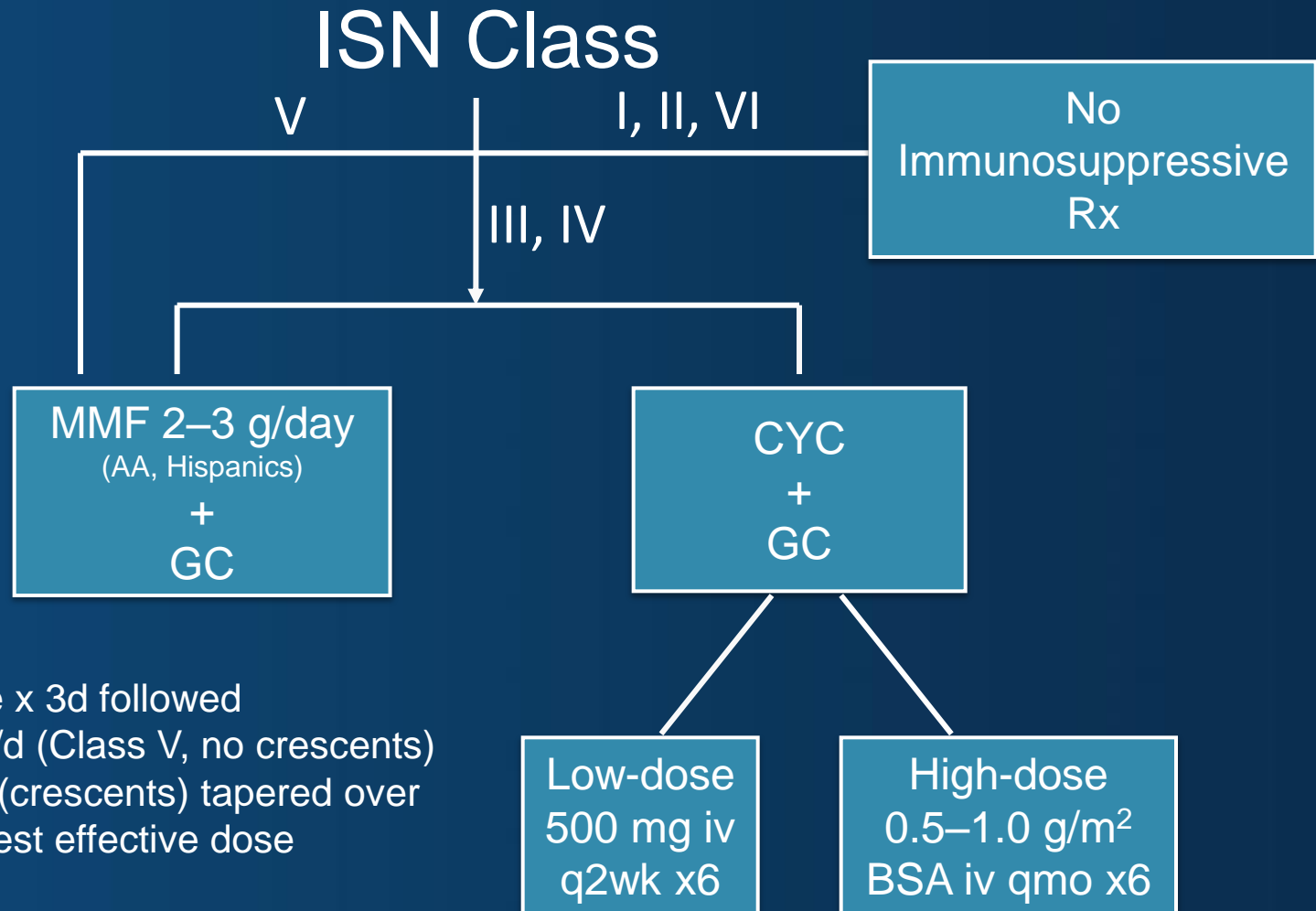
Clinical, serological, and laboratory tests cannot accurately predict renal biopsy findings in most cases (LOE:2B).

# Kidney Biopsy

- Case: Pt had kidney biopsy showing Class IV-G (A) plus V with 10% crescents and microthrombi. No necrosis. Immunofluorescence shows IgG/IgM/IgA/C1q/C3 deposits (full house pattern), EM shows subendo/subepithelial deposits.
- ISN/RPS 2003 Classification for Lupus Nephritis
  - Classification for Lupus Nephritis
    - I- Normal with minimal mesangial deposits
    - II- Mesangioproliferative (12-25%)
    - III- Focal (< 50% of glomeruli) (16-22%)
      - III (A): active lesions (proliferative, subendo deposits)
      - III (A/C) : active and chronic lesions
      - III (C): chronic lesions
    - IV- Diffuse (> 50% of glomeruli) (37-46%)
      - Diffuse segmental (IV-S) or global (IV-G)
      - IV (A, A/C, or C): same as III
    - V- Membranous (11-21%) (subepi deposits) (May be combined III/IV)
    - VI- Advanced sclerosing (> 90% glomeruli) (4%)



# Lupus Nephritis ACR Guidelines: Induction Rx





# Prednisone Therapy for LN: Clinical Considerations (LOE: 3C)

- When to use intravenous pulse methylprednisolone
  - Class IV or IV/V with cellular crescents and/or fibrinoid necrosis
  - Dose: 500-1000mg intravenous q day x 3 doses
- Initial corticosteroid dose
  - Prednisone (1mg/kg divided): Class IV or IV/V with crescents
  - Prednisone (0.5mg/kg): Class III, IV, or V without crescents
- Prednisone taper: after 4 weeks on full dose taper by 2.5mg every 2 weeks to 10mg/day by 6 months if no relapse

# Induction Therapy for Class III/IV LN: Clinical Considerations

- Cyclophosphamide vs mycophenolate mofetil are equivalent in most situations during first 6 months (LOE:1A).
  - Cyclophosphamide preferred (LOE:2B) for:
    - Poor prognostic factors: rapidly progressive renal deterioration (50% dec in creatinine from baseline) and/or cellular crescents/fibrinoid necrosis (esp > 25% of glomeruli)
    - Poor compliance
- Cyclophosphamide regimens:
  - NIH protocol (0.5-1.0 mg/m<sup>2</sup> IV monthly x 6) (LOE:1B)
  - Euro-Lupus protocol (500mg IV q 2weeks x 6): best to give to Caucasian patients. Not tested in nonwhite races.
  - Other considerations: mesna, leuprolide

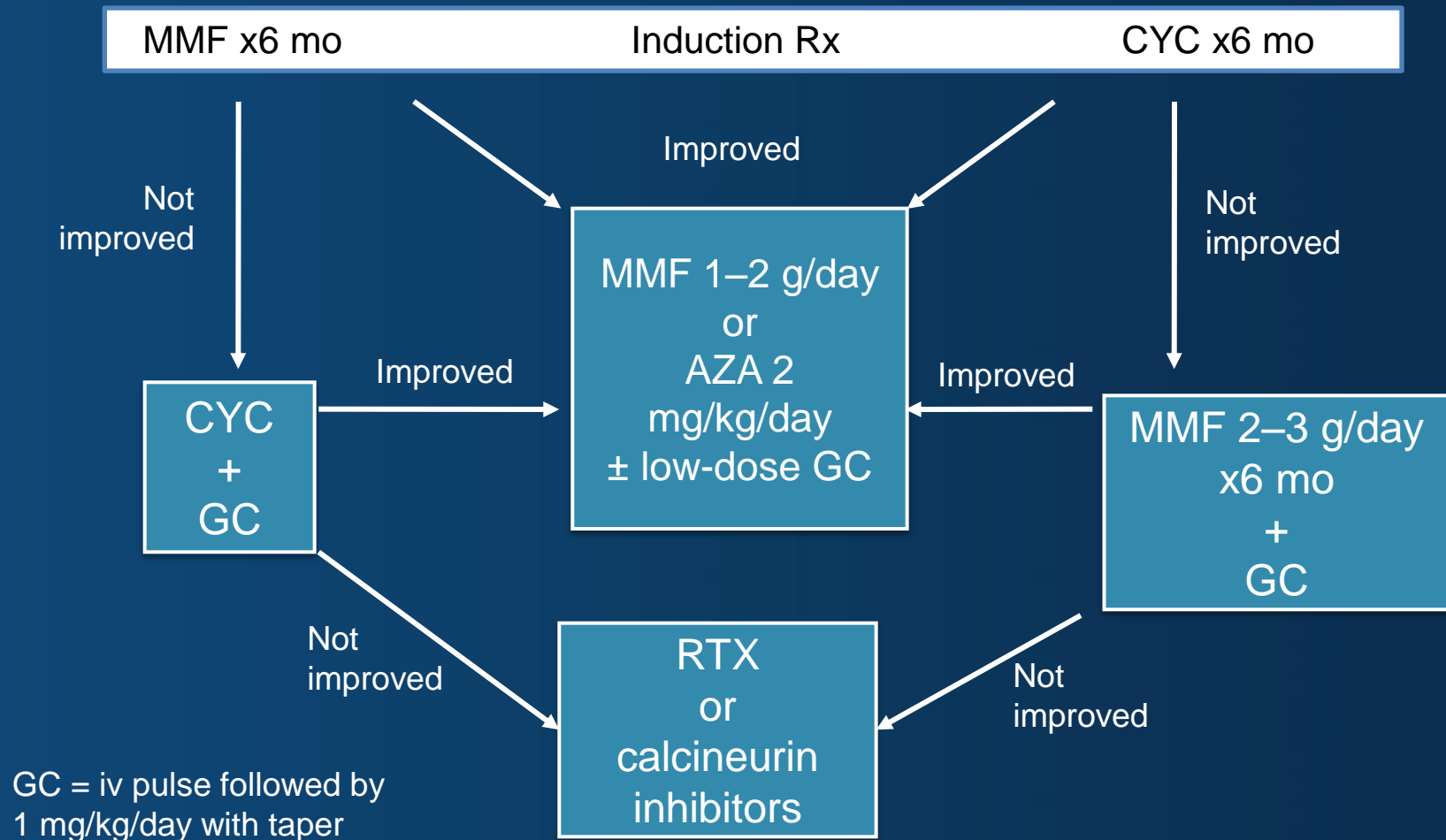
# Induction Therapy Class III/IV LN: Clinical Considerations

- Mycophenolate mofetil (MMF) and mycophenolic acid (MPA) dosing
  - Patients with LN Class V (pure membranous) and nephrotic range proteinuria should be treated with MMF and prednisone (0.5mg/kg/d with taper) for 6 months (LOE:2B).
    - In selected pts that are non-nephrotic and intolerant to MMF can consider azathioprine (LOE:4C)
  - Patients with LN Class III/IV without adverse prognostic factors can be treated with MMF or CYC and prednisone (0.5mg/kg/day with taper) for 6 months (LOE:1A).
    - In selected pts that are intolerant to MMF and CYC can consider azathioprine (LOE:2C)
  - All ethnicities with LN have similar responses to MMF
    - African-Americans and Hispanics may respond better to MMF than CYC
  - Dose: MMF 2000-3000mg/day; MPA 1440-2160mg/day
    - Asians may respond to lower doses (MMF:2000mg/day) compared to other ethnicities that need higher dose.

# Induction Therapy: Response Goals by 6 Months

- Complete response (LOE:1B)
  - Improvement of CrCl to normal or within 10% of normal, decrease in proteinuria to less than 0.5 gm/day, and no cellular casts.
- Partial response (LOE:1B)
  - Improvement of proteinuria by > 50% to non-nephrotic range and CrCl normal or within 10% of normal (Cr < 1.4mg/dL) with no cellular casts. May take up to 12 months or longer to achieve.
- Kidney survival
  - A > 25 % reduction of proteinuria by 2 months, 75% reduction by 3 months, and/or reduction to < 1 gram/d and a normal C3 by 6 months predict a good renal outcome.
  - Overall 30% achieve complete remission (CR) by 6 months and 65-80% achieve at least partial remission (PR) or better by 12 months.
  - Failure to achieve CR or PR by 12-24 months is associated with end-stage renal disease within 5-10 years.
    - Class IV: 20-30% ESRD
    - Class V: 10% ESRD

# Lupus Nephritis ACR Guidelines: Maintenance Rx



# Maintenance Therapy for LN

- For patients who achieved CR or PR at 6 months on CYC or MMF with taper of prednisone ( $\leq 10\text{mg/d}$ ) (LOE:1A):
  - MMF: 1000-2000mg/d
  - Azathioprine: 2mg/kg/d. Best results in Caucasians. Consider if pregnancy planned.
- Continue maintenance therapy for at least 3 years (LOE:3C). Prednisone tapered to 5-7.5 mg/day by 12 months if possible.

# Refractory Disease: Recommendations for Change in Therapy

- Patients who worsen within 3 months (> 50% increase in creatinine or proteinuria) or fail to respond (achieve partial remission) with 6 months of induction therapy should have change in therapy (LOE: 4C).
  - All pts should get 3 days of intravenous pulse methylprednisolone.
  - Pts on MMF could switch to CYC
  - Pts on CYC could switch to MMF
  - Pts who fail MMF or CYC can add or switch to rituximab or calcineurin inhibitors (especially Class V LN)
  - Belimumab being studied for induction and maintenance of certain presentations of LN.

# Lupus Nephritis ACR Guidelines: Adjunctive Treatments

## All patients

Hydroxychloroquine

ACEi +/-ARBs >0.5 g/d proteinuria

BP <130/80

Statins: LDL >100 mg/dL

Calcium, vitD, D/C smoking, immunizations

- ASA and/or anticoagulation for mild thrombotic microangiopathy (TMA) on biopsy. If TMA predominant lesion treat with plasma exchange and anticoagulation.
- Anticoagulation for nephrosis and albumin < 2.0gm/d



# Lupus Nephritis Monitoring Schedule

	BP	U/A	Urine Pr/Cr	Serum Cr	C3/C4	antiDNA
Active LN	1	1	1	1	2	3
Previous LN, now inactive	3	3	3	3	3	6
No prior hx of LN	3	6	6	6	6	6

Monitoring schedule: # months

# Case

- Patient treated with IV pulse methylprednisolone for 3 days followed by prednisone 30mg BID and MMF 1.5 grams BID.
- She was also placed on calcium, vitamin D, lisinopril, hydroxychloroquine, and ASA.
- At 3 months her creatinine was 1.2mg/dL and proteinuria decreased to 2.8 grams/day. Her C3,C4, and anti-dsDNA were improved but still abnormal. She was on MMF and prednisone 35 mg q day.
- At 6 months Her creatinine was 0.9mg/dL, proteinuria 1.2 grams/ day. Her C3 was normal, C4 low, and anti-dsDNA mildly elevated at 60 units. She was maintained on MMF and prednisone 10mg q day.

# Special Situations

- Pregnancy and lupus nephritis
  - Pregnancy should be planned. Ideally LN (and lupus) should be inactive for 6 months with proteinuria < 1 gram/d and CrCl > 50ML/min.
    - Serum C3/C4 should rise during normal pregnancy
  - Patients should be off MMF and CYC for 3 months before conception
  - Hydroxychloroquine, prednisone, and azathioprine can be used during pregnancy. ASA to reduce preeclampsia risk.
  - Blood pressure control without ACEi or ARBs. Can use labetalol or nifedipine.
  - Close surveillance for postpartum flare of lupus and LN.
- Pediatric lupus nephritis
  - Children at increased risk for LN (2x risk compared to adults).
  - Children frequently present with LN and have more active disease and damage.
  - Steroid side effects worse in children including growth retardation

# Special Situations

- End-stage renal disease
  - Up to 30% of patients progress to ESRD within 15 yrs
  - Disease activity tends to decrease in patients with ESRD on dialysis
  - Lupus activity and serology should be controlled 3-6 months prior to renal transplant.
  - Renal transplantation is best with living donor and pre-emptive transplant
  - Post-transplantation recurrence of lupus nephritis is a rare cause of allograft rejection.

# Case

- A 25yo woman with SLE for 6 months is admitted with generalized seizures. Her friends reports she has had more problems with arthritis and severe depression. Notably she stopped her prednisone due to weight gain a month ago. Past history is significant for an episode of optic neuritis 3 months ago treated with prednisone.
- Physical exam shows she is afebrile, pulse 90 reg, BP 155/95mmHg. She is postictal and unable to follow commands. She has a malar rash, oral ulcers, synovitis of hands and wrists, and livedo reticularis over her lower extremities. Neuro exam is difficult but nonfocal.
- Laboratories show Hct 32%, WBC 3400/MicroL, plts 124,000/microL. Chemistries are normal except for creatinine 1.2 mg/dL and albumin 3.1 mg/dL. Urinalysis shows 2+ protein, small blood, and 1-2 granular casts/HPF.
- Brain CT scan in ER showed no infarct or bleed.
- Serologies from 3 months ago showed positive ANA, positive anti-SS-A, anti-ds DNA > 300, low C3 62 mg/dL, low C4 <8 mg/dL, and the presence of a lupus anticoagulant.

# Case

- Questions
  - Is this patient CNS dysfunction more likely due to NPSLE or a non-lupus cause?
  - What are the NPSLE syndromes?
    - How does the pathogenesis differ between them?
  - What is the diagnostic workup?
    - What laboratory tests are helpful?
    - When should a spinal tap be done?
      - What should be ordered?
    - What is the best radiographic test: CT vs MRI, MRA vs angiogram?
  - How should the treatment be tailored to the NPSLE manifestation?
  - What is the long term prognosis for patients with NPSLE?

# Neuropsychiatric Lupus Erythematosus (NPSLE)

- Approximately 20% of SLE pts develop NPSLE during their lifetime (LOE:2B).
  - Most (60%) of NPSLE occurs at SLE onset or within first year of disease.
  - Most (50%) occur in the presence of generalized SLE activity.
- Risk factors (5x increase in risk)(LOE:2B)
  - Generalized SLE activity (especially for seizures and cognitive dysfunction)
  - Previous NPSLE events or concurrent NPSLE manifestations
  - Antiphospholipid antibodies (especially for stroke, seizures, progressive cognitive dysfunction, myelopathy, and chorea)

# Neuropsychiatric Syndromes

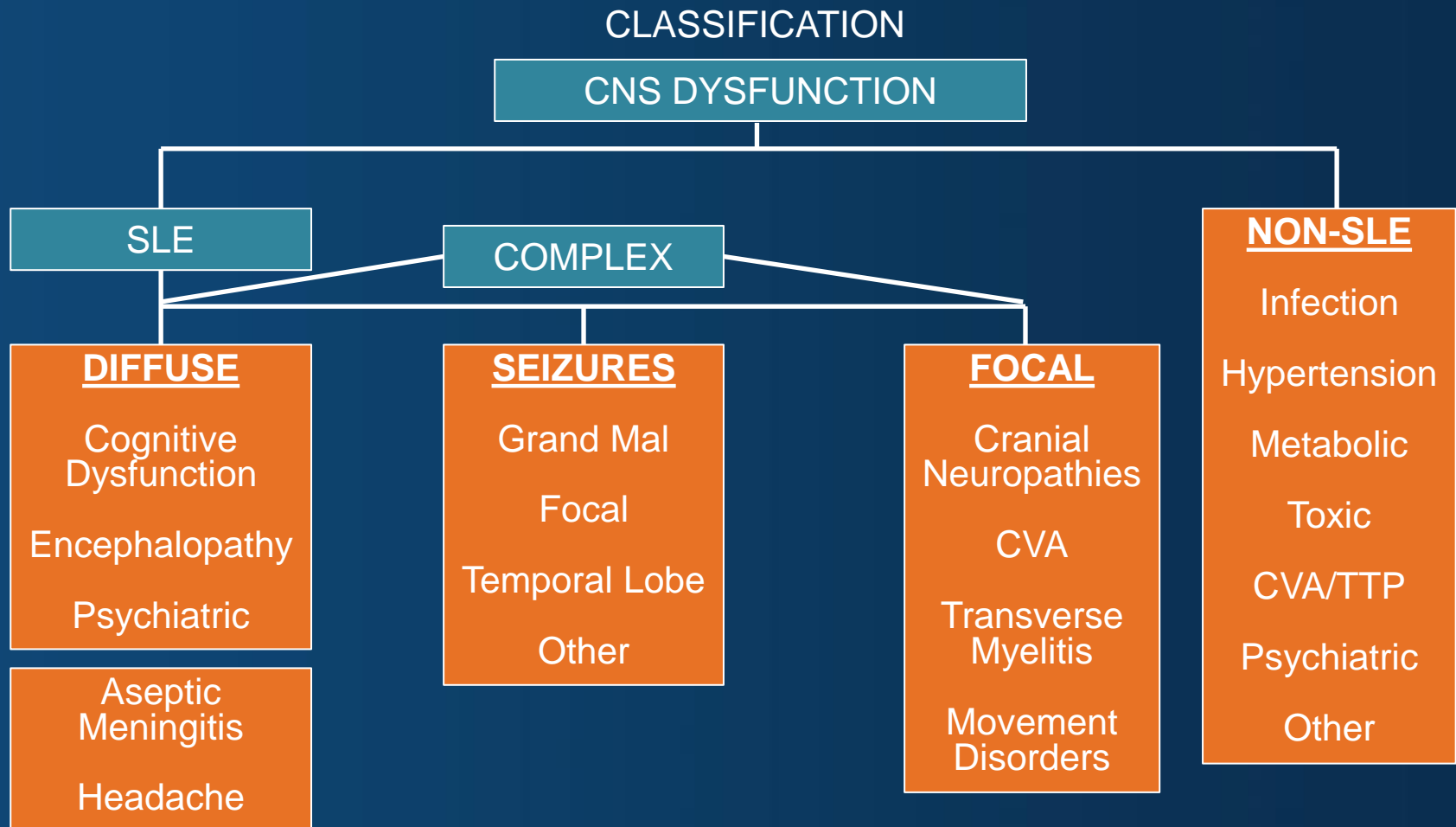
- CNS (80% of all NPSLE events)
  - Acute confusional state (delirium to coma)
  - Cognitive dysfunction (mild to dementia)
  - Psychosis
  - Anxiety disorder
  - Mood disorder
  - Headache
  - Seizures
  - Demyelinating syndrome
  - CVA (stroke)
  - Transverse myelitis
  - Movement disorders
  - Aseptic meningitis
- PNS (20% of all NPSLE events)
  - Cranial neuropathy
  - Polyneuropathy
  - Plexopathy
  - Mononeuropathy
  - Guillain-Barre(AIDP)
  - Autonomic disorder
  - Myasthenia gravis



# Neuropsychiatric Syndromes

- Case definitions
  - Prevalence in SLE (57-91% of SLE pts vs 56% of controls)
    - Sensitivity 91% ; Specificity 46%
- If exclude minor syndromes without objective findings (anxiety, headaches, mild depression, subjective cognitive complaints, polyneuropathy with negative EMG/NCV)
  - Prevalence of NP lupus 2-19%
    - Sensitivity 91% ; Specificity 93%

# NPSLE Classification for Clinicians



- Overall: 40-50% of CNS dysfunction due to SLE and 50-60% due to nonSLE cause.
- Overall: 40% present with diffuse/seizure, 40% focal sx's, and 20% complex.

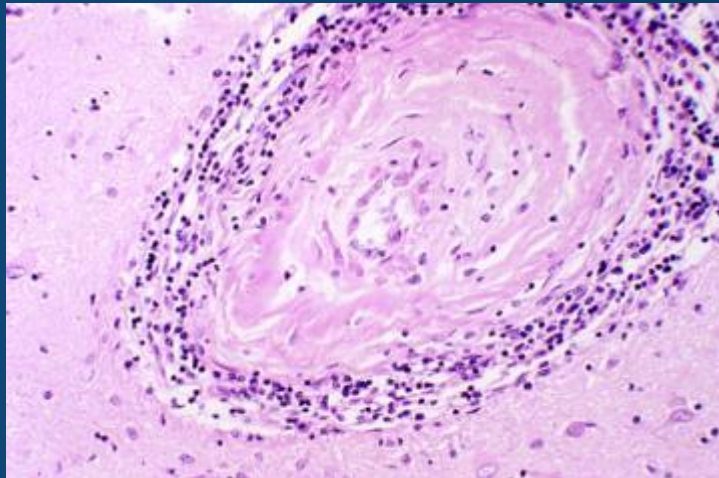
# Theories of Pathogenesis

- Vascular occlusion
- Antineuronal antibodies
- Cytokine and small molecule effects
- Others: choroid plexus dysfunction, neuroendocrine-immune system
- Combination
  - Different clinical presentations have different or combined pathogenesis.
  - Knowing the suspected pathogenesis dictates therapy.

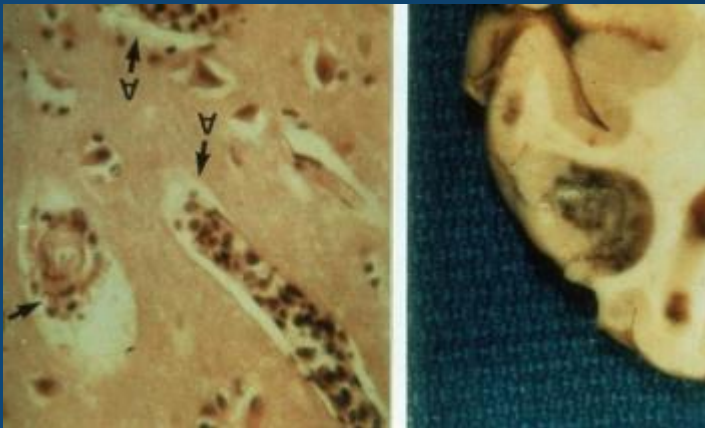
# Vascular Occlusion (Focal sx's)

Correlates with high SLE activity

- Vasculitis

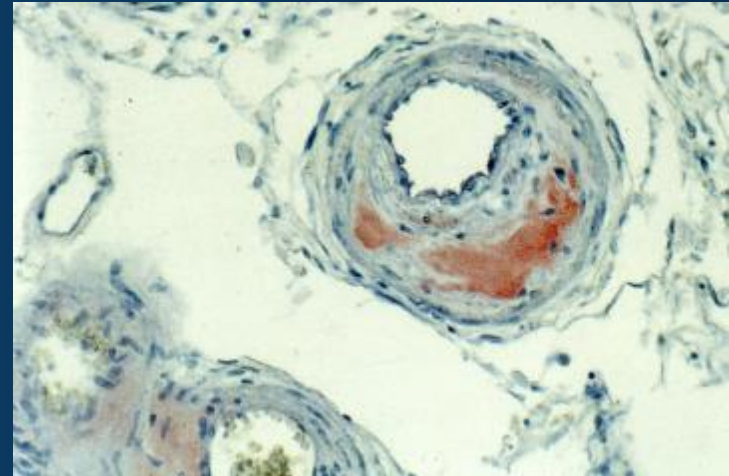


- Leukoagglutination

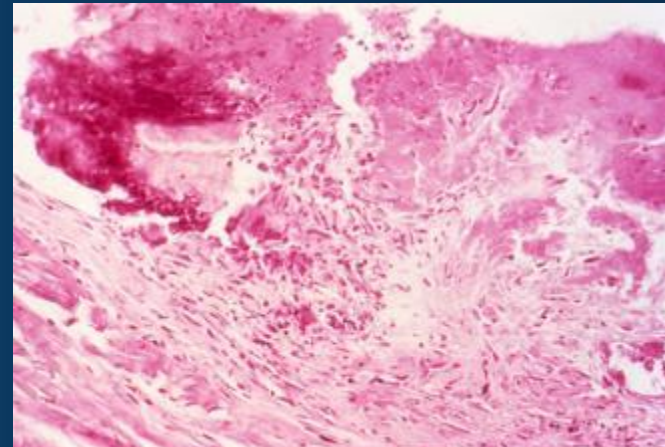


Correlates with antiphospholipid abs

- Bland vasculopathy



- Clot

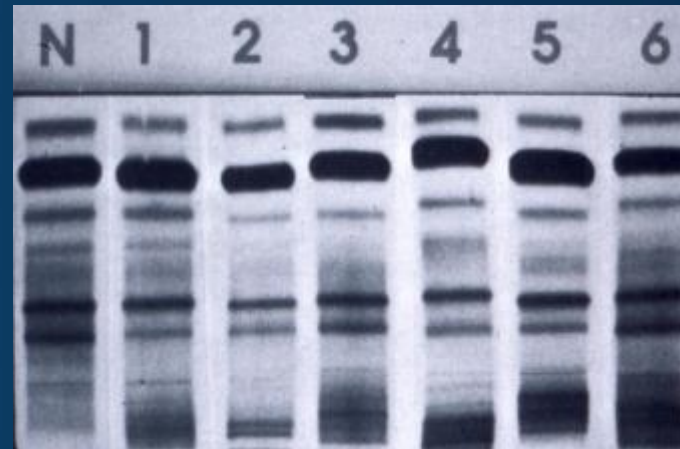
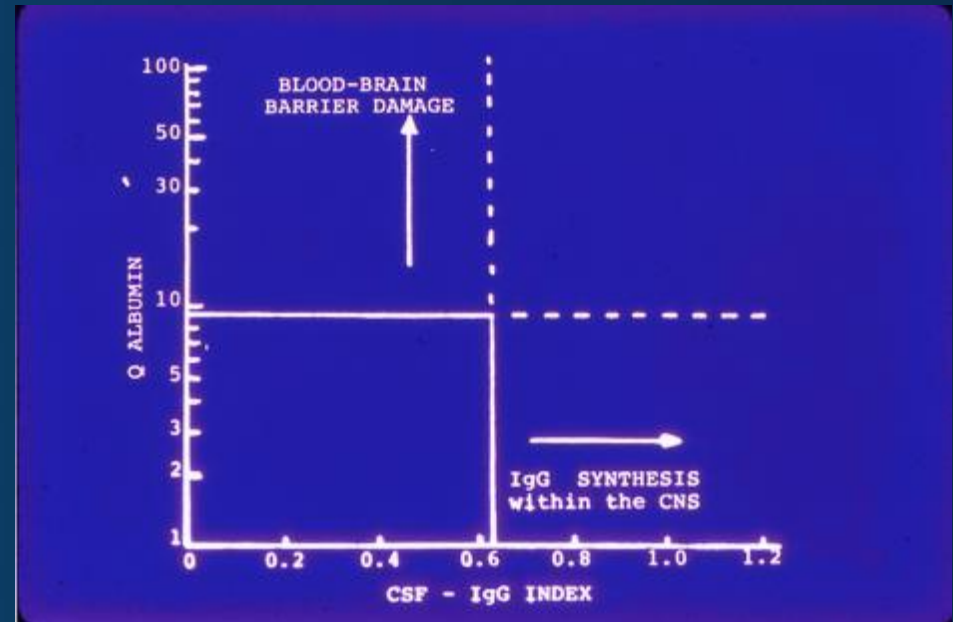


# Antineuronal antibodies

- Serum antineuronal antibodies (associated with certain diffuse and focal sx's). Over 20 described but only a few can be tested for.
  - Neural tissue specific:
    - Antineuronal (neuroblastoma cells)
    - Aquaporin-4 (anti-NMO)
  - Non-neural specific:
    - Anti-ribosomal P
    - Antiphospholipid antibodies
    - AntiDNA/NMDA receptor (anti-NR2)
- CSF antineuronal antibodies
  - Correlates with diffuse symptoms
  - Origin of antibodies
    - Serum antibodies cross BBB
    - Intrathecal synthesis

# CSF Immunologic Tests

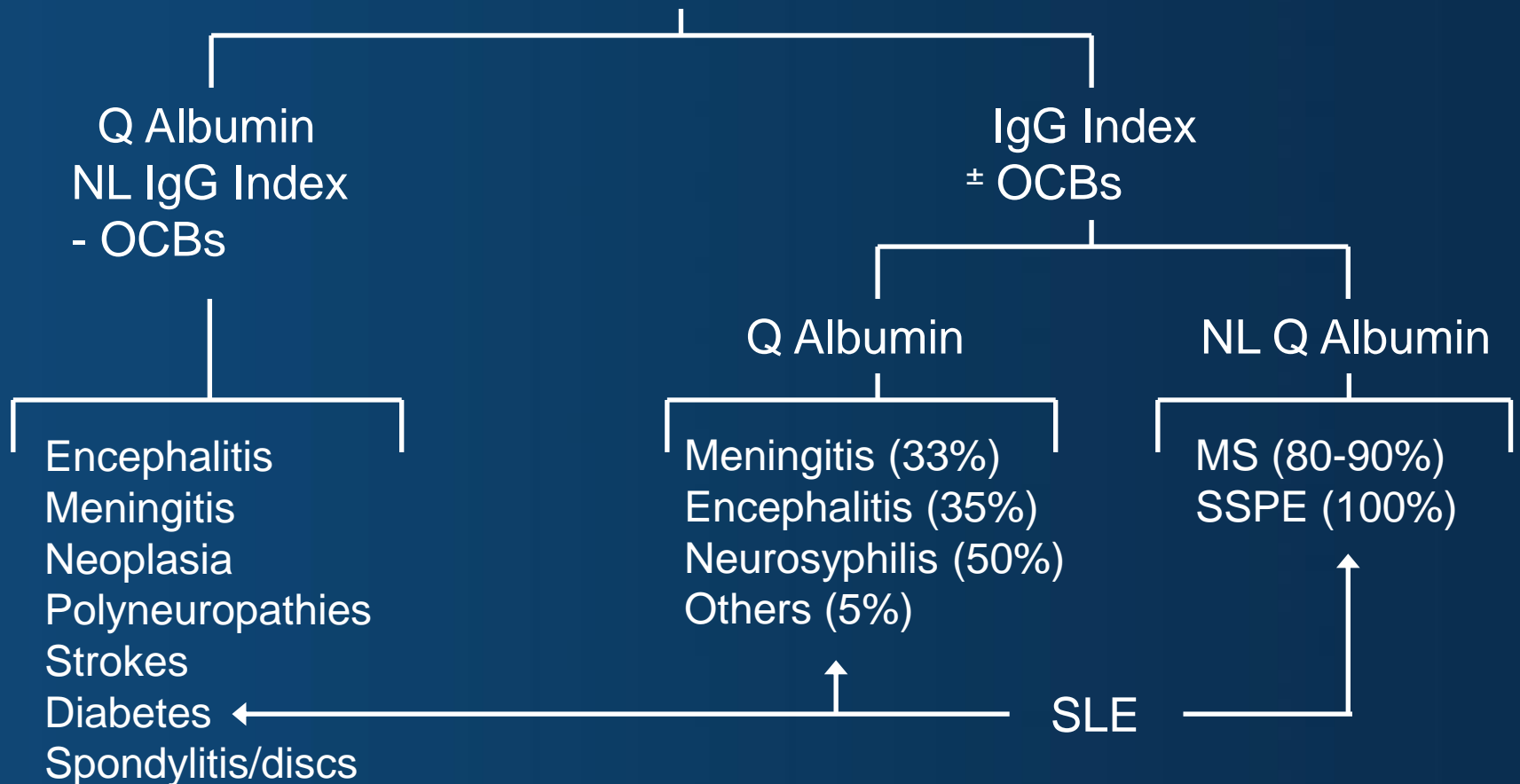
- Q albumin =  $\frac{\text{CSF albumin} \times 10^3}{\text{Serum albumin}}$
- IgG index =  $\frac{\text{CSF IgG} \times 10^3}{\text{Serum IgG} \times \text{Q albumin}}$



- Oligoclonal bands

# How to Interpret CSF Immunologic Protein Results

## CSF Immunologic Protein Assays



# Theories of Pathogenesis

- Cytokine and small molecule effects
  - Multiple cytokines, chemokines, and enzymes are elevated in the serum and CSF of patients with NPSLE.
  - Induction of intrathecal cytokines and matrix metalloproteinases caused by uptake of intrathecal autoantibodies/immune complexes by glial cells.
- Others: choroid plexus dysfunction, neuroendocrine-immune system
- Combination of mechanisms common especially in those presenting with both diffuse and focal manifestations (complex presentations)



# Diagnostic Tests (LOE: 2D)

- CBC with peripheral smear (R/O TTP)
- Chemistries, liver-associated enzymes, urinalysis
- C3/C4, anti-dsDNA antibody level
- Antiphospholipid antibodies
- CSF: routine, Q albumin, IgG index, OCBs, appropriate cultures and viral PCRs (when indicated)
- MRI (T1/T2, FLAIR, DWI, and gadolinium-enhanced T1) (LOE:1A)
- EEG (for seizures)
- Other tests when indicated: specific autoantibodies, C-reactive protein, echo, carotid U/S, neuropsychometric tests, MRA, cerebral angiogram, nerve conduction studies

# Secondary Causes of CNS Dysfunction in SLE pts

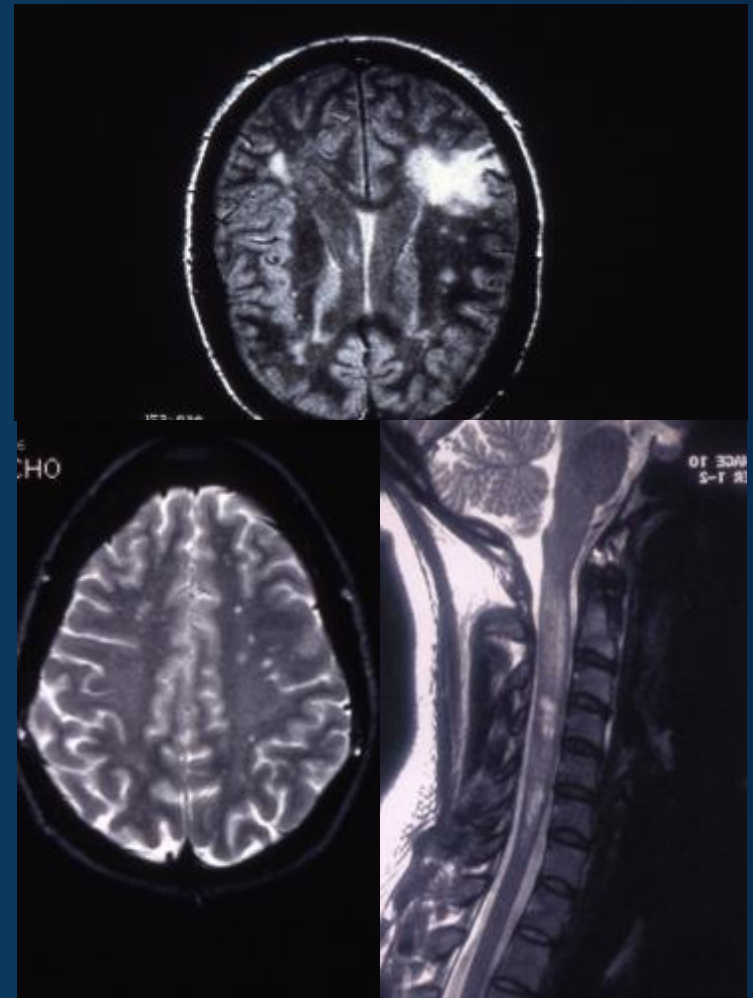
- Infection
- Medication
- TTP
- Hypertension(RPLS)
- Uremia
- Electrolyte imbalances
- Fever
- Thyroid disease
- Atherosclerotic strokes
- Subdural hematoma
- Berry aneurysm
- Cerebral lymphoma
- Fibromyalgia
- Reactive depression
- Sleep apnea
- Other primary neurologic or psychiatric disease

# Autoantibody and NPSLE Manifestations

- Antiphospholipid antibodies: stroke, seizures, progressive dementia, myelopathy, and chorea.
- Anti-ribosomal P: psychosis, depression, active NPSLE.
- Anti-aquaporin 4/anti-neuromyelitis optica (anti-NMO): optic neuritis, longitudinal transverse myelitis. Most patients also have anti-SS-A antibodies.
- Serum and CSF anti-neuronal antibodies: more common in patients with active NPSLE.
- Anti-dsDNA/anti-NMDA receptor (anti-NR2): severe cognitive dysfunction.

# Neuroradiographic Imaging

- CT scan: hemorrhage, subdural
- MRI with gadolinium
  - Focal sx/s/seizures > diffuse sx/s
  - Beware white matter hyperintensities: common in patients with HBP, CVD, DM, smoking, ↑ lipids, migraines, age > 50, aPLabs
- MRA vs angiogram
  - Only consider if have larger brain lesions involving grey and white matter



# Diagnostic Approach

- Initial diagnostic workup is to rule out secondary causes especially infection (CBC, CSF, cultures), TTP (peripheral smear, platelets, LDH), metabolic (chemistries), hypertension/RPLS (MRI), sleep apnea (snoring), and medications.
- Assess lupus activity: clinical sx's, C3, C4, anti-dsDNA.
- Diffuse symptoms: CSF IgG index/OCBs, CSF antineuronal antibodies, serum anti-ribosomal P. MRI frequently normal (50%) but helps to rule out other causes.
- Focal symptoms: vasculitis (skin vasculitis, CSF with ↑ cells and protein), antiphospholipid antibody syndrome (skin livedo, positive aPLabs, CSF with mild ↑ protein but few cells), MRI (focal lesions in > 80%), echo (if suspect emboli), anti-NMO (optic neuritis, transverse myelitis)
- Seizures/complex presentations: all of above
- PPV 92%, Sensitivity 90%, Specificity 92% for above tests

# Case

- CNS manifestation: seizures, progressive depression, hx optic neuritis, off prednisone
- Initial evaluation: secondary causes unlikely.
- Assess lupus activity: clinical (arthritis, nephritis) and serologies (low C3, high anti-dsDNA) suggest active lupus.
- Diffuse and seizure sx: Lupus anticoagulant (seizures) and anti-ribosomal P positive. CSF showed 3 cells (lymphs), protein 62 mg/dL, IgG index 0.72, and 5 OCBs. Blood and CSF cultures negative.
- MRI shows several scattered white matter hyperintensities. None enhance with contrast. EEG shows left sided epileptiform discharges.
- Past hx of focal sx (optic neuritis): anti-NMO antibody positive

# Treatment (A,B,C and 5 'Ps')

- Aspirin
- Biologics
- Warfarin (Coumadin)
- Hydroxychloroquine (Plaquenil)
- Fluoxetine (Prozac)
- Prednisone
- Powerful cytotoxics
- Plasma exchange

# Treatment

- Minor manifestations
  - Sx therapy: ASA, hydroxychloroquine, antidepressants/psychotics, analgesics, anti-seizure meds. Control blood pressure.
- Major manifestations: Diffuse CNS symptoms
  - Sx therapy
  - Corticosteroids (1 mg/kg in divided doses for 4-6 wks then taper)
    - Double the prednisone dose or use dexamethasone(12-20mg day) if fail to respond to prednisone (1mg/kg/day) within 72hrs.
  - Cytotoxics: cyclophosphamide > others
    - IV cyclophosphamide ( 0.75-1.0 gm/m<sup>2</sup> /day) for 3-6 months
    - Other methods of cyclophosphamide: low dose IV (500mg IV q2weeks x 6 weeks) or daily oral cyclophosphamide
  - Other: pulse methylprednisolone (1 gram/day x3 doses if severe presentation); plasma exchange (coma and no response to other therapy in 3-7 day); rituximab (1 gram x 2 or 375mg/m<sup>2</sup> weekly x 4 weeks)



# Difficult Clinical Situations

- Severe, refractory NPSLE
  - One approach (after 3 day methylprednisolone pulse)
    - Prednisone 30mg BID or dexamethasone 6mg BID and start taper as soon as improvement occurs
    - Cyclophosphamide 500mg IV day 1
    - Rituximab 1000mg IV day 2 with 100mg methylprednisolone premed
    - Cyclophosphamide 500mg IV day 15
    - Rituximab 1000mg IV day 16 with 100mg methylprednisolone premed
    - Cyclophosphamide 500mg IV days 30, 45, 60, 75 (ie q2wks)
    - Day 90 start mycophenolate mofetil (MMF) 500mg BID and increase to 1500mg BID over 2-4 weeks

# Treatment

- Major manifestations: Focal
  - Antiplatelet agents
  - Corticosteroids
  - Vasculitis: cyclophosphamide(may need IV q3wks)
  - Clotting: anticoagulants
    - Acute: heparin (follow heparin levels). Caution if lesion >3 cm or cardioembolic stroke. Follow with CT scans
    - Chronic: warfarin (INR 3.0). Follow factor X levels(keep less than 20%)
  - Other: plasma exchange/IVIg
- Maintenance therapy: after 3-6 months of induction therapy transition to MMF.

# Case

- Treatment
  - IV methylprednisolone 30mg BID with transition to oral prednisone
    - Calcium and vitamin D
  - Levetiracetam for seizures
  - ASA and hydroxychloroquine for aPLabs
  - Fluoxetine for depression
  - Mycophenolate mofetil for concern of anti-ribosomal P and anti-NMO.
- Follow up
  - Recovered but stopped medications after discharge from hospital with recurrence of symptoms.
  - Readmitted. Medications restarted. IV cyclophosphamide started instead of MMF.

# Prognosis

- NPSLE recurrences: 20-40%
- Second leading lupus cause of death: 7-19% mortality
- Poor prognostic signs
  - Status epilepticus
  - Strokes
  - Coma
- Damage index: worse in those with recurrent episodes and/or aPLabs
  - Diffuse: cognitive deficits
  - Focal: residual deficits