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Professor Neurology-ALL INDIA INSTITUTE OF MEDICAL SCIENCES DELHI INDIA

- DM Neurology, NIMHANS, Bangalore 1996,
- Awarded the NIH fellowship in EPILEPSY at the prestigious UCLA - USA from 2005-2006. Awarded Penry minifellowship in Epilepsy from the Wake forest university in North Carolina. Alumni of the San Servolo school of Epilepsy.
- ILAE Faculty 1000, ILAE Task force member for stigma in epilepsy, Pediatric epilepsy surgery subcommision-ILAE.
- Neuroscience Task force member of the DBT for Epilepsy, She heads the Disability Task force for epilepsy.
- Co-ordinator National Epilepsy Control program- India- Ministry of Health, Co-PI Centre of excellence for refractory epilepsy- DBT.
- Executive member of the IES, a member of IEA, Member of International Professional societies like AAN, AES, AASM.
- Core committee of Guidelines for epilepsy management in India (GEMIND).
- Numerous research publications in epilepsy. She has research projects in Epilepsy funded by Department of Science and Technology, COPI- Center of Excellence Epilepsy.
- Her main areas of interest are Epilepsy especially Drug Refractory epilepsies, epilepsy surgery, Women with epilepsy and functional neuroimaging in Epilepsy. Sleep disorders and cognition.
- She also runs rural outreach programs in Epilepsy in tribal Orissa and North east.
- Delivered guest lectures at various National and International epilepsy conferences.
- National Course Director of Epilepsy and EEG workshops of IES.
- Numerous Orations, awards and 253 papers in peer reviewed journals and books.
- Organizes epilepsy awareness days on 17th nov and has written patient handouts for epilepsy.
NEUROLOGICAL MANIFESTATIONS OF SYSTEMIC DISEASES

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Almost all !!!!!!!

- Infections
- Metabolic
- Endocrine
- Inflammatory
- Autoimmune
- Nutritional
- Neoplastic
- Vascular
- Degenerative
Rheumatological disorders

- Systemic autoimmune disorders
  - Primarily affect connective tissue, vessel walls or joints
- Many of these disorders also affect nervous system
  - Presenting symptom
  - During the course of illness
- Entire neuraxis is vulnerable: Brain→muscle
Neurorheumatological disorders

- Once the nervous system is involved
  - High disease activity
  - Increased morbidity

- Most of these conditions are treatable & hence early diagnosis is essential

- But are not diagnosed correctly at times
Neurorheumatological disorders

- Prevalence: not exactly known
  - In a study, prevalence of rheumatological & autoimmune disorders was 11% in neurological patients

- Most common disorders
  - Sjogren syndrome
  - Lupus
<table>
<thead>
<tr>
<th>Rheumatological condition</th>
<th>Neurological features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing spondylosis</td>
<td>Myelopathy</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>Stroke, venous sinus thrombosis; migraine; chorea; demyelinating disease; myelitis</td>
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<tr>
<td>Behçet disease</td>
<td>Stroke, venous sinus thrombosis; brainstem syndromes; cranial neuropathies; meningitis; seizures</td>
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<tr>
<td>Cogan syndrome</td>
<td>Deafness; vestibular involvement</td>
</tr>
<tr>
<td>Dermatomyositis Polymyositis</td>
<td>Inflammatory myositis</td>
</tr>
<tr>
<td>Immunoglubulin4- (IgG4-) related disease</td>
<td>Meningitis</td>
</tr>
<tr>
<td>Mixed connective tissue disorder</td>
<td>Inflammatory myositis</td>
</tr>
<tr>
<td>Primary vasculitides syndromes</td>
<td>Neuropathies; stroke; encephalopathy; meningitis; demyelinating disease</td>
</tr>
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<td>Rheumatological condition</td>
<td>Neurological features</td>
</tr>
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<tr>
<td>Sarcoidosis</td>
<td>Meningitis; cranial neuropathies; neuropathies; myositis; demyelinating disease; parenchymal disease</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>Inflammatory myositis</td>
</tr>
<tr>
<td>Sjogren syndrome</td>
<td>Neuropathies; cranial neuropathies; myelopathy; demyelinating disease</td>
</tr>
<tr>
<td>Susac syndrome</td>
<td>Deafness; encephalopathy; demyelinating disease</td>
</tr>
<tr>
<td>Systemic lupus erythematosus (SLE)</td>
<td>Aseptic meningitis; stroke, venous sinus thrombosis; demyelinating disease; headache; chorea; seizures; psychiatric manifestations; myelopathy; cranial &amp; peripheral neuropathies; myasthenia</td>
</tr>
<tr>
<td>Rheumatoid arthritis (RA)</td>
<td>Myelopathy; neuropathies; myositis; pachymeningitis; rheumatoid nodules in brain</td>
</tr>
<tr>
<td>Temporal arteritis</td>
<td>Headache; optic neuropathy; stroke</td>
</tr>
</tbody>
</table>
Sjogren syndrome

- Chronic autoimmune disease primarily involving exocrine (salivary & lacrimal) glands

Types
- Primary
- Secondary (in association with other connective tissue disorders)
Sjogren syndrome

- Nervous system involvement in 20% patients
  - Presenting feature in 25-95%
- Series of 82 patients of Sjogren with neurological manifestations
  - 36% isolated neurological symptoms
  - 47% preceded sicca syndrome
  - Antibody positivity: 21% at time of presentation; 43% over 7 years follow-up
Sjogren syndrome

- Neurological manifestations
  - Peripheral neuropathies: 7 types
  - Patient can have >1 type
  - Central nervous system lesions
    - Non-focal
    - Focal
Sjogren syndrome: neuropathies

1. Sensory ataxic neuronopathy (39%)
   - Subacute to chronic; progressive
   - Normal motor power, generalized areflexia & severe proprioceptive loss
   - Nerve conduction studies: absence of sensory action potentials; normal motor action potentials
   - MRI cervical spine may show T2 hyperintensity in posterior column
   - Dorsal root ganglionitis; lymphocytic infiltrations
2. Painful sensory neuropathy (20%)
   - Progressive painful dysaesthesias
   - Loss of pain & temperature sensation with relative preservation of proprioception
   - Motor power normal; reflexes may be present
   - NCS: normal or minor abnormalities
   - Skin biopsy: reduced epidermal nerve fiber density suggestive of small fiber involvement
   - Small fiber neuronopathy
Sjogren syndrome: neuropathies

3. **Trigeminal sensory neuropathy (16%)**
   - U/L or B/L
   - Pathologically it is trigeminal ganglionitis

4. **Autonomic neuropathy (3%)**
   - Adie’s pupil, postural hypotension, hypohidrosis

5. **Mononeuritis multiplex (12%)**

6. **Multiple cranial neuropathies (5%): III to XII**

7. **CIDP-like neuropathy (4%)**
Sjogren syndrome: neuropathies

- The antibody positivity is Sjogren associated neuropathy is <50%
- Nonserological ancillary testing is more sensitive than autoantibodies in neuropathy
  - Lip biopsy
  - Schirmer test
  - Rose Bengal test
Sjogren syndrome: neuropathies

- Lip biopsy
  - Minor salivary gland biopsy shows foci of lymphocytic infiltration
  - Seen in 37-75% of patients with neuropathy

- Schirmer test
  - The test is positive when there is <5 mm of moistening of the filter paper after 5 min
  - Positive in 56-89% of patients with neuropathy
Sjogren syndrome: neuropathies

- There are no guidelines for management of Sjogren syndrome associated neuropathies
- Treated with steroids & IVIG
  - Response to these drugs is modest
  - Only few patients improve with these drugs
- Some reports of use of rituximab
Sjogren syndrome

- Association between Sjogren syndrome & demyelinating lesions is not well established

In NMO, incidence of Sjogren syndrome & presence of SS-A antibodies is high

- This is indicative of presence of other autoimmune diseases in NMO

- Treated like NMO

- Incidence of MS-like lesions is not increased in Sjogren syndrome
SLE

- SLE can present with many neurological manifestations
  - Collectively called neuropsychiatric SLE (NPSLE)
  - Can occur in absence of systemic features or serological antibodies
  - Has poorer prognosis & increased mortality
  - Presenting feature of SLE in 28-40% patients
  - Prevalence of neurological manifestation in SLE 14-80% in adults; 22-95% in children
Neuropsychiatric syndromes associated with SLE

- Cognitive dysfunction
- Acute confusional state
- Seizure disorder
- Demyelinating disorder
- Chorea
- Strokes
- Aseptic meningitis
- Headache
- Autonomic disorder
- Anxiety disorder
- Mood disorders
- Psychosis
- Myelopathy
- Cranial neuropathies
- Mononeuritis
- Polyneuropathy
- Plexopathy
- Myasthenia gravis
NPSLE

- Most common features
  - Headaches 54%
  - Seizures 42%
  - Visual failure 32%
  - Fatigue 27%
  - Hemiparesis 24%
  - Memory impairment 24%
  - Confusion 24%
  - Personality change 20%
  - Depression 18%
NPSLE

- Aetiopathogenesis
  - Multifactorial
  - Microangiopathy, compliment activation, proinflammatory cytokines & atherosclerosis
  - Pathological abnormalities
  - Demyelination, chronic ischemia, & neuronal damage
  - Autoantibodies
NPSLE

- Number of autoantibodies are seen in SLE
  - Certain associations are known
  - Antiphospholipid antibodies (aPLs) & strokes as well as cognitive impairment
  - Anti-glutamate receptor antibody & cognitive dysfunction & psychiatric manifestations
- Other antibodies are not consistently found with NPSLE
NPSLE

- MRI abnormalities
  - Cortical atrophy
    - Associated with disease duration & cognitive impairment
  - WM lesion: periventricular, subcortical
  - Infarcts
  - Many more...
- B/L parietooccipital hypometabolism on PET
**NPSLE**

- Treatment depends on nature & severity of neurological syndrome
  - Both symptomatic Rx & immunosupression
  - Started with steroids or hydroxychloroquine
  - In more severe disease, oral or intravenous pulse cyclophosphamide is added
  - Azathioprine, methotrexate, mycophenolate are used for maintenance
  - Rituximab or TNFa inhibitors are other options
NPSLE- how aggressive

- Headache & depression
  - No correlation with disease activity; escalation of immunosuppression is not required

- Psychosis
  - Related to disease activity; immunosuppression & antipsychotic drugs needed

- Seizures
  - Usually long-term AEDs not necessary; rarely immunosuppression in refractory cases
NPSLE

- Delirium
  - Multifactorial: uremia, hypoxia, other metabolic derangements, posterior reversible encephalopathy syndrome (PRES), & strokes

- Ischemic stroke
  - Risk is increased in SLE patients
  - Related to aPLs which are positive in 65%
  - Need long term anticoagulation
NPSLE

- Myelitis
  - About 80% are due to NMO
- Peripheral neuropathies
  - Less common (1-13%)
  - Axonal polyneuropathy, mononeuritis multiplex, cranial neuropathies (III, V, VI & VII) & small fiber neuropathy
  - Treated with steroids, IVIG, plasmapheresis, cyclophosphamide, rituximab as per severity
Antiphospholipid syndrome (APS)

- Episode of arterial or venous thrombosis or recurrent foetal loss in presence of aPLs in moderate to high titres or a lupus anticoagulant (LA) which is present for at least 2 occasions 12 weeks apart

- Primary
- Secondary in association with SLE or other connective tissue disorders
Antiphospholipid syndrome (APS)

- Neurological manifestations
  - Ischemic stroke: some cardioembolic
  - Venous sinus thrombosis
  - Cognitive impairment
  - Transient global amnesia
  - Headaches & migraine-like events
- Demyelinating diseases
  - Peripheral neuropathy
Antiphospholipid syndrome (APS)

- Treatment
  - Both antithrombotic drugs & immunosuppressants
  - Patients with positive LA
    - Aspirin for primary stroke prevention
    - Oral anticoagulation for secondary stroke prevention
Rheumatoid arthritis

- Neurological manifestations
  - Cervical myelopathy - AAD
  - Pachymeningitis
  - Strokes due to vasculitis
  - Peripheral neuropathy
    - Entrapment syndromes
    - Axonal polyneuropathy
    - Vasculitic mononeuritis multiplex
    - Myositis
Vasculitis

- Vasculitis involves central as well as peripheral nervous system
  - **Primary**
  - **Secondary: with systemic vasculitic disorders**
    - Idiopathic systemic vasculitis
    - Systemic vasculitis secondary to autoimmune diseases
    - Systemic vasculitis secondary to non-immune disorders: infections, drugs, cancer
CNS vasculitis

- Potentially treatable; often underdiagnosed
  - Clinical presentation can be extremely variable
  - No classic presentation
  - No diagnostic test
  - Sensitivity & specificity of all currently available tests are suboptimal

- Types
  - Primary angiitis of CNS (PACNS)
  - Secondary
CNS vasculitis

- Treatment
- Initiated with steroids & cyclophosphamide

<table>
<thead>
<tr>
<th>Oral prednisolone 1 mg/kg</th>
<th>Oral cyclophosphamide 2 mg/kg</th>
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</thead>
<tbody>
<tr>
<td>I/V methylprednisolone</td>
<td>I/V cyclphosphamide 1 gm/month</td>
</tr>
</tbody>
</table>

- Continued for 6-12 months till remission is achieved
- Other immunosuppressants used thereafter for maintenance 2 to 3 years

Azathioprine, methotrexate, mycophenolate

- Rituximab is alternative for cyclophosphamide
Drugs in neurorheumatology
- Non-targeted

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Route</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoid</td>
<td>Multiple</td>
<td>IV, oral, IM</td>
<td>Acute therapy</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Folate inhibition</td>
<td>Oral, IV, subcutaneous</td>
<td>Steroid sparing</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Inhibits purine synthesis</td>
<td>Oral</td>
<td>Steroid sparing</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Inhibits DNA/ribonucleic acid synthesis in leukocytes</td>
<td>Oral</td>
<td>Steroid sparing</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Alkylating agent</td>
<td>Oral, IV</td>
<td>Acute therapy in severe disease</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>T-cell inhibition</td>
<td>Oral</td>
<td>Short-term treatment</td>
</tr>
</tbody>
</table>
### Targeted Antibody Treatments

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Target</th>
<th>Indications</th>
<th>Adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rituximab</strong></td>
<td>CD20</td>
<td>RA, SLE, vasculitis, Sjogren’s syndrome, polymyositis</td>
<td>Infusion reactions, opportunistic infections, PML</td>
</tr>
<tr>
<td><strong>Infliximab</strong></td>
<td>TNF</td>
<td>RA, Behcet disease, dermatomyositis, polymyositis</td>
<td>Opportunistic infections, demyelinating lesions, heart failure, malignancies, hepatotoxicity</td>
</tr>
<tr>
<td><strong>adalimumab</strong></td>
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</table>
Carry home messages

- Neurorheumatological disorders are not uncommon, treatable & underdiagnosed
- Any ganglionopathy, small fiber neuropathy & neuropathy of unknown cause → suspect Sjogren syndrome
- In a patient of SLE with stroke → look for antiphospholipid antibodies
- Will require long term anticoagulation
Carry home messages

- Myelitis in a rheumatological disorder → look for NMO
- Meso-diencephalic „stroke-like“ lesion → suspect Behçet disease
- Vasculitis often requires treatment with cyclophosphamide/rituximab with steroids
- Neurosarcoidosis requires „other“ imagings for its diagnosis
Thank you

Think of it, Look for it, Search for it, & you may find it.