Optic Neuritis
Differential Diagnosis Including MS and NMO and their Treatments
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Objectives
- Optic neuritis (ON) and its differential diagnosis
- Acute treatment of optic neuritis
- Multiple Sclerosis (MS) and Neuromyelitis Optica (NMO)
- Long term treatment options
  - Macular edema with fingolimod

Optic Neuritis
- A type of optic neuropathy
- Inflammation of the optic nerve.
- DDx:
  - Idiopathic
  - Demyelinating diseases: multiple sclerosis (MS) and neuromyelitis optica (NMO)
  - Systemic autoimmune diseases: SS, SLE, sarcoidosis
  - Infections: syphilis, Lyme disease, HIV, herpes zoster, mononucleosis, and mycoplasma pneumonia
  - Metabolic: B12 deficiency

Etiologies of Optic Neuritis

Optic Neuritis
- Bilateral Optic Neuritis – DDx
  - MS (Most common)
– NMO (More commonly bilateral)
– Lyme
– Syphilis
– B12 deficiency
– HIV
– Sarcoid

7 Diagnosing CNS Inflammation

7.1 Multiple Sclerosis (MS)
- Clinically Isolated Syndrome (CIS) (?RIS)
- Optic neuritis (ON)
- Transverse myelitis (TM)

7.2 Acute Disseminated Encephalomyelitis (ADEM)

7.3 Neuromyelitis Optica (NMO) – Devic’s disease

7.4 Sarcoid

7.5 Collagen Vascular diseases (Lupus, Sjögren's, RA)

7.6 Vasculitis
- Primary CNS angiitis
- Secondary vasculitis: ANCA +, Behçet’s disease

7.7 Paraneoplastic antibodies

8 Initial Symptoms of MS

8.1 Limb Weakness - 40%
8.2 Decreased vision/ Optic neuritis - 22%
8.3 Tingling and unusual sensations such as electrical, itching or 'sunburned'/ Paresthesias - 21%
8.4 Double Vision/ Diplopia - 12%
8.5 Dizziness/ Vertigo - 5%
8.6 Urinary Bladder urgency, frequency, hesitancy - 5%

8.7 Also
- Pyramidal signs (Hyperreflexia, clonus, spasticity)
- Posterior column sensory deficits (vibration > proprioception)
- Cerebellar (intention tremor, dysmetria)

9 Evidence of past optic neuritis

9.1 Optic disk temporal pallor
9.2 Afferent pupil defect
9.3 Red desaturation
9.4 Decreased contrast
9.5 Central scotoma
9.6 Abnormal VEP
11 □ Visual Evoked Potential
- Can be abnormal in asymptomatic patients.
- See a latency because of demyelination. Axonal loss will cause a loss of amplitude.

12 □ Role of MRI in evaluating ON

13 □ Role of MRI in evaluating ON
- Do you see white matter lesions?
  - Rule out
    - Stroke
    - Vasculitis
    - Sarcoid
  -

14 □ Acute Relapses
- Rule out pseudorelapses
  - “This is one of my typical relapses”
  - No fever, URI, UTI,…
- Do you need to treat?
  - Are symptoms worsening?
  - When did symptoms begin?
- How aggressively to treat?
- Acuity recovers faster, but no long term effects.

15 □ Steroid Treatment of MS “Attacks” or “Relapses” or “Exacerbations”
- Shortens attacks
- Does not alter severity of neurologic impairment
- Older studies indicated steroids do not affect ultimate recovery or course of MS
- Oral methylprednisolone may be equivalent to IV
- IV methylprednisolone may transiently delay further attacks in pts with Optic Neuritis
- ?? if periodic pulse IV steroids may slow clinical and MRI progression

16 □ Acute Treatment
- Steroids
  - Decrease inflammation
  - 3-5 days of IV methylprednisolone (1 gr) or dexamethasone (200 mg)
  - Side effects: Anxiety, problems sleeping, high FSBG, worsen stomach ulcers,…
- Plasmapheresis
Similar to dialysis
- Side effects: hypotension, blood clots, and infection.

- Cyclophosphamide
  - Chemotherapy (800–1000 mg/m²)
  - Used in severe relapses

17 Acute Treatment
- Severe transverse myelitis

18 Transverse Myelitis

- Inflammatory lesion of the spinal cord
- At the first occurrence, ≥2 brain lesions = 88% chance of conversion to MS in 20 years. 0 lesions = 19% risk of MS
- Presents typically with:
  - sensory (spinal level),
  - motor,
  - autonomic (bladder, bowel, sexual) dysfunction.
  - Lhermitte’s (paresthesias that radiate down the spine or limbs with neck flexion)
  - Paroxysmal tonic spasms (involuntary dystonic contractions of limb and trunk muscles).

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20 Transverse Myelitis

- Causes
  - Post Infection/vaccination (60% in children)
  - Demyelination (MS, NMO, ADEM)
  - Idiopathic (15-30%)
  - Systemic inflammatory/autoimmune diseases (SLE, Behcet's disease, Sjogren's, sarcoid)
  - Paraneoplastic, neoplastic
  - compressive,
  - postradiation,
  - vascular.

21 Radiologically Isolated Syndrome
Asymptomatic patients with classic MS findings on MRI.
Will they go on to develop MS?
- 1/3 will develop clinical MS over 2-5 yrs.
- 91% develop radiographic dissemination over 6-30 mos
Time to a first clinical event by (A) + spinal cord lesions, (B) age at first MRI suggestive of demyelinating disease, (C) sex, and (D) stratified based on the presence of 0, 1, 2, or 3 risk factors.

23 □ Multiple Sclerosis

24 □ What is MS?

• "Multiple sclerosis is a chronic, often disabling disease that attacks the central nervous system. MS is thought to be an autoimmune disease." – National MS Society
• "Multiple sclerosis is a potentially debilitating disease in which your body's immune system eats away at the protective sheath that covers your nerves." - Mayo
• "Multiple sclerosis is an inflammatory disease in which the fatty myelin sheaths around the axons of the brain and spinal cord are damaged, leading to demyelination and scarring as well as a broad spectrum of signs and symptoms." – Wikipedia
• "Multiple sclerosis is a nervous system disease that affects your brain and spinal cord. It damages the myelin sheath,...It may be an autoimmune disease" – MedlinePlus (NIH)

25 □ What is MS?

• Autoimmune
• Inflammatory
• Demyelinating???
• Affects the Central Nervous system

26 □ 2010 International Panel Criteria

27 □ Multiple Sclerosis Diagnosis

• Diagnosis of relapsing MS requires multiple discrete neurological events, arising from lesions in CNS white matter, disseminated over time, without an alternative explanation.

• Newer criteria, magnetic resonance imaging (MRI), spinal fluid studies, and evoked potential studies are allowed to demonstrate lesion dissemination in space and time.

• In progressive-onset MS, dissemination in time is increasing symptoms or signs over a one-year period.

28 □ Definitions

• A flare (relapse, attack, bout, episode, exacerbation) – ≥1 symptom from MS with objective neurological deterioration lasting ≥24 hours in the absence of fever and following a neurologically stable period of ≥30 days.

• Dissemination in Space – 2 or more of the following: 1) juxtacortical, 2) periventricular, 3) infratentorial, 4) spinal cord. Optic Nerve is not included yet...
• **Dissemination in Time** – 1) new T2 lesion on a scan done ≥30 days after the onset of the initial clinical event, or 2) asymptomatic contrast enhancing lesion

29 □ **Demographics of MS**

- Main age of onset 15 to 45 years
- Gender ~70% women
- Geography Incidence increases with distance from equator in both directions
- Incidence 12,000 new cases per year
- Prevalence 0.1% of US population (400,000)
- Race Caucasians > other ethnic groups

30 □ **Prognosis – ALL MS courses**

*data from before current therapies*

- 50% will require aid to walk within 10 years
- 50% will develop cognitive deficits
- 50%-80% will not be working in 10 years
- Loss of lifetime earnings
- Loss of productivity

31 □ **Prognostic Indicators**

**Good:**
- Optic neuritis at onset
- Sensory onset
- Little disability at 5 years
- Relapsing/remitting course
- Full recovery from attacks
- Few OCB at diagnosis

32 □ **Four Basic Disease Courses of MS:**

*Most Common Is Relapsing-Remitting*

33 □ **Diagnostic Tests in MS**

- Magnetic resonance imaging (MRI)
- Spinal fluid analysis
- Visual Evoked potentials

34 □ **MRI Use in MS**
• Useful in making the diagnosis of MS and in ruling other diagnoses out. Establish dissemination in Space (>1 of the following: 1) juxtacortical, 2) periventricular, 3) infratentorial, 4) spinal cord).

• Useful in monitoring MS therapies as many MS lesions (plaques) are clinically silent.

• There is often a huge disconnect between the MRI appearance and the clinical appearance.

### 35 MRI use in MS

**Typical**
- Multiple T2/FLAIR white matter lesions
- Lesions >3 mm
- Often periventricular (*) or juxtacortical (#)

**FLAIR lesions result from:**
- Gliosis (Sclerosis)
- Inflammation
- Demyelination
- Edema (rare)

*T2 Lesions correlate poorly with disability

### 36 MRI use in MS

**Typical**
- Often ovoid and perpendicular to ventricles (Dawson’s Fingers)

### 37 MRI use in MS

- Lesions can coalesce and be quite extensive
- Note – Not even that bad.

### 38 MRI use in MS

**Typical**
- T1 black holes can be seen in the acute setting with gadolinium enhancement (sometimes ring-enhancing) and in lesions causing atrophy.
- Black Hole burden correlates with disability ($r^2 =0.05$)
MRI use in MS

Typical

• Atrophy of the corpus callosum (•) and cortex (•) is common in advanced disease

•

MRI use in MS

Typical

• Short (<3 Segment) Spinal Cord Lesions. Acutely show cord swelling and later atrophy of cord if damage is permanent.

•

MRI use in MS

Not Typical in MS

• Tumor-like mass Lesions with edema (tumefactive MS, but MS pts do get brain tumors!!!)

• Exclusively Punctate (<3mm) Lesions (leukoariosis – vascular ischemic changes, migraine)

• Anterior Temporal Lobe & occipital lobe lesions (CADASIL)

• Longitudinally Extensive Spinal Cord Lesions (>3 Segments – NMO, post infectious, vascular TM)

• Sparing of Corpus Callosum

• Diffusion Restriction (MS pts do get strokes!!!)

• Gray Matter Lesions (Cortex, Thalamus) Maybe not!!

•

Predictive Power of Baseline MRI

Cerebrospinal Fluid in CSF

• Nucleated cell count - < 5/mm³ in 75% of MS

• Glucose – normal

• Protein – normal in 60%

  • > 100 mg/dl – very rare

• ↑ myelin basic protein – not specific

• Intrathecal IgG, IgM synthesis
  – Oligoclonal Bands in CSF
  – Increased IgG Index (>0.68)
    = IgG CSF/IgG serum
    albumin CSF/albumin serum

Differential Diagnosis of Oligoclonal Bands

• Viral encephalitis

• CNS Lyme - >70%; also + Abs in CSF to B. burgdorferi,

• HIV (CNS AIDS)
- Subacute sclerosing panencephalitis (SSPE, measles)
  - Highest number of OCB
- S/P Gastric bypass surgery
- Acute disseminated encephalomyelitis (ADEM)
  - Transient

### Pathology

### Hallmarks of MS Pathology
- Mononuclear inflammatory cells
- Demyelination
- Relative axon sparing
- Astrocyte hypertrophy
- Cervical spinal cord disproportionately involved
- Periventricular lesions

### What Causes MS?

### MS Rate Estimates
(λs indicates risk ratio compared with general population)

#### Genetic Susceptibility
- MHC association: HLA-DR2 for those of northern European descent
- Relative risk of ≈2 to 3× for DRB1*1501 and DRB1*1503
- Genetic susceptibility explained by the MHC locus is estimated at between 20% and 50%1
- Homozygosity for DRB1*1501 → more severe course, earlier onset2
- Human chromosome 6p21.3

#### Other MS Susceptibility Genes
- Genome-wide analysis of SNPs in studies in ≈1000 subjects, validated in UK Wellcome Trust samples and National Institute of Mental Health samples
- Identified alleles of IL-2RA gene and IL-7RA gene associated with MS susceptibility risk, as well as HLA-DRA region on chromosome 6
MHC Linkages
- HLA DRB1*1501 increases susceptibility to MS
- HLA A*02 and HLA B*44 reduce susceptibility with the later possibly reducing FLAIR lesions and preserving brain volume.
- HLA C*05 may play a role.

What Causes MS?

Evidence for Immune System Involvement in MS
- Spinal Fluid Antibodies
- HLA (major histocompatibility) associations (because they are involved in T lymphocyte function)- HLA DR2 (15), DR4
- Female predominance is typical of autoimmune diseases
- Autoimmune Animal model (EAE)
- Response to drugs that act on the immune system

What Causes MS?

Evidence for a role of viruses/other infectious agent
- Epidemiologic evidence
- Geographic clustering
- Migration data
- Demyelinating animal models, e.g. visna in sheep, where viruses (lentiviruses) have long incubation periods

Vitamin D and Risk of MS
- Sun exposure decreases with higher latitudes.
- MHC vitamin D response element (VDR) in the promoter region of HLA-DRB1
- In a prospective study:
  - The risk of developing MS significantly decreased with increasing baseline levels of serum vitamin D
  - Patients taking high doses 14,000 IU daily had 41% fewer relapses than controls who took 1,000 IU daily and 17% had a relapse.
MRI in disease monitoring

Comparing across trials...

Things to Consider

• Relative efficacy
• Side effects
  – injection site reactions
  – flu-like symptoms
  – transaminase elevations
  – Infections – HSV, PML
  – QT prolongation
  – Macular edema
• Compliance
• Cost - >$60,000 per year
• Patient assistance programs

Injection Site Reaction from Copaxone

Macular Edema with Fingolimod

• 0.2% of patients will develop
• Increases 5-10x if diabetic or higher if uveitis
• <10% occurs after 4 months. Monitor at baseline and 3 months.
• R/O in fingolimod patients with blurred vision.

MS Variants
(or are they?)

Acute Disseminated Encephalomyelitis (ADEM)

• An acute or subacute inflammatory process of the CNS.
• Histology - multiple foci of perivascular demyelination.
• May occur after an acute viral or bacterial infection, immunization, or without a preceding cause.
• Quick onset with encephalitis-like symptoms such as fever, fatigue, headache, nausea and vomiting, and in severe cases, seizures and coma.
• The incidence rate is ~8 per 1,000,000 people per year.
• Children > adults - average age around 5 to 8 years old
• Monophasic. Recurrent cases do occur - ?MS
• Treatment is IV steroids.

Bickerstaff brainstem encephalitis vs Miller Fisher syndrome
• Bickerstaff as the name implies affects the brainstem and can lead to confusion and coma
• May be on a spectrum with Miller Fisher syndrome with a triad of ophthalmoplegia, ataxia and areflexia.
• Miller Fisher syndrome is associated with serum anti-GQ1b IgG antibody
• Good prognosis
• Treatment usually with plasmapheresis or IVIG

Weston-Hurst syndrome
• = Acute hemorrhagic leukoencephalitis (AHL, or AHLE), acute necrotizing hemorrhagic leukoencephalitis (ANHLE), acute necrotizing encephalopathy (ANE), or acute hemorrhagic encephalomyelitis (AHEM)
• Hyperacute and frequently fatal form of ADEM.
• Characterized by necrotizing vasculitis of venules and edema.
• Treat aggressively with IVIG, cyclophosphamide, plasma exchange, and corticosteroids.

Marburg (Acute MS)
• severe, acute MS
• ? If on a spectrum with RRMS
• monophasic illness
• malignant course with death as a possible outcome
• Poorly responsive to steroids

Balo’s concentric sclerosis

Tumefactive MS
• Size greater than 2 cm
• Presence of a mass effect, edema, or ring enhancement
• May be associated with better prognosis
• Rule out:
  – gliomas
  – metastases
  – abscesses

Neuromyelitis Optica (NMO)
Devic’s Disease

Background
• Neuromyelitis optica (NMO) – is also known as Devic’s disease and optic-spinal MS.
Mainly affects the optic nerves and spinal cord and both the gray and white matter.

**History of NMO**
- Allbutt (1870) recognized an association of spinal cord disease with vision loss.
- Erb (1880) provided the first thorough description of NMO.
- Eugene Devic (1894) presented a review of 16 cases of NMO – mostly severe, monophasic illness.

**Variant of Multiple Sclerosis??**
- Until recently, it was thought that NMO was a more severe variant of MS.
- The pathology differs between MS and NMO as do treatments. NMO responds better to immunosuppression (worse with interferons) and MS to immunomodulation.

Pathology suggested a humoral autoimmune component in NMO with vasculocentric deposition of complement (A, E), IgG (B), and IgM (C).

**Autoimmune antibody in NMO**
- NMO-IgG outlines CNS microvessels, pia, subpia, and Virchow-Robin space.
  - Sensitivity 73% (95% CI 60-86)
  - Specificity 91% (95% CI 79-100)

**New NMO guidelines**
- Optic neuritis
- Myelitis
- At least two of the following three criteria:
  - MRI evidence of a contiguous spinal cord lesion 3 or more segments in length
  - Brain MRI nondiagnostic for multiple sclerosis
  - NMO-IgG seropositivity
  *
- CNS involvement beyond the optic nerves and spinal cord is compatible with NMO.
- Symmetric periaqueductal lesions

- Symmetric diencephalic lesions

100 Diagnosis of NMO

101 Diagnosis of NMO—seronegative

102 anti-AQP4 titer after high-dose IV methylprednisolone (HIMP)

103 Treatment of NMO

- An International Consensus Group\(^1\) recommends
  - Azathioprine, mycophenolate, rituximab, or prednisone first line therapy
- ABC-R therapies are usually ineffective (IFNβ probably worsens NMO)
- There are reports of natalizumab and fingolimod exacerbating NMO
- Trials underway with antiCD19 and IL6.
- Tocilizumab may be an option if nonresponsive to antiCD20.\(^2\)

104 Overlap of ON with Lupus and Sjogrens

105 MS vs NMO

- MS
  - Short Spinal cord lesions (<2 vertebral segments)
  - Affects white matter in the periphery of cord
  - + brain MRI
- NMO
  - >3 vertebral segments
  - Located centrally within the cord affecting both white and gray matter.
  - May extend into brainstem (hiccups, N/V)
  - + NMO-IgG

106 Thank You!!

Any questions???