The Many Faces of MS

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Multiple Sclerosis (MS)

- Most common acquired disease of myelin
- Predilection for young to middle aged females
- Defined by a clinical presentation of a spectrum of signs and symptoms.
- Individual bouts of inflammatory demyelination may be accompanied by clinical symptoms (relapses). In most cases, there is some degree of recovery, producing a relapsing-remitting course.
- Diagnosis is based on clinical features and MRI findings. Laboratory tests may support the diagnosis but are not diagnostic by themselves.

Epidemiology:

- Ten times more common in temperate climates compared with tropical
- Highest prevalence in northern Europeans
- Rare in Asians
- Almost unknown in African blacks
- Less common in African Americans compared with Caucasian Americans

Etiology:

- Initiating cause is unknown
- Auto-immune-mediated inflammatory demyelinating and axonal injury
- While no infectious cause has been found, it is thought that viruses may trigger the response
- Genetic influences are also present
- Evidence is mounting that points to 3 important associations:
  - Epstein-Bar Virus—prior bout of mononucleosis or high antibody titers
  - Vitamin D Deficiency—studies have shown that higher levels are associated with less MRI activity, less brain atrophy and less clinical progression.
  - Smoking—predisposes development of MS and can make MS worse. Evidence is not as strong as Vitamin D deficiency
Pathophysiology:

- Activated T cells cross the blood brain barrier and launch attacks on myelin and nerve fibers. The result is obstruction of nerve signals. Viral infection may be the trigger that activates the T cells.
- The two characteristic features of MS lesions are:
  - Inflammation (activated T cells, monocytes and B cells)
  - Demyelination and axonal damage

Clinical Presentation of MS:

- **Common Signs**
  - Optic neuritis
  - Internuclear ophthalmoplegia
  - Nystagmus
  - Spasticity/hyperreflexia
  - Babinski sign (corticospinal tract)
  - Dysmetria/tremor
  - Sensory impairment
  - Mood disturbances

- **Common Symptoms**
  - Paresthesias
  - Ataxia or unsteadiness
  - Vertigo
  - Fatigue/muscle weakness
  - Urinary disturbances
  - Dysarthria
  - Mental disturbances
  - Diplopia/vision loss

MS Diagnosis:

Diagnosis is made on clinical grounds with current trends emphasizing MRI findings. Additional testing can provide evidence to support the diagnosis when the clinical and MRI findings are ambiguous.

What Are the Accepted Criteria for a Diagnosis of Multiple Sclerosis?

- Symptoms and signs indicating disease of the brain or spinal cord
- Evidence of two or more lesions -- or abnormal areas on the brain -- from a MRI scan
- Objective evidence of disease of the brain or spinal cord on doctor's exam
- Two or more episodes lasting at least 24 hours and occurring at least one month apart
- No other explanation for the symptoms
- Other supportive investigations include cerebrospinal fluid (CSF) and VEP
Diagnostic Categories:
- Possible MS
- MS
- Not MS

Role of MRI in Diagnosis

Establishing Dissemination in Space:

Barkhof et al and Tintore et al have proposed diagnostic criteria for MS based on MRI findings. Their criteria support a diagnosis of MS based on the presence of 3 out of 4 of the following MRI findings:

- 1 gadolinium enhancing or 9 T2 enhancing lesions
- 1 infratentorial lesion
- 1 juxtacortical lesion
- 3 periventricular lesions

Note: 1 spinal cord = 1 brain lesion

Establishing Dissemination in Time:

- First scan 3+ months after onset of clinical signs
  - Presence of Gd+ lesion not associated with initial clinical event
  - If no Gd+ lesion at the first scan:
    - Follow-up scan 3+ months later
    - New T2 or Gd+ lesion will suffice
- First scan at time of clinical event or <3 months after clinical event
  - Second scan 3+ months after clinical event with Gd+ lesion
  - If no Gd+ lesion at second scan, further (3rd) scan 3+ months after second scan, with Gd+ or new T2 scan

Lumbar Puncture in Diagnosis of MS:

Most MS patients have evidence of increased IgG production as evidenced by “oligoclonal” bands on electrophoresis. While these are not diagnostic of MS when seen alone, their presence is useful in establishing the likelihood of the disease when the MRI is normal.

MS Treatment

Interferons—Immune modulators that have antiviral properties
- Avonex (interferon beta-1a)
- Rebiff (interferon beta-1a)
- Betaseron (interferon beta-1b)
- Plegridy (peginterferon beta-1a)
- Extavia (interferon beta-1b)

Copaxone (glatiramer acetate)
- Immune modulator that blocks attacks on myelin
All of the above have immune-modulating activities that accomplish the following
  o Reduced number of relapses
  o Reduced severity of relapses
  o Reduced development of new areas of inflammation seen on MRI
  o Evidence of delaying short-term disease progression

Second Line Therapy
  o **Gilenya (fingolimod)**
    o First ORAL immune modulator; sequesters lymphocytes to limit migration into CNS
    o Not for clinically isolated events
    o Higher dosages are associated with macular edema
    o Has now been approved as first line therapy
  o **Tecfidera (dimethyl fumarate)**
  o **Aubagio (teriflunomide)**
    o Immune modulator with anti-inflammatory properties

Third Line treatment:
  o **Tysabri (natalizumab)**
    o Implicated in progressive multifocal leukoencephalopathy (PML)
    o Must pretest for JCV
    o Strict prescribing guidelines (TOUCH program)
    o MS specialists are now beginning to use this as first line therapy. Studies are ongoing
  o **Novantrone (mitoxantrone)**
    o Set limit of doses due to cardiotoxicity

Visual System Manifestations of MS

Typical Optic Neuritis

- Demyelination caused by inflammatory demyelination of the optic nerve
- Idiopathic or associated with multiple sclerosis
- Myelin sheath is the focus of the attack; axons are relatively spared

Visual Prognosis for Idiopathic/Typical Optic Neuritis

- Visual prognosis in optic neuritis is typically favorable. In the ONTT, 95% of the placebo patients recovered to 20/40 or better within one year. Complete recovery typically takes up to 8 weeks.
- Despite a good visual outcome, most patients will have some permanent, measurable deficits including abnormalities in color vision, contrast sensitivity and brightness sense. Many of these patients will have permanent, residual visual complaints despite normal Snellen acuity.
Magnetic Resonance Imaging and Optic Neuritis

*MRI is indicated in optic neuritis patients for the following reasons:*

- Look for a lesion or process involving the optic nerve that would be from a disorder other than primary demyelination
- Look for evidence of demyelinating changes in the brain. If white matter changes are apparent, it is an indication that the patient has disseminated disease and the chances that the patient will develop further clinical signs of MS increase.

**Optic Neuritis and MS--Optic Neuritis Study Group 2008** (15 year follow-up to ONTT)

- 15-year risk of MS was 50% overall
  - 25% risk of MS when MRI is normal
  - 75% risk of MS when MRI shows one or more lesions

191 patients in the ONTT had normal MRIs on entry into the study. Of this group with normal MRIs, the following situations were associated with **NO development of MS** at the 15 year follow-up point:

- Painless initial presentation (n=18)
- NLP (n=6)
- Severe edema (n=22)
- Hemorrhage (n=16)
- Exudate (n=8)

**Summary of Typical Optic Neuritis:**

- Young, healthy adult; usually female
- Sudden visual loss with progression of symptoms for a week or less with visual improvement beginning within one month.
- Vision loss is accompanied by pain and may be associated with a swollen or normal appearing optic nerve
- No evidence of any other associated systemic disorder or additional involvement
- Associated with multiple sclerosis

**Atypical Optic Neuritis**

- Inflammatory optic neuropathy that is part of a systemic infectious or inflammatory disorder.
- Visual outcome is often influenced by treatment.

**Atypical Optic Neuritis is Characterized by Any of the Following:**

- Falls outside the 18-46 year age span
- Painless
- Occurs in both eyes simultaneously
- Continues to worsen beyond 14 days of onset
- Abnormalities in history or exam suggestive of other systemic illness
• Evidence of retinitis, vitritis, uveitis

Other Causes of Optic Neuritis

Connective Tissue disease

• Lupus
• Sjogren's syndrome
• Behcet's disease

Infections

• Viral illness
• Bacterial

Infiltrative

• Sarcoidosis

Optic Neuritis in Children

• More commonly bilateral with disc swelling.
• Visual prognosis good
• Prognosis with respect to MS much better than in adults when bilateral. Prognosis mirrors that of adults when unilateral.

Management of Optic Neuritis

• When clinical features are typical, MRI is useful as a predictor of future MS
• Inform mentally competent adults of the association between optic neuritis and MS or refer for neurology consult
• When clinical features are atypical, complete work-up should be done to rule out other etiologies (CBC, ESR, ACE, Chest X-Ray, FTA-ABS, ANA, Lyme titer etc). MRI and Lumbar puncture are usually indicated as well.

Treatment (Results of the Optic Neuritis Treatment Trial)

There is no effective treatment for typical optic neuritis. The Optic Neuritis Treatment Trial (ONTT) studied 448 adult patients with a diagnosis of typical optic neuritis. Patients were randomized into a placebo group, a group receiving oral prednisone for 14 days and a group receiving methyl-prednisolone for three days followed by oral prednisone for 11 days. The ONTT's treatment conclusions are as follows:

1) Treatment with high-dose intravenous followed by oral corticosteroids accelerated visual recovery but provided no long-term benefit to vision.

2) Treatment with "standard-dose" oral prednisone alone did not improve the visual outcome and was associated with an increased rate of new attacks of optic neuritis.

3) Treatment with intravenous followed by oral corticosteroid regimen reduced the rate of development of
MS during the first 2 years, particularly in patients with signal abnormalities consistent with demyelination on brain MRI at the time of study entry. By 3 years, this treatment effect had subsided.

Is there a role for early treatment in patients after a clinically isolated MS event?

- The CHAMPS study answered this clinical question

CHAMPS (Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study)

- 383 patients with first acute demyelinating event at high-risk of developing MS
- All patients were treated initially with corticosteroids
- Study group received weekly injections of Avonex
- Clear cut treatment benefit; reduction of progression to clinically definite MS by 50%
- 192 of the above total were isolated optic neuritis patients. The treatment benefit was the same.

Implications of CHAMPS

- A treatment is now available that alters the rate of development of clinically definite MS after a first demyelinating event
- While an MRI is not necessary to diagnose optic neuritis, an MRI is needed to determine who is at greatest risk for MS so that preventative treatment can be initiated.
- Optometrists must be able to promptly diagnose optic neuritis so that further work-up and treatment can be initiated by the appropriate specialist.

Ocular Motility Disturbances in MS:
The most common motility disturbances of MS center around the anatomical region from the pontine level of the brainstem to the midbrain and comprise internuclear opthalmoplegias and skew deviations:

Internuclear Ophthalmoplegia

In order to make conjugate, horizontal gaze movements, there must be communication between the third and sixth nerve nuclei since components of both of their respective nerves are utilized for lateral gaze. (third nerve, medial rectus muscle for adduction and sixth nerve, lateral rectus muscle for conjugate abduction). Communication between the third and sixth nerve nuclei is achieved via the medial longitudinal fasciculus and if there is an interruption in this pathway, internuclear opthalmoplegia (INO) results. For example, if the MLF on the left side of the brainstem was not working, the left eye would not be able to adduct on attempted gaze to the right, however, the right eye would be able to abduct normally. In addition to the adduction deficit, there is usually an observed laterally beating nystagmus in the abducting eye which is thought to be the result of excess innervation to the abducting eye.
Skew Deviation

- Vertical misalignment of the eyes
- Caused by imbalance of pre-nuclear inputs (vestibular or cerebellar) to the nuclei involved in vertical alignment.
- Comitant or incomitant
- Brainstem/cerebellar lesion; often seen in association with INO

In addition to INO and skew deviations, nystagmus is another common finding in MS because vestibular nuclei and their connections are located throughout the brainstem. Finally, cranial nerves may be involved if demyelination occurs at their nuclei or fascicles with the sixth nerve being most commonly affected. When the cerebellum is involved, disorders of eye movements include jerky pursuit eye movements (cogwheeling pursuits), saccadic intrusions and problems with motor coordination that can be elicited on neurologic examination.

Tumefactive MS

- Extremely rare form of the disease
- Involves brain lesions that are two cm or larger and appear to be tumors
- Lesions are more aggressive than typical MS lesions.
- Other causes of inflammatory lesions must be ruled out.