Multiple Sclerosis

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Overview

- Definition
  - A chronic demyelinating disease primarily affecting the CNS
  - Episodic reversible neurologic dysfunction
  - Variable clinical course and unpredictable course with four major categories: relapsing-remitting (85%), secondary progressive, primary progressive (10%), and progressive-relapsing (5%)
  - Ocular disease presents as optic neuritis, uveitis, or neuro-ophthalmological disease
  - The majority of patients may show excellent recovery; permanent visual disability is possible if not treated adequately
  - 72% patients with magnetic resonance imaging (MRI) abnormalities convert to multiple sclerosis within 15 years
- Age of onset
  - 30–50 years, but can range from childhood to 60s
- Gender/race
  - F:M = 2:1
  - No racial predilection
- Systemic association
  - Demyelination of the nerves lead to neurological defects affecting the central nervous system
  - Episodic focal neurological defects, paresis and paresthesia may occur
  - Cranial nerve dysfunction is common
  - Difficulty in walking, coordination, and fine motor activity
  - Slurring of speech and difficulty in movements of tongue are common

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Optic Neuritis in MS

- Epidemiology
  - In 15–20% of patients, optic neuritis is the presenting feature of their disease
  - 50–75% of patients with MS will develop optic neuritis during their lifetime (usually in relapsing-remitting stage)
- Laterality
  - Usually unilateral, with bilateral cases in 10% of the cases
  - Sequential involvement of both eyes is common
- Symptoms
  - Periorbital or ocular pain that is increased with extraocular movements and usually lasts several days
  - Acute monocular vision loss with great variability
  - Visual field defects such as diffuse loss, central scotoma, arcuate and nasal-step scotomas, and altitudinal defects occur
  - Impaired color vision and contrast sensitivity (>75%)
  - Phosphenes: bright fleeting, flashes of light that tend to be connected to eye movement
  - Uhthoff's phenomenon: worsening of vision provoked by small increases in body temperature attributed to exercise, hot baths or showers, or hot weather conditions
  - Pulfrich's phenomenon: anomalous stereoscopic perception of objects in motion due to asymmetrical conduction between the optic nerves
- Exam findings
  - Relative afferent pupillary defect
  - Optic nerve head may be swollen with peripapillary flame-shaped hemorrhages, and loss of spontaneous pulsations
  - Optic nerve head may appear normal in retrobulbar optic neuritis

Uveitis in MS

- Epidemiology
  - Occurs in 1–3% of MS patients
  - 80–90% of the time presents as intermediate uveitis (anterior uveitis may occur)
  - Third most common cause of intermediate uveitis (after pars planitis and sarcoidosis)
  - No clear pattern in onset between uveitis and MS: one may precede the other and can be separated by many years
  - Incidence is higher in individuals with HLA-DR15 allele
- Laterality
  - Typically bilateral
- Course
  - May be recurrent or chronic

- Symptoms
  - Floaters
  - Decreased vision due to macular edema
- Exam findings
  - AC inflammation (may be granulomatous or non-granulomatous)
  - Vitritis (+/− snowbanking)
  - Retinal periphlebitis (>50%)
  - CME more common in patients with prior optic neuritis
  - Other complications: cataract, glaucoma, ERM, retinal neovascularization, VH, tractional RD

Neuro-ophthalmological Disease in MS

- Oculomotor palsies are common in MS, frequently involving the sixth cranial nerve
- Deficits in pursuit, saccades, and vestibular eye movement
- Ocular flutter, opsoclonus, and saccadic oscillations
- Various types of nystagmus including vertical, vestibular, pendular. Periodic alternating, or convergence-retraction with pupillary light-near dissociation
- Internuclear ophthalmoplegia (INO): limitation of adduction of the ipsilateral eye and rapid nystagmus during abduction of the contralateral eye due to lesions in the medial longitudinal fasciculus
- Miscellaneous: oscillopsia, skew deviation, Charles Bonnet syndrome

Imaging

- FA
  - Optic nerve leakage (except retrobulbar optic neuritis)
  - Peripheral retinal vascular leakage
  - Macular leakage
- OCT
  - ERM
  - CME
  - Optic nerve atrophy from prior optic neuritis
- Visual evoked potential (VEP)
  - Well-preserved wave form but delayed response in 75% of patients

Laboratory and Radiographic Testing

- MRI brain and spine with gadolinium: 3 of the 4 below meet the revised McDonald diagnostic criteria
  - 1 gadolinium-enhancing lesion or 9 T2 hyperintense lesions if enhancing lesions are not present

  - ≥1 infratentorial lesion
  - ≥1 juxtacortical lesion
  - ≥3 periventricular lesions
- Cerebrospinal fluid analysis
  - Elevated IgG index (comparison of IgG levels in CSF and in serum)
  - ≥2 oligocolonal bands via electrophoresis
  - Lymphocyte cell count should be <50/mm^3 and protein should be <100 mg/dL; otherwise seek alternate Dx
- HLA-DR15 can be obtained in patients presenting with intermediate uveitis to assess the risk of MS development (and thus avoiding use of TNF-alpha inhibitors)

Differential Diagnosis

- For neurological manifestations, MS has a board DDx, ranging from ischemic/inflammatory (neurosarcoidosis, disseminated SLE), infectious (Lyme disease, syphilis, PML), toxins (ethambutol), to demyelination (acute transverse myelitis, neuromyelitis optica)
- Other causes of intermediate uveitis with retinal vasculitis
  - Autoimmune: idiopathic (pars planitis), sarcoidosis, inflammatory bowel diseases
  - Infectious: TB, Lyme, syphilis, Whipple's disease, toxocariasis
  - Masquerade: lymphoma

Treatment

- Acute disease exacerbation
  - Intravenous corticosteroids
    Usually first line in cases with acute optic neuritis, uveitis, and neuro-ophthalmological defects
    Accelerates visual recovery in cases with optic neuritis but has no effect on long-term visual outcome
  - Plasmapheresis
    May be indicated in patients with exacerbation of severe, rapidly progressive form of MS and optic neuritis unresponsive to corticosteroids
  - Intravenous immunoglobulins
    Conflicting evidence in cases of optic neuritis
- Treatment algorithm for long-term control
  - In patients with intermediate uveitis, but no neurological symptoms:
    If HLA-DR15 positive, significant retinal periphlebitis on FA, or has a strong family history of demyelinating diseases ➔ refer to neurology for further workup; *be cautious with TNF-alpha inhibitors*

If HLA-DR15 negative, no significant retinal periphlebitis on FA, and no strong family history of demyelinating disease ➔ approach as usual (see above for DDx and see corresponding chapters)

– In patients who present with uveitis, and subsequent confirmed diagnosis of MS:

  Refer to neurology for disease-modifying agents (DMAs), including
  - Injectables: interferon beta-1a/1b, glatiramer acetate
  - Infusions: alemtuzumab, mitoxantrone, ocrelizumab, natalizumab
  - Oral: fingolimod (beware of CME risk), teriflunomide, dimethyl fumarate
  - Off-label: methotrexate, mycophenolate mofetil, azathioprine, cyclophosphamide, rituximab

– In patients with established MS diagnosis but present with a uveitis flare-up:

  Manage the flare-up with a brief course of corticosteroids – topical or regional depending on location of inflammation

  If uveitis remains steroid-dependent or recurs frequently, then coordinate with neurology on choosing a DMA that may be more effective for both CNS and eye (i.e., interferon beta-1a/1b and glatiramer acetate; ocrelizumab should in theory be effective as it is similar to rituximab), or any of the off-label meds as they all are effective in ocular inflammatory diseases

  Avoid TNF-alpha inhibitors, and possibly IL-6 inhibitor (tocilizumab) as well

Referral/Co-management

- Neurology
- Physical medicine and rehabilitation