MULTIPLE SCLEROSIS

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BASICS

DESCRIPTION

- An autoinflammatory disease causing demyelination, neuronal loss, and scarring within the white matter of the brain and spinal cord.
- Four recognized forms of multiple sclerosis (MS) (1):
  - Relapsing-remitting multiple sclerosis (RRMS): episodic flare-ups occurring over days to weeks between periods of neurologic stability. During attacks, new symptoms may present, whereas previous symptoms may worsen. Complete recovery or residual deficits may ensue following each bout.
  - Secondary progressive multiple sclerosis (SPMS): beginning as RRMS, progressive deterioration of neurologic function ensues; not associated with attacks, (progression may continue or halt). ~2% risk per year of RRMS becoming SPMS
  - Primary progressive multiple sclerosis (PPMS): steady decline of neurologic function from onset of disease without episodic flares
  - Progressive relapsing multiple sclerosis (PRMS): steady decline of neurologic function from onset of disease with episodic flare-ups

Pregnancy Considerations

- Most patients experience lower exacerbation rates during pregnancy. Following delivery, the immune system reverts and MS flares become more likely.
- Breastfeeding does not affect the risk of MS relapse.
- Relapse during postpartum can be safely treated by IVIG and corticosteroids (2)[C].

EPIDEMIOLOGY

- Age: Peak incidence ages 15 to 45 years, mean age 28 to 31 (slightly earlier in women than men)
- Gender: Studies suggest F:M between 1.4:1 and 3:1
- Latitude: Prevalence tends to rise with increasing distance from the equator, although newer data reveals this latitude gradient may be declining (3,4).

Incidence

- Women (worldwide): 3.6 cases/100,000 person-years
- Men (worldwide): 2.0 cases/100,000 person-years

Prevalence

- United States: ~350,000 MS patients
- Worldwide: ~2,500,000 MS patients

ETIOLOGY AND PATHOPHYSIOLOGY

- MS lesions: Inflammatory cells, mainly T lymphocytes and macrophages, surround vasculature within the CNS, creating sites of inflammation. These cells then disrupt the blood–brain barrier and infiltrate the surrounding white matter, meanwhile preserving the vessel wall. B lymphocytes, as well as myelin-specific autoantibodies also infiltrate the CNS and cause degeneration of the myelin sheaths.
- Following demyelination, faster salutatory nerve conduction velocities (impulses jumping between nodes of Ranvier) are replaced with considerably slower continuous nerve velocities.
- Astrocytes begin to proliferate and cause gliosis.
- Oligodendrocytes, which have survived, or ones formed from precursor cells, are able to partially remyelinate stripped axons, producing irreversible scars.
- In each MS lesion, axonal damage may occur, but it is the cumulative axonal loss over time that is responsible for the progressive and irreversible neurologic disability seen in MS patients.
- Most axons are typically lost from the lateral corticospinal (motor) tracts of the spinal cord.

Genetics

- Strong predisposition: HLA DRB1 (5)
- Proposed predisposition: IL2RA and IL7RA
- Race: Caucasian > Africans or Asians

RISK FACTORS

- Genetic: DRB1 locus on chromosome 6 has strongest MS risk association; DRB1*15 and *16 produce major histocompatibility complexes (MHC) with high binding affinity to myelin basic proteins (MBPs) (3,5).
- Geographic: Previously distance from equator showed association with increased risk, though now declining. However, sun exposure (ultraviolet B (UVB) radiation necessary for endogenous vitamin D production) appears to have inverse relation to MS incidence (3).
- Infectious: viral infections (especially EBV, HHV) (3,5)
- Race: Caucasian > African, Asian, Native American, although this is decreasing (5)
- Others: tobacco smoking (6)

GENERAL PREVENTION

Further research is required to determine prevention from environmental risk factors. A goal of therapy is to prevent new attacks and disability.

COMMONLY ASSOCIATED CONDITIONS

- Internuclear ophthalmoplegia (INO): Injury to the medial longitudinal fasciculus (MLF) causes impaired adduction to the affected eye.
- Optic neuritis: inflammation of optic nerve resulting in loss of vision
- Uhthoff phenomenon: Symptoms worsen with exposure to higher than usual temperature.
- Lhermitte sign: electric-like shocks extending down the spine caused by neck movement, especially flexion

DIAGNOSIS

- A person with MS can present with a number of neurologic signs and symptoms depending on the locations of the lesions within the CNS (5)[C].
- Clinical diagnosis: ≥2 attacks; objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with history of a previous episode. Flare-up duration must be at least >24 hours. Relapses must be separated by ≥1 month. ≥1 out of 2 neurologic signs must be present. The second clinical sign may be obtained through an abnormal paraclinical exam such as MRI or evoked potentials or may be supported by an abnormal paraclinical exam (5,7)[C].
- For patients with steady decline of neurologic function for ≥6 months without flares, intrathecal IgG may be used to support the diagnosis (5)[C].

HISTORY

Symptoms may include fatigue, depression, emotional instability, epilepsy, memory loss, diplopia, sudden vision loss, facial palsy, dysarthria, dysphagia, muscle weakness or spasms, ataxia, vertigo, falls, hyperesthesia or paresthesia, pain, bowel or bladder incontinence, urinary frequency or retention or impotence (5)[C].

PHYSICAL EXAM

- Optic disc swelling or pallor
- INO
- Nystagmus in abducting eye
- Ataxia
- Intention tremor
- Hypesthesia or paresthesia
- Cerebellar dysarthria (scanning speech)
- Spasticity (especially in lower extremities)

DIFFERENTIAL DIAGNOSIS

- Lyme disease
- Systemic lupus erythematosus (SLE)
- Antiphospholipid antibody syndrome
- Epilepsy
- Progressive multifocal leukoencephalopathy (PML)
- CNS neoplasms
- Guillain-Barré syndrome
- Metachromatic leukodystrophy
- Sarcoidosis
- Stroke
- Vascular malformation
- HIV, neurosyphilis
- Cobalamin (vitamin B_{12}) deficiency
- Acute disseminated encephalomyelitis (ADEM)
- Behçet disease
- Normal pressure hydrocephalus

DIAGNOSTIC TESTS & INTERPRETATION

- CSF: Increased monocyte cell count and intrathecally formed IgG levels. Total protein within CSF may be normal or increased. The presence of oligoclonal bands (OCB) is used to determine amount of IgG intrathecally synthesized. ≥2 OCBs is diagnostic (5)[B]
- Tests used for exclusion of alternative diagnoses: antinuclear antibodies (ANAs), serum cobalamin level, erythrocyte sedimentation rate (ESR), and testing for syphilis
- MRI of head/spine (more sensitive than CT):
  - T_2 (spin-echo) image: hyperintense lesions
  - T_2 image: hypointense lesions
  - Gadolinium (Gd): Given IV, leakage of Gd into the parenchyma represents an increase in BBB permeability due to vascular breakdown.
- McDonald criteria (5):
  - Dissemination in space: ≥1 T_2 lesion on MRI in at least 2 out of 4 CNS regions typically affected by MS: periventricular, juxtacortical, infratentorial, or spinal cord or by waiting for another clinical attack implying a different CNS location
  - Dissemination in time: simultaneous presentation of asymptomatic Gd-enhanced and nonenhancing lesions at any moment or a new T_2 and/or Gd-enhanced lesion on an MRI when compared baseline scans.

Diagnostic Procedures/Other

Evoked potentials (EPs): Assess function in visual, auditory, and somatosensory or motor CNS pathways by measuring CNS electric potentials evoked by stimulation of either the brain or selected peripheral nerves; a marked delay in a provoked CNS EP, without a clinical manifestation, is suggestive of a demyelinating disorder (5).

TREATMENT

GENERAL MEASURES

- Three main categories currently exist for MS treatment: treatment for acute relapses, treatment for reducing MS-related activity using disease-modifying agents, and symptomatic therapy (2,5)[B]
- For apparent acute relapse, rule out infectious etiology prior to treatment.

MEDICATION

- Acute relapses (2)[B]
  - – Methylprednisolone 1 g/day IV for 3 to 5 days; without subsequent oral tapering; a second course may be given.
    - ○ Adverse effects: fluid retention, potassium loss, weight gain, GI disturbances, acne, and emotional lability
- Reduction of MS biologic activity, interferon-β (IFN-β) (1,5,8)
  - – Avonex (IFN-β_{1a}) 30 μg IM weekly
  - – Rebif (IFN-β_{1a}) 22 or 44 μg SC 3 times per week
  - – Betaseron (IFN-β_{1b}) 0.25 mg SC every other day
  - – Extavia (IFN-β_{1b}) 0.25 mg SC every other day
    - ○ CBC w/ diff., Plt, LFTs at 1, 3, and 6 months after starting Tx
    - ○ TFTs every 6 months if Hx of thyroid dysfunction Reduction of MS biologic activity, non-IFN-β (1,5,8)
    - ○ Glatiramer acetate (Copaxone) 20 mg SC daily or 40 mg 3 times per week
      - ■ Common adverse reactions: injection site reaction, nausea, chest pain, hypertonia, diaphoresis
      - ■ No recommended routine tests
  - – Natalizumab (Tysabri): 300 mg IV every 4 weeks
    - ○ Restricted distribution in the United States; call 1-800-456-2255 for more info.
    - ○ MRI at baseline
  - – Alemtuzumab (Lemtrada) 12 mg IV daily for 5 days, then 12 months later 12 mg IV for 3 days
    - ○ Premedicate with corticosteroids (methylprednisolone 1,000 mg) first 3 days of each treatment. Also consider antihistamines, antipyretics; antiviral prophylaxis (for herpetic viral infections) beginning on the first day of treatment and continue at least 2 months and until CD4+ lymphocyte count is $\geq$200/mm^3
  - – Fingolimod (Gilenya): 0.5 mg PO daily
    - ○ EKG at baseline
    - ○ Serious adverse reactions: QT prolongation, AV block; 6-hour observation following first dose
  - – Teriflunomide (Aubagio): 7 to 14 mg PO daily
    - ○ Avoid pregnancy, teratogenic; pregnancy test at baseline
    - ○ Use reliable contraception during Tx.
- Symptomatic therapies (5)[B]:
  - – Ataxia: clonazepam, propranolol, ondansetron
  - – Spasticity: baclofen, diazepam, tizanidine, dantrolene, cyclobenzaprine hydrochloride
  - – Pain: NSAIDs, carbamazepine, gabapentin, phenytoin, amitriptyline, mexiletine
  - – Bladder dysfunction: (urgency) propantheline bromide, oxybutynin, tolterodine tartrate; (retention) phenoxybenzamine, terazosin hydrochloride, bethanechol
  - – Constipation: high-fiber diets, fluids, natural or other laxatives, stool softeners, bulk-producing agents, suppositories
  - – Sexual dysfunction: tadalafil, sildenafil, vardenafil
  - – Weakness/fatigue: dalfampridine, amantadine, methylphenidate
  - – Tremors: clonazepam, β-blockers, primidone
  - – Depression: fluoxetine, other SSRIs, tricyclic antidepressants, nontricyclic antidepressants

ADDITIONAL THERAPIES

- Cognitive behavioral therapy
- Physical and occupational therapy
- Water therapy: Swimming, in cool water, is typically well-tolerated.
- Strenuous physical activity appears to confer protective benefit and slow the disease progression in pediatric patients.

COMPLEMENTARY & ALTERNATIVE MEDICINE

- Omega-3: immunomodulary properties
- Vitamin D supplementation, sunlight exposure

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Treat relapses with corticosteroids to minimize disease progression and duration of relapse. Maintain regular activity, but avoid overwork and fatigue. Rest during periods of acute relapse (2)[B].

Patient Monitoring

Assessing the severity of neurologic impairment from MS can be done using the Kurtzke Expanded Disability Status Score (EDSS): 0 indicates a normal neurologic exam and 10 indicates death due to MS. The EDDS uses a functional status (FS) score, covering the following: pyramidal symptoms, cerebellar, brainstem, sensory, bowel and bladder, visual/optic, and cerebral/mental functions. EDDS scoring system (9)[C]:

- 1.0 – No disability, minimal signs in 1 FS
- 2.0 – Minimal disability in 1 FS
- 3.0 – Moderate disability in 1 FS or mild disability in 3 to 4 FS, but fully ambulatory
- 4.0 – Ambulatory without aid or rest for ~500 m
- 5.0 – Ambulatory without aid or rest for ~200 m
- 6.0 – Intermittent/constant unilateral assistance (cane, crutch, or brace) must be able to walk 100 m
- 7.0 – Unable to walk beyond 5 m even with aid; essentially restricted to wheelchair, wheels self and transfers alone; active in wheelchair for ~12 hrs/day
- 8.0 – Essentially restricted to bed, chair, or wheelchair; may be out of bed most of the day; retains self-care functions, generally effective use of arms
- 9.0 – Helpless, bed-bound; but patient can communicate, eat
- 10.0 – Death due to MS

DIET

High fiber, bulk laxatives, fluids to prevent constipation

PATIENT EDUCATION

National Multiple Sclerosis Society: 1-800-344-4867 or www.nationalmssociety.org/

PROGNOSIS

- Differs in each individual; depends on the form of MS, the individual's sex and age, the initial presentation of the disease, and the amount of disability
- Average life expectancy is 5 to 10 years less than unaffected people.
- Specific clinical features suggesting more favorable course: early onset, RRMS form, female sex, <2 relapses within first year of diagnosis, and minimal functional decline after 5 years (5).
- Mortality secondary to MS relapse is unusual; death more commonly associated with a complication of MS such as infection in a person with more disability.

COMPLICATIONS

Depression or emotional instability, paraplegia, chronic pain, sexual dysfunction, delirium, impaired vision (9)

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ADDITIONAL READING

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CODES

ICD10

G35 Multiple sclerosis

CLINICAL PEARLS

- Immune-mediated inflammatory disease causing demyelination, neuronal loss, and scarring within the white matter of the CNS
- Charcot classical MS triad: nystagmus, intention tremor, and dysarthria
- Acute relapses are treated with steroids; disease-modifying medications are used for chronic treatment; currently, there is no treatment for promoting remyelination or neuronal repair.
- Based on limited clinical data, IVIG is not thought to be effective therapy for relapsing remitting MS (10).
- Autologous stem cell transplantation for MS shows promise, but more rigorous research is needed (11,12).

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