

Multiple Sclerosis

Clinical Background

Multiple sclerosis (MS) is a relapsing and often progressive autoimmune disorder of the white matter of the central nervous system.

Epidemiology

- Incidence
 - 250,000 to 350,000 patients in the U.S. with MS
 - Highest prevalence in Northern Europe (30/100,000 persons)
- Age – mean onset is 20s-30s
- Sex – M<F, 1:2

Risk Factors

- Genetics
 - Most cases of MS are sporadic
 - 31% concordance rate among monozygotic twins
 - Presence of *HLA-DR2* increases risk of MS

Pathophysiology

- Immune-mediated disorder that is associated with the synthesis of immunoglobulins by the central nervous system (CNS) reflecting local immune response
- Pathologic hallmark is the demyelinated plaque
- Lesions have a predilection for optic nerves, periventricular white matter, brain stem, cerebellum and spinal cord white matter
- Forms
 - Relapsing-remitting
 - Progressive
 - Primary
 - Secondary

Clinical Presentation

- Early
 - Sensory disturbances
 - Unilateral optic neuritis – may be initial presentation; pain with vision loss
 - Diplopia (internuclear ophthalmoplegia)
 - Lhermitte sign (trunk and limb paresthesias evoked by neck flexion)
 - Limb weakness
 - Clumsiness
 - Ataxia, gait problems
 - Transverse myelitis
- Late
 - Cortical signs – aphasia, apraxia, seizures
 - Extrapyrmidal signs – chorea, rigidity
 - Cognitive impairment
 - Vertigo
 - Progressive quadriparesis and sensory loss

- Spasticity

Treatment

- Corticosteroids – high doses used most often in acute relapses
- Interferons – beta 1-a, beta 1-b
- Glatiramer acetate
- Mitoxantrone
- Possible adjunct therapies include methotrexate, plasma exchange, intravenous immune globulin

Diagnosis

- Indications for testing – course of neurologic symptoms (sensory and/or motor) that do not fit other known neurologic diseases
- Laboratory testing
 - Lumbar tap with fluid analysis
 - Oligoclonal bands present in about 90% of patients
 - Not specific for MS – may occur in CNS disease involving autoimmune disorders, infection or trauma
 - cell count – rule out presence of infectious agent (meningitis)
 - Lymphocyte pleocytosis
 - Glucose, protein, lactate – normal in MS
 - Myelin basic protein – increased in about 80% of patients during active attack and remains elevated for 5-6 weeks
 - IgG index – >7 is indicative of MS
- Imaging studies
 - MRI – presence of gadolinium enhancing lesions – use of revised McDonald diagnostic criteria (Nielsen, et al, 2007) may be helpful
- Diagnosis involves combination of cerebrospinal fluid (CSF), MRI and clinical presentation
- Other testing
 - Evoked potential testing (visual) positive
- Diagnosis for MS generally includes a lumbar tap with fluid analysis, MRI, and evoked potential testing plus an appropriate clinical setting
 - Definitive diagnosis per McDonald criteria requires ≥ 2 clinical attacks and ≥ 2 lesions on an MRI

Prognosis

- Largely unpredictable from individual to individual
- 10% do well >20 years (so-called benign MS)
- 70% have secondary progression
- Relapses are frequent in the first two years after disease is identified

Differential Diagnosis

- Metabolic disorders
 - B12 deficiency
 - Leukodystrophies
- Autoimmune disorders
 - Sarcoidosis
 - Sjögren syndrome
 - Systemic lupus erythematosus

- Antiphospholipid syndrome
- Chronic inflammatory demyelinating polyradiculopathy
- Behçet disease
- Vascular disorders
 - Cavernous hemangioma
 - Central nervous system vasculitis
 - AV fistula
- Neoplastic disorders
 - Spinal cord tumors
 - Paraneoplastic disorders
- Infectious disorders
 - HIV myelopathy
 - HTLV-1 myelopathy
 - Lyme disease
 - Meningovascular syphilis
 - Herpes simplex virus
 - Varicella Zoster virus
 - Progressive multifocal leukoencephalopathy (PML)
- Vasculitis
 - Primary angiitis
 - Polyarteritis nodosa (PAN)
 - Wegener's granulomatosis

Lab Tests

Indications for Laboratory Testing

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at www.aruplab.com.

Test Name and Number	Recommended Use	Limitations	Follow Up
Oligoclonal Band Profile with MBP 0080341 Method: Refer to individual components	Assist in the clinical assessment of suspected multiple sclerosis (MS) Profile includes: - IgG, Serum - IgG, CSF - IgG Index - Albumin, CSF - Albumin, Serum by Nephelometry - Albumin Index - CSF IgG/Albumin ratio - CSF IgG Synthesis Rate - CSF Oligoclonal Bands	Isoelectric focusing and immunofixation is considered to be the gold standard test for the detection of oligoclonal bands in CSF MBP will increase in patients with head trauma or anoxic brain damage	
Immunoglobulin G, CSF Index 0050676 Method: Nephelometry	Assist in the clinical assessment of suspected multiple sclerosis (MS)		

Cell Count, CSF 0095018 Method: Cell Count/Differential	Rule out presence of infectious agent (meningitis)		
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Additional Tests Available

Test Name and Number	Comments
Oligoclonal Bands in CSF & Serum 0081135 Method: Isoelectric Focusing/Immunofixation	Isoelectric focusing and immunofixation is considered to be the gold standard test for the detection of oligoclonal bands in CSF
Myelin Basic Protein 0080515 Method: Enzyme-Linked Immunosorbent Assay	Assist in the clinical assessment of demyelination activity for multiple sclerosis (MS) Order in conjunction with oligoclonal bands testing MBP will increase in patients with head trauma or anoxic brain damage
Oligoclonal Band Profile 0080440 Method: Isoelectric Focusing/Immunofixation/Nephelometry	Isoelectric focusing and immunofixation is considered to be the gold standard test for the detection of oligoclonal bands in CSF Assist in the clinical assessment of suspected multiple sclerosis (MS) Order in conjunction with MBP
Protein, Total, CSF 0020514 Method: Reflectance Spectrophotometry	Normal value in multiple sclerosis
Glucose, CSF 0020515 Method: Enzymatic	Normal value in multiple sclerosis
Lactic Acid, CSF 0020516 Method: Enzymatic	Normal value in multiple sclerosis

Guidelines

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General References

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