NEUROLOGY UPDATE IV: MULTIPLE SCLEROSIS

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Learning Objectives

Upon completion of this module, participants should be familiar with:

- Current recommendations for the diagnosis and monitoring of patients with multiple sclerosis
- Current pharmaceutical treatment approaches to the treatment of multiple sclerosis
- Current recommendations and recent updates in lifestyle modifications, alternative and complementary therapies, and rehabilitation as they pertain to multiple sclerosis

Introduction to Multiple Sclerosis

Multiple sclerosis (MS) in an autoimmune condition that results in widespread, immune-mediated damage to the brain, spinal cord, and optic nerves. Pathologic hallmarks of MS are inflammation and demyelination in white matter tracts and gray matter structures, pathologic change to glial cells, and axonal transection. Patients with MS can exhibit myriad neurological symptoms as a consequence of these pathologic processes. Multiple sclerosis tends to have an age of onset between 20 and 40 years, however, pediatric and older-age onset MS can occur. The female to male distribution is approximately 3 to 1.

Diagnosis of Multiple Sclerosis

The diagnosis of multiple sclerosis is made through a combination of clinical information and the use of diagnostic MRI. The Consortium of Multiple Sclerosis Centers (CMSC) recently published consensus guidelines on the use of MRI as a diagnostic tool for MS, including ideal sequences and methodologies for identifying lesions typical of MS.[1] Standard sequences for whole brain MRI were suggested, which include a sagittal T2/FLAIR image and gadolinium-enhanced T1 sequences, in addition to whole spinal cord imaging for those with symptoms of myelitis, insufficient features on brain MRI to support diagnosis, or those > 40 years old with non-specific brain MRI findings. Lesions on T2-weighted imaging typical of multiple sclerosis are described as: periventricular (touching the ventricles), juxtacortical (touching the cortex), infratentorial (cerebellum or brainstem), and spinal cord. Lesions with active inflammation will demonstrate gadolinium enhancement on T1-weighted MRI.

The official diagnostic criteria, termed the McDonald Criteria (revised in 2010),[2] require demonstration of disease activity in space and in time through a combination of MRI criteria and clinical events. These criteria are summarized in the table below:

Summary of McDonald Criteria for Multiple Sclerosis Diagnosis	
Clinical Presentation	**Additional Data Needed for MS Diagnosis**
≥ 2 attacks consistent with a demyelinating event; objective evidence of 1 clinical lesion with reasonable history of a prior attack	None
≥ 2 attacks consistent with a demyelinating event; objective evidence of 1 clinical lesion	Dissemination in space[a]
1 attack consistent with a demyelinating event; objective evidence of ≥ 2 clinical lesions	Dissemination in time[b]
1 attack consistent with a demyelinating event; objective evidence of 1 clinical lesion	Dissemination in space[a] AND Dissemination in time[b]
Insidious neurological progression suggestive of MS without any clinical attacks	1 year of disease progression plus 2 of 3 below: - 1 or more brain lesion typical for MS - 2 or more spinal cord lesions typical for MS - Positive CSF (unique oligoclonal bands or elevated IgG index)
[a] Dissemination in space criteria: ≥ 1 T2 lesion in at least 2 of 4 MS-typical regions (periventricular, juxtacortical, infratentorial, spinal cord); or await a further clinical attack implicating a different CNS site [b] Dissemination in time criteria: Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time; or a new T2 and/or gadolinium enhancing lesion(s) on follow up MRI; or await a 2nd clinical attack.	

Defining the Clinical Course of Multiple Sclerosis

The means of defining the clinical course of multiple sclerosis have changed over time, including a recent update to the phenotypic descriptors used in clinical care and research.[3] Most patients with multiple sclerosis have a course defined by relapses followed by remissions. Those with a one-time event consistent with a demyelinating syndrome, but who fall short of meeting McDonald Criteria are labelled as having clinically isolated syndrome (CIS). Those with a relapsing phenotype who meet McDonald Criteria have relapsing-remitting MS (RRMS). These patients may or may not continue to have activity, which is defined in current criteria as either clinical relapses and/or MRI activity (contrast-enhancing lesions; new or unequivocally enlarging T2 lesions).[3] Given the integration of MRI activity into this criteria, re-evaluation of MRIs on a yearly basis are recommended.[1, 3] Patients who have progressive disability accumulation are termed as primary progressive (PPMS) if their disability progressively accumulated from the onset of their disease and secondary progressive (SPMS) if they initially had a relapsing course. These terms are further modified on an ongoing basis to characterize whether or not these patients are also exhibiting activity (per the terms above) and/or progression (progressive disability accumulation).[3]

Treatment of Multiple Sclerosis

The use of disease modifying immunomodulatory drugs is indicated in patients with CIS considered high risk for MS and those with RRMS. The goals of treatment in this population are to reduce the likelihood of future relapses, new MRI lesions, and disability progression. Only 1 of the currently FDA-approved drugs is indicated currently for SPMS and no drugs have shown efficacy in those with PPMS, including a recent negative trial for fingolimod.[4] The current FDA-approved immunomodulatory drugs are shown below:

Medication	Indications	Route of administration	Potential Adverse Effects	Recommended Monitoring
Interferon beta-1a (two standard formulations and one pegylated) and interferon beta-1b (two formulations)	High risk CIS RRMS	Intramuscular or subcutaneous injection	Flu-like symptoms, fatigue, depression, increased spasticity, transaminitis, rare autoimmune hepatitis, and injection site reactions	CBC and liver function testing every 3-6 months
Glatiramer acetate (three formulations)	High risk CIS RRMS	Subcutaneous injection	Injection site reactions, lipoatrophy of skin at injection sites, and rare systemic panic attack–like syndrome	None
Natalizumab	RRMS	Intravenous	Black-box warning of increased risk of PML, common adverse effects of headache and chest discomfort, and rare hepatotoxicity, infusion reactions and anaphylactic reactions	Rigorous, regimented, industry-sponsored monitoring (TOUCH™ program) and JC virus antibody testing
Alemtuzumab	RRMS	Intravenous	Infusion reactions including headache and rash. Upper respiratory, urinary tract, and herpes virus infections. Autoimmune thrombocytopenic purpura. Autoimmune thyroid disease.	Pre-treatment screening for varicella vaccination need. Thyroid function monitoring every 3 months. Monthly CBC, serum creatinine, and urinalysis.
Fingolimod	RRMS	Oral	Transaminitis, lymphopenia, increased risk of serious herpesvirus infection, hypertension, bradycardia (usually only with the first dose), and macular edema	Cardiac monitoring after administration of first dose, ophthalmologic screening, liver function testing, and CBC
Dimethyl fumarate	RRMS	Oral	Diarrhea, nausea, abdominal cramping, flushing, lymphopenia	Frequent monitoring of CBC in first 6 months after administration and then every 6 months thereafter
Teriflunomide	High risk CIS RRMS	Oral	Alopecia, respiratory infections (including TB), pancreatitis, transaminitis, lymphopenia, hypertension, and peripheral neuropathy	Monitor CBC, hepatic panel, amylase, lipase, and blood pressure frequently in the first 6 months, every 6 months thereafter.
Daclizumab HYP	RRMS	Subcutaneous	Inflammatory rashes (serious in 2%), autoimmune hepatitis, infections, lymphadenopathy, anaphylaxis	Screening for tuberculosis and hepatitis B/C before initiation. Monthly liver function testing.
Mitoxantrone	RRMS, SPMS	Intravenous	Black-box warnings for cardiotoxicity and acute myeloid leukemia; other adverse effects of infection, nausea, oral sores, alopecia, menstrual irregularities, and blue discoloration of urine	Required monitoring of cardiac function by echocardiography or multigated radionucleotide angiography before each infusion and regular CBC

Multiple sclerosis attacks can be treated with high dose corticosteroids, typically for 5 days. Multiple studies have now shown there are no significant differences in efficacy or side effects between intravenous steroids (i.e. methylprednisolone 1000mg IV daily) and equivalently-dosed oral (i.e. prednisone 1250mg or methylprednisolone 1000mg daily) formulations.[5, 6] Those refractory to steroid treatment may respond to plasma exchange or ACTH.

Nutrition and Lifestyle Modifications

Vitamin D deficiency increases the risk of development of multiple sclerosis and vitamin D levels are correlated with disease activity. Supplementation of vitamin D modifies immunologic markers in favor of a less autoimmune phenotype and has been shown to reduce the number of enhancing lesions on MRI over 1 year. Thus far, however, evidence for improvements in clinical outcomes has been lacking.[7]

Dietary studies have not shown evidence for one particular diet as being ideal for those with multiple sclerosis, including a lack of benefit found for low fat diets with fish oil supplementation.[8] There is mounting evidence that a high-sodium diet may be associated with greater disease activity.[9]

Smoking cessation is recommended for those with multiple sclerosis, as cigarette smoking has been shown to be linked with faster rates of conversion to SPMS.[10]

Complementary and Alternative Medicine in Multiple Sclerosis

The use of complementary and alternative medicine approaches in multiple sclerosis were recently reviewed by the American Academy of Neurology, and guidelines were published.[8] Level A evidence was cited for the use of oral cannabis extract for the symptoms of spasticity and pain. Similar evidence was found for synthetic tetrahydro-cannabinol (THC) and oromucosal nabiximol spray, although this was classified as Level B. Magnetic therapies were also cited as a potential treatment for fatigue in multiple sclerosis (Level B). Reflexology was cited as possibly effective for paresthesia (Level C) and ginkgo biloba was cited as possibly effective for fatigue (Level C).

A number of strategies were found in this review to be ineffective, including bee sting therapy, gingko biloba for cognitive deficits, and the “Cari Loder Regimen” of nutritional supplements.[8]

Rehabilitation in Multiple Sclerosis

Rehabilitation strategies for those with neurological deficits were recently reviewed by the American Academy of Neurology, and guidelines were published.[11] According to these guidelines, weekly home/outpatient physical therapy is probably effective for improving balance, disability, and gait in multiple sclerosis, but not for upper extremity function. Further, inpatient exercises followed by home exercises or comprehensive multidisciplinary outpatient rehabilitation were both cited as possibly effective for improving disability. Motor and sensory balance training or motor training were also found to be possibly effective for improving static balance in those with multiple sclerosis.

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