

AMERICAN ACADEMY OF NEUROLOGY MULTIPLE SCLEROSIS FELLOWSHIP CORE CURRICULUM

MS Section Education Working Group

Introduction

Multiple Sclerosis (MS) is the most common demyelinating disease of the CNS and the second most common cause of disability among young adults. The complex and interdisciplinary management issues of the MS patient demand the participation of health care professionals from a variety of integrated and interactive disciplines, with coordination of care often provided by the neurologist. It is therefore essential for the neurologist to have a thorough grounding in the disease across its broad spectrum, from basic scientific underpinnings including immunopathology to the broad array of its clinical manifestations and patient care needs.

Conventional neurologic training usually provides brief encounters in clinic and classroom settings that foster fragmented exposure to the disease. Basic genetics, neuroimmunology and epidemiology are covered in the first two years of medical school, but often without clinical correlation. In the M3 and M4 years, emphasis is placed on clinical presentation and differential diagnosis without exploring the full bench to bedside spectrum of demyelinating disorders. The student clerkship experience with clinical MS care may be limited to interacting for a few days with an MS patient who is hospitalized for an acute and limited care need; such as an IV steroid infusion for an acute MS exacerbation. During residency, diagnosis and therapeutics are more fully explored, but often with limited individual patient continuity for what is a lifelong disorder; and often in departmental partitions that obscure the benefits of coordinated multi-disciplinary disease management. Further, pro-active care approaches such as wellness management so actively favored by the MS patient are limited in the university setting.. Scheduling demands and time constraints contribute to this fragmentation in MS training of the student and resident physician. With increasing financial pressures, and competition for health care resources, it is important to demonstrate that the optimal care of persons with chronic neurologic conditions such as MS is best implemented by specialist physicians (neurologists) who are most familiar with all of the medical, rehabilitative, psychosocial and vocational needs proper MS disease management requires..

The AAN Section on MS Core Curriculum is designed to provide a concise yet comprehensive educational resource about MS, that may be utilized by neurologists to help understand and manage multiple facets of this complicated and interdisciplinary disease process. Basic science facts are presented and will serve as a context for understanding immunopathology and current therapeutic approaches, including immunomodulatory and symptomatic treatments. Clinical phenomenology and diagnostic evaluations are discussed in detail, including unusual presentations and symptoms, and the expanding differential diagnosis of CNS demyelinating disease beyond its “classic” and “conventional” borders.. Finally, guidelines for the comprehensive management of persons with MS are provided, using information from each of the health care disciplines that are commonly involved. These latter include nursing, psychosocial and vocational strategies that are often not extensively covered in standard

neurologic training. In addition to presenting factual information about MS, the Core Curriculum will also allow neurologists access to the opinions and practices of MS specialists, and a brief bibliography of selected references for further reading. Ideally, this knowledge base will also have the breadth to be valuable to other health care professionals as well.

Training Curriculum in Multiple Sclerosis

The Core Curriculum is broadly written, and may have applicability at several levels of training. It is anticipated that a fellowship training program in MS will provide access to both in-patient and out-patient experiences, ideally within the setting of a dedicated MS clinic or rehabilitation facility, with the presence of a multidisciplinary health care team. This will provide education in the comprehensive management that is central to the care of persons with MS. Additionally, there should be opportunity for research either in a clinical area, including didactic instruction in clinical research methodology and statistics, and/or in collaboration with a basic scientist (e.g., immunology, pathology, neurophysiology). The fellow should have the capacity to :

- *Recognize common and unusual presentations and manifestations of MS, NMO and CNS demyelinating disease variants.
- *Generate a differential diagnosis of the broad spectrum of Multiple Sclerosis, its variants, and its mimics
- *Describe the basic immunopathophysiology of MS
- *Discuss sensitivities, specificities, and indications for paraclinical and emerging tests that are used to help establish (or rule out) a diagnosis of MS.
- *Manage primary and secondary symptoms of MS.
- *Describe treatment of MS with disease modifying agents.
- *Lead the health care team in the rehabilitative approach to caring for persons with MS.
- * Serve as an expert consultant for questions of complicated management issues in persons with MS.
- * Design innovative treatment approaches utilizing neurologic and rehabilitative strategies.
- * Provide a critical review of current literature regarding research and clinical trials in MS
- * Implement clinical or basic science research in an MS or MS related area.
- * Appreciate the vital role played in comprehensive clinical care of the MS patient played by subspecialty and other medical providers; including physiatry and rehabilitative medicine, physical therapy, occupational therapy, speech pathology, neuropsychology, psychiatry, urology, neurosurgery and indications for device placement, and complementary and alternative therapies

Prerequisites

Fellowship candidates and practitioners should be board eligible or board certified in Neurology or other appropriate specialty. Allied health professionals, e.g., nurses, therapists, etc. should have had practical experience in the care of persons with MS for a period of no less than two years.

Facilities

Exposure should be provided to patients in both in-patient and outpatient settings. Ideally, this would include acute care hospitals, rehabilitation units or free-standing facilities, ambulatory clinic settings and/or a dedicated MS center. There should be access to state of the art neuroimaging and electrodiagnostic technology, as well as an appropriate medical library and computer based information.

Personnel

Medical personnel should include board certified neurologists who are board certified Neurologists with subspecialty interest in MS or general Neurorehabilitation. Access to other medical specialists who may be needed in the management of persons with MS, such as ophthalmologists, gynecologists, urologists, psychiatrists or surgeons should be available.

Additional personnel should have representation from rehabilitation therapists, nurses, psychologists and case managers who have training and/or certification in working with persons with MS. Additionally, there should be input and access to basic scientists in the fields that are relevant to MS research, e.g., immunology, pathology, neurophysiology, etc.

Timetable

The fellowship program should be at least one year in duration.

Methods of evaluation

Fellows should be able to sit for an examination which will assess their knowledge of basic science principles and clinical care. Practitioners should be eligible to take a shorter more clinically based examination for which they may receive CME credit.

Methods of Evaluation

The AAN Section on MS will be available to help analyze comments and provide appropriate solutions for areas of deficiency.

Goals

The overall goals of the Core Curriculum are as follows:

1. To provide a comprehensive knowledge base encompassing basic science and clinical aspects of Multiple Sclerosis.
2. To enable neurologists in fellowship training to become familiar with principles of comprehensive management of persons with MS
3. To be a resource for information about current research directions and clinical trials.

Objectives

Each sub-topic will have a specific set of objectives, which relate to informational content. After completing each unit, the trainee should be able to perform the following.

I. Genetics & Epidemiology

- . Provide a summary of current epidemiologic facts about MS.
 - . Geography
 - North-South gradient
 - Clusters, epidemics
 - Incidence and prevalence
 - b. Migration studies
 - c. Racial/ethnic distribution
- . Describe the genetics of MS, from population studies to molecular mechanisms.
 - . HLA associated loci
 - . Risk related to affected family member
 - . Twin studies
 - . Molecular sites of genetic contribution to susceptibility (TCR, MHC expression, immunoglobulin)
 - Emerging data on the proteomic profiles of MS lesions
- . Provide information regarding gender bias in MS.
 - . Sex ratio
 - . Differences in disease severity between sexes
 - . Effects of pregnancy, menses, menopause **breast feeding**
- D. Discuss possible roles of stress and trauma and infection in etiology of MS
- E. Vitamin D
- F. Smoking

II. Neurophysiology

- . Discuss electrical transmission in normal nerves.
 - . Architecture of normal myelinated nerves
 - . Generation of action potentials
 - . Saltatory conduction
- . Describe disorders of conduction in demyelinated nerves.
 - . Decreased conduction velocity, conduction block, temporal dispersion
 - . Ephaptic transmission
 - . Heat sensitivity
 - . Ion channel distribution

III. Neuroimmunology

- . Describe normal mechanisms for immune reactivity and self tolerance
- . Describe possible mechanisms for loss of self-tolerance (Autoimmunity)
- . List possible candidates for “MS antigen” (e.g., MBP, MOG)
- . Discuss role of infections in etiology of MS
- . Describe role of cytokines in MS
- . Describe role of adhesion molecules in MS
- . Discuss T cell biology
 - Subtypes
 - Regulatory mechanisms
- . Role of other immune cells

Antigen presenting cells
Glial cells
B cells

- . Describe the role of the blood brain barrier in MS and trafficking of lymphocytes into the CNS

IV. Neuropathology

- . Present gross pathologic and histologic findings associated with MS lesions.
 - . Inflammation, edema, demyelination, gliosis, axonal transection
 - . Distribution of plaques in the CNS
 - . Histologic differences between acute and chronic plaques
 - . Immunocytochemistry of the MS lesion
 - Lassman/Luchinetti subtypes
- . Describe mechanisms of oligodendrocyte and myelin damage in MS.
 - . Antibody/ compliment mediated
 - . Cell mediated
 - Role of T cell, astrocytes, macrophages
 - . Cytokines
 - . Chemokines
- C. Discuss possible mechanisms of axonal damage in MS.
- D. Discuss potential mechanisms of remyelination

. Diagnostic

- . List diagnostic criteria for diagnosis of MS
 - . Schumacher
 - . Poser, Paty, Scheinberg
 - Mc Donald
 - Revised 2005 McDonal criteria (Polman)
- . Generate differential diagnosis of MS in several categories
 - . Other autoimmune(e.g., collagen vascular)
 - Sjogren's
 - SLE
 - RA
 - Behcet's
 - Undifferentiated connective tissue syndromes
 - Overlap syndromes
 - Neurosarcoidosis
 - . Infectious
 - HIV
 - HAART associated HIV myelopathy
 - Lyme
 - HTLV-1
 - Neurosyphilis and treponemal diseases

- . Vascular
 - Vasculitis
 - ANCA associated vasculitides
 - CADASIL
 - Binswanger's
 - Antiphospholipid Syndrome (APS)
 - Susac's Syndrome
 - Embolic disease
 - Hypertensive disease
- . Hereditodegenerative
 - Spinocerebellar ataxias and trinucleotide repeat disorders
 - Multiple Systems Atrophy, cerebellar type (MSA-C)
 - OPCA
 - Metachromatic leukodystrophy
 - Adrenoleukodystrophy
 - Hereditary ataxias including Friedrich's ataxia
 - Mitochondrial diseases
- . Neoplastic
 - Brainstem glioma
- . Structural
 - ACM
 - Syrinx
 - Structural myelopathy (tumor or disc)
 - Primary brain tumor
- . Toxic/metabolic
 - B 12 deficiency
 - Cigeratoa intoxication
 - Nitrous oxide toxicity syndrome
 - Vitamin E deficiency
 - Copper deficiency
- . MS variants
 - Balo's**
 - Schilders
 - Marburg
 - Neuromyelitis Optica (NMO)
 - Diagnostic criteria
 - Role of aquaporin-4 antibody
 - Treatment options
 - Opticospinal MS and NMO spectrum disorders

C. Describe sensitivities and specificities of paraclinical tests

- . MRI
 - Indications for specific MR sequences
- . Evoked potentials
- . Cerebrospinal fluid
 - Electrophoretic and isoelectric focusing technologies for CSF analysis
- . Discuss indications for each testing modality

- D. List appropriate tests to exclude diagnosis of MS (e.g. collagen vascular serologies)
- E. List several reasons why it is important to communicate a diagnosis
 - 1. Clarify diagnosis
 - 2. Begin treatment
 - 3. Allay anxieties about possible other disease processes
 - 4. Begin planning for the future

VI. Clinical

- A. Discuss natural history including different temporal and clinical courses

CIS

- . R/R
- . SP
- . PP
- . PR
- . Mild
- . Evidence for immunologic differences between above

- . Present guidelines for defining prognosis
 - a. Prognostic indicators
 - . Age
 - . Gender
 - . Race
 - . Type of initial symptoms
 - . Interval to next attack
 - . Degree of recovery from attack
 - . Disease subtype
 - b. Statistics re: cumulative disability years after diagnosis
 - c. Role of MRI in formulating prognosis and monitoring disease activity

- . Outcome measures

- . EDSS
- MSFC
- ?OCT
- . MRD
- . Quality of life scales
- . Composite scales
- MSFC

- D. Describe common and uncommon symptoms in MS

- a. Visual

- Optic neuritis
- Scotomata
- Diplopia/Blurred vision
- Intranuclear ophthalmoplegia (INO)
- Decomposition of smooth pursuit eye movements

Glissades on rapid saccadic eye movements from latent INO
Nystagmus and oscillopsia
Ophthalmoplegia
Chiasmal and post chiasmal syndromes

b. Motor

Hemiparesis
Paraparesis
Monoparesis
Muscle spasms
Spasticity

c. Sensory/pain syndromes

Paresthesias
Dysesthesias
L'hermitte's Sign
Anaesthesia
Trigeminal neuralgia
Anaesthesia dolorosa
Allodynia
Musculoskeletal pain
Spasticity
Secondary lumbosacral pain syndrome
Piriformis Syndrome
Other pain syndromes

d. Genitourinary

Urgency, frequency, hesitancy, nocturia, incontinence
Failure to store bladder
Failure to empty bladder
Bladder dyssynergia
Constipation, tenesmus, fecal incontinence
Impotence, anorgasmia, decreased libido, dyspareunia

e. Cerebellar

Tremor
Incoordination
Ocular dysmetria
Scanning/telegraphic speech
Ataxia

f. Brainstem

Dysphagia
Dysarthria
Vertigo/dizziness

g. Cognitive

Memory

Neuropsychology profile of MS

Judgement
Word finding

- Attention and concentration
- Mood disturbances
- h. Fatigue
- E. Describe common clinical signs
 - a. Visual
 - Nystagmus
 - INO
 - Afferent pupillary defect
 - Disc pallor
 - Ophthalmopareses
 - Opsoclonus
 - Smooth pursuit decomposition
 - Glissades
 - Ocular dysmetria
 - b. Pyramidal
 - Weakness
 - Spasticity
 - Hyperreflexia
 - Upper motor neuron findings in absence of hyper-reflexia
 - c. Sensory
 - Loss of posterior column modalities
 - Hyperpathia
 - d. Brainstem
 - Peripheral facial weakness
 - Dysarthria
 - Trigeminal neuralgia
 - Myokymia
 - e. Cerebellar
 - Tremor/incoordination
 - Ataxia
 - . Spinal cord
 - Transverse myelitis
 - Brown-Sequard syndrome
 - Sensory level
 - Sweat level
 - . Cognition/psychologic
 - Impairment of higher intellectual function/dementia
 - Emotional lability
 - Pseudobulbar Palsy
 - Depression
 - Euphoria
 - e. Other
 - Seizures

Dystonia
Absence of abdominal reflexes
Hearing impairment/tinnitus

VII. Prophylactic management

A. Present results from clinical trials of FDA approved immunomodulatory drugs

1. Beta-interferon 1b
 - Relapsing remitting
 - Secondary progressive
 - CIS(BEYOND)
2. Beta interferon 1a
 - Relapsing remitting
 - CIS (CHAMPS)
3. Glatiramer acetate
 - Relapsing remitting
 - CIS(PROMISE)
4. Mitoxantrone
 - Secondary progressive
 - Progressive/relapsing
5. Natalizumab
 - /Relapsing/remitting
- 6. Fingolimod**
 - Relapsing/remitting**

6. Rituximab/Ocrelizumab
7. Off label medications and immunotherapies
8. Emerging immunotherapies; oral, MAb, other

B. Discuss guidelines for initiation and maintenance of therapy

1. AAN guidelines for indications for therapy; NMSS Consensus statement
2. Guidelines and interpretation of antibody testing for interferons and natalizumab
3. Indications for stopping or changing therapy

C. List common side effects (and their management) for each of the above agents

- . Interferon
 - . Side effects
 - a. Fever, chills, myalgia
 - b. Spasticity
 - c. Elevated liver function tests/leukopenia
 - d. Site reactions, site necrosis
 - e. Menstrual irregularities

. Management

- a. Injection techniques
 - b. Dose adjustments
 - c. NSAIDs, acetaminophen, steroids
 - 2. Glatiramer acetate
 - a. Site reactions
 - b. Immediate post injection vasomotor reaction (IPIR)
 - c. Lipodystrophy
 - 3. Mitoxantrone
 - Side effects
 - Secondary leukemia
 - Reduction of measured LVEF and cardiomyopathy
 - Leukopaenia
 - Menstrual irregularities and premature menopause risk
 - Fever/infection
 - Hair loss
 - 4. Natalizumab
 - CNS opportunistic infection
 - Progressive Multifocal Leukoencephalopathy
 - HSV encephalitis, meningitis
 - CNS toxo, other
 - 5. Fingolimod
- . Provide information about on going trials and research of other immunomodulating agents
- A. IVIG
 - . Clinical trials
 - Relapsing remitting
 - Progressive
 - . Side effects
 - a. Blood borne infection
 - b. Allergic reaction
 - c. Headache
 - d. Aseptic meningitis
 - . Thromboembolic phenomena
 - B. Chemotherapy
 - Azathioprine
 - . Cyclophosphamide
 - . Methotrexate
 - Mycophenolate Mofetil
 - . Others
 - . T cell/peptide vaccination
 - . Hormone therapy
 - . Adhesion molecule antibody
 - . Others
 - Rituximab
 - Alemtuzumab

Plasma Exchange

VII. Symptomatic management

- A. Discuss treatment of acute exacerbations
 - 1. Steroid regimens
 - 2. IVIG
 - 3. Plasmapheresis
 - . Rehabilitative modalities
 - Therapies
 - Assistive devices
 - Environmental and vocational modifications
 - . Pseudoexacerbations
 - Treat underlying precipitant, e.g., infection
- B. Present primary symptoms and discuss their management
 - 1. Weakness
 - a. Pharmacologic
 - Steroids
 - 4-AP/Fampridine(Ampyra®)
 - IVIG
 - b. Rehabilitative
 - Therapy
 - Assistive devices/Orthotics
 - Functional Electrical Stimulation
 - Exercise
 - . Spasticity
 - . Physiology
 - Definition
 - Final common pathway
 - Denervation supersensitivity
 - Loss of descending inhibitory pathways
 - . Treatment
 - a. Pharmacologic
 - Baclofen/Baclofen pump
 - Tizanidine
 - Benzodiazepines
 - Dantrium
 - Botox
 - Gabapentin
 - b. Rehabilitative
 - Therapies,exercise, stretching
 - Assistive devices
 - C. Spasticity scales, e.g. Ashworth
 - . Sensory/Pain

- . Types of pain syndromes
 - Neuropathic
 - Musculoskeletal
 - Structural (e.g. compression)
- a. Pharmacologic
 - Anti-convulsants
 - Anti-depressants
 - Analgesics
- b. Rehabilitative
 - Therapies; physical modalities
 - Biofeedback
- . Intrathecal analgesic or baclofen pump
- . Genitourinary-Bladder
 - a. Anatomy & physiology of normal micturition and defecation
 - Structure of bladder, urethra, pelvic floor
 - Sympathetic and parasympathetic pathways
 - Cerebral, spinal centers for micturition
 - b. Algorithm for diagnosis of bladder dysfunction
 - UA/C&S
 - PVR/Bladder scan
 - Urodynamics
 - Cystoscopy, IVP
 - c. Bladder history
 - d. Treatment of failure to store bladder
 - Anticholinergics
 - Antidepressants
 - DDAVP
 - e. Treatment of failure to empty
 - Physical maneuvers, e.g. crede
 - Catheterization
 - Pharmacologic
- 5. Genitourinary-Bowel
 - a. Bowel history
 - b. Pharmacologic
 - Bulk agents
 - Stool softeners
 - Laxatives
 - Suppositories
 - Enemas
 - Motility agents
 - Anti-diarrheal agents
 - c. Timed evacuations
 - d. Nutritional and fluid intake guidelines
- 6. Genitourinary-Sexual dysfunction (male)

- a. Normal male anatomy and innervation
- b. Physiology of normal sexual response
- c. Impotence/erectile dysfunction
 - Neurogenic
 - Evaluation
 - Treatment
 - Pharmacologic
 - Papaverine
 - MUSE
 - Yohimbine
 - Sildenafil
 - Other phosphodiesterase inhibitors
 - Structural
 - Implants
 - Prostheses
 - Psychologic
 - Iatrogenic (medication related)
- c. Ejaculatory dysfunction
- d. Decreased libido

- 7. Genitourinary - Sexual dysfunction(female)
 - a. Normal female anatomy and innervation
 - . Physiology of normal sexual response
 - . Symptoms of sexual dysfunction
 - Anorgasmy
 - Decreased libido
 - Inadequate lubrication
 - Altered or painful sensation
 - d. Treatment
 - Pharmacologic
 - Alternative methods of stimulation

- 8. Fatigue
 - a. Definition & characteristics of MS fatigue
 - Incidence and impact
 - Diurnal variation
 - Relationship to heat
 - b. Pharmacologic
 - Amantadine
 - Pemoline
 - Methylphenidate
 - Modafinil
 - Others
 - c. Rehabilitative
 - Energy conservation
 - Assistive devices
 - Cooling devices

9. Tremor/Ataxia
 - a. Pharmacologic
 - Beta blockers
 - Benzodiazepines
 - Barbiturates
 - Botox
 - Odansetron
 - Deep brain stimulator
 - b. Rehabilitative
 - Assistive devices
 - Weights
 - Therapeutic exercises
 - c. Deep brain stimulation
10. Dysphagia
 - a. Diagnostic evaluation
 - ST consult
 - Videofluoroscopy
 - b. Treatment
 - Exercises/Swallow strategies
 - Alteration of food/liquid consistencies
 - Feeding tubes
11. Visual
 - a. Optic neuritis
 - Treatment with steroids
 - b. Oscillopsia
 - Clonazepam
 - Frenzel lenses
 - c. Diplopia
 - Steroids
 - Eye patch
12. Psychologic/Cognitive
 - A. Symptoms
 - a. Depression
 - b. Euphoria
 - c. Emotional lability
 - d. Personality changes
 - e. Cognitive impairment
 - B. Treatment
 - a. Evaluation
 - Neuropsychologic testing
 - Psychiatric/psychologic consultation
 - b. Medications

- Antidepressants
- Anti-anxiety agents
- Anti-psychotics
- c. Counseling
- d. Social service assistance

C. List secondary symptoms and prevention

1. UTI
 - a. Acidification/antibiotic prophylaxis
 - b. Drainage of retained urine
 - c. Adequate hydration
2. Malnutrition
 - a. Treatment of dysphagia
 - b. Nutritional supplements
3. Impaired skin integrity
 - a. Identify risk factors for skin breakdown
 - Moisture
 - Shear
 - Pressure
 - Immobility
 - b. Wound care
4. Contractures
 - a. Relieve spasticity
 - b. Maximize mobility
 - c. Botox
 - d. Surgical remediation
5. Aspiration
 - a. Identify patients at risk
 - b. Treat dysphagia
6. Osteoporosis
 - a. Incidence in patients with MS
 - b. Predisposing factors
 - Steroids
 - Immobility/decreased weight bearing
 - Poor nutrition
 - c. Prevention
 - Calcium supplementation
 - Weight bearing exercises
 - Increased mobility
 - d. Treatment
 - Alendronate
 - SERMs

C. Describe tertiary symptoms and treatment approaches

1. Social/ Familial issues
 - Marital difficulties
 - Parenting issues
 - Role changes
 - Financial hardship
2. Vocational
 - Reasonable accommodations
 - Employment modifications
 - Vocational retraining
3. Legal
 - ADA parameters
 - Medical Power of attorney/advance directives
 - Reimbursement for medical care
 - Estate planning

. Research

. Basic Science

- Immunology/molecular biology
- Neurophysiology
- Genetics

Proteomics

- Myelin/glial cell biology
- Infectious agents
- Animal models

. Clinical

- Therapeutic agents/clinical trials
- Neuroimaging modalities
- Health services delivery
- Psychosocial/Vocational/Economic
- Clinical phenomenology
- Rehabilitation
- Epidemiology
- Outcomes measurement
- Database creation and utilization