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 approached 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 methodoloy 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 phsyiatry 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.
l. 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

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 McDonald 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’hermite’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, anorgasm, 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
   Hypereflexia
   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/leukopaenia
         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
      a. Clinical trials
         Relapsing remitting
         Progressive
      b. Side effects
         a. Blood borne infection
         b. Allergic reaction
         c. Headache
         d. Aseptic meningitis
         e. 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
         Uroynamics
         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
      Anorgasmic
      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 consultaion  
      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