AMERICAN ACADEMY OF NEUROLOGY
MULTIPLE SCLEROSIS
FELLOWSHIP CORE CURRICULUM

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Introduction

Multiple Sclerosis (MS) is the most common demyelinating disease of the CNS and the third most common cause of disability among young adults. The complex management issues that are often present in the care of individuals with MS may demand the participation of health care professionals from a variety of disciplines, although the team is usually led by a neurologist. It is therefore essential for the neurologist to have a thorough grounding in the basic science and clinical phenomenology of MS.

Conventional neurologic training usually provides the components of an education in MS in a scattered fashion. Basic genetics, neuroimmmunology and epidemiology are covered in the first two years of medical school, often without concomitant clinical correlation. In the third and fourth years, the emphasis is on clinical presentation and diagnosis. The student experience with treatment may be limited to interacting for a few days with an MS patient who is hospitalized for steroid bolus to treat an acute exacerbation. During residency, diagnosis and therapeutics are more fully explored, but even then the resident may not have the opportunity to learn about and participate in the long term management of persons with MS, utilizing a comprehensive approach involving an entire health care team. 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 that occur.

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 disease process. Basic science facts are presented and will serve as a context for understanding current therapeutic approaches. Clinical phenomenology and diagnostic evaluations are discussed in detail, and include unusual presentations and symptoms. 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, 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.
*Generate a differential diagnosis of conditions that may have similar clinical presentations to MS.
*Describe the basic immunopathophysiology of MS
*Discuss sensitivities, specificities, and indications for paraclinical 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.

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.

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 have completed at least one year of sub specialty training in MS or general Neurorehabilitation. Access to other medical specialists who may be needed in the management of persons with MS, such as gynecologists, urologists, psychiatrists or surgeons should be available.

Additional personnel should have representation from therapists, nurses, psychologists and case management 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 in MS.

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)

. Provide information regarding gender bias in MS.
. Sex ratio
. Differences in disease severity between sexes
. Effects of pregnancy, menses

D. Discuss possible roles of stress and trauma and infection in etiology of MS

ll. 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

lll. 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

lV. 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
. Generate differential diagnosis of MS in several categories
. Other autoimmune(e.g., collagen vascular)
Sjogren's
SLE
. Infectious
HIV
Lyme
HTLV-1
. Vascular
Vasculitis
Embolic disease
Hypertensive disease
. Hereditodegenerative
Spinocerebellar atrophy
OPCA
Adrenoleukodystrophy
Hereditary ataxias
Mitochondrial diseases

. Neoplastic
Brainstem glioma
. Structural
ACM
Syrinx
Structural myelopathy (tumor or disc)
Primary brain tumor
. Toxic/metabolic
B 12 deficiency
Cigeratoa intoxication
. MS variants
Balo's
Schilders
Marburg
Devic's

C. Describe sensitivities and specificities of paraclinical tests
. MRI
. Evoked potentials
. Cerebrospinal fluid
. 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

Vl. <u>Clinical</u>

A. Discuss natural history including different temporal and clinical courses
. R/R
. SP
. PP
. PR
. Mild
. Evidence for immunologic differences between above

. Present guidelines for defining prognosis

a. Prognostic indicators
. Age
. Gender
. 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
. MRD
. Quality of life scales
. Composite scales
MSFC

D. Describe common and uncommon symptoms in MS

a.Visual
Optic neuritis
Scotomata
Diplopia/Blurred vision

b. Motor
Hemiparesis
Paraparesis
Monoparesis
Muscle spasms

c. Sensory/pain syndromes
Paresthesias
Dysesthesias
L'hermitte's Sign
Anaesthesia
Anaesthesia dolorosa
Allodynia
Musculoskeletal pain
Other pain syndromes

d. Genitourinary
Urgency,frequency, hestitancy, nocturia, incontinence
Constipation, tenesmus, fecal incontinence
Impotence, anorgasmy, decreased libido, dyspareunia

e. Cerebellar
Tremor
Incoordination
Ataxia

f. Brainstem
Dysphagia
Dysarthria
Vertigo/dizziness

g. Cognitive
- Memory
- 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

b. Pyramidal
- Weakness
- Spasticity
- Hypereflexia

c. Sensory
- Loss of posterior column modalities
- Hyperpathia

d. Brainstem
- Perpiheral facial weakness
- Dysarthria
- Trigeminal neuralgia

e. Cerebellar
- Tremor/incoordination
- Ataxia

. Spinal cord
- Transverse myelitis
- Brown-Sequard syndrome
- Sensory level

. Cognition/psychologic
- Impairment of higher intellectual function/dementia
- Emotional lability
- Depression
- Euphoria

e. Other
- Seizures

Dystonia
Absence of abdominal reflexes
Hearing impairment/tinnitus

Vll. Prophylactic management

A. Present results from clinical trials of FDA approved immunomodulatory drugs
1.Beta-interferon 1b
Relapsing remitting
Secondary progressive
2. Beta interferon 1a
Relapsing remitting
3. Glatiramir acetate
Relapsing remitting
4. Mitoxantrone
Secondary progressive
Progressive/relapsing

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
3. Indications for stopping 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. Glatiramir acetate
a. Site reactions
b. Immediate post injection vasomotor reaction
3. Mitoxantrone
Side effects
a. Leukopaenia
b. Menstrual irregularities

c. Fever/infection
d. Hair loss
e. Cardiac toxicity

. 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

. Others

. T cell/peptide vaccination

. Oral myelin

. Hormone therapy

. Adhesion molecule antibody

. Others

Vll. <u>Symptomatic management</u>

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

IVIG

b. Rehabilitative

Therapy

Assistive devices/Orthotics

Functional Electrical Stimulation

. 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
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
        Modanafil
        Others
    c. Rehabiltative
        Energy conservation
        Assistive devices
        Cooling devices
9. Tremor/Ataxia
    a. Pharmacologic
        Beta blockers
        Benzodiazepines
        Barbiturates
        Botox
        Odansetron

    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 prohpylaxis
        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
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 mesurement
Database creation and utilization