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MULTIPLE SCLEROSIS

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I. INTRODUCTION

Multiple Sclerosis (MS) was first described in depth by the famous French Neurologist Jean-Martin Charcot in 1868 (1). However, Multiple Sclerosis had likely been present for the preceding several centuries. In the USA, Multiple Sclerosis was considered a rare disease until the mid 20th century. The current estimates of Multiple Sclerosis in the USA exceed 400,000. In addition to cerebral and ophthalmic involvement, spinal cord damage is seen in most Multiple Sclerosis patients. In fact, much of the disability is secondary to spinal cord damage. Many of the challenges facing Multiple Sclerosis patients are similar to those facing others with spinal cord dysfunction. Weakness, spasticity, pain, decreased mobility, as well as bowel, bladder, and sexual dysfunction are common occurrences from spinal cord involvement in Multiple Sclerosis.

As we learn more of the pathogenesis of Multiple Sclerosis, the definition is evolving from the standard older textbook definition of a relapsing-remitting, inflammatory, demyelinating disorder. In fact, the disease course and pathogenesis are much more complex. Axonal and neuronal damage along with a degenerative type of pathology, lead to continual damage and repair processes (2). Without treatment, most patients who begin with relapsing-remitting MS (RRMS) develop a progressive disease after several years.

This chapter provides an overview of the pathogenesis, immunology, demographics, definition, epidemiology, etiologic considerations, diagnosis, disease course, differential diagnosis, clinical manifestations, disease modifying therapies, symptom management, rehabilitation, and emerging therapies.

II. DEMOGRAPHICS

Multiple Sclerosis is one of the leading causes of disability in young adults in the USA. The onset is usually between the ages of 18-40, but some children and older adults are also being diagnosed (3). Women are more often affected than men (3:1) with relapsing-remitting MS (RRMS). In primary progressive MS (PPMS), the disease is progressive from the onset and gender differentiation is not found. In the USA, Caucasians who live in temperate climates and whose families have emigrated from Northern Europe have the highest risk. Multiple Sclerosis was thought to be uncommon or rare in Latin America, Asia, and Middle East. However, the prevalence of MS in these countries has increased (sometimes dramatically) in the last several years. While African Americans are less likely to get MS than Caucasians, African Americans still have a significant risk. People who live in high-risk areas before adolescence and then move to a low risk area, are less likely to get MS

than those who remain in a high-risk area. If one moves from a high-risk area to a low-risk area after adolescence, the risk of MS remains high. Environmental exposure to a virus (es) or toxic influences combined with a genetic susceptibility are the most likely explanation of this high-risk, low-risk phenomenon. Clusters of MS also support the hypothesis of environmental exposure. However, MS is not thought to be communicable disease. Epidemiology studies continue to evaluate factors associated with the pathogenesis (4)

A genetic link has been demonstrated (5, 6). The risk of MS in close family members of MS patients is increased from the general population risk of 1 per 1000 (0.1%) to 2-5%. In monozygotic twins when one twin has MS, the risk of MS is as high as 30% in the other twin.

III. RISK FACTORS FOR DEVELOPING MULTIPLE SCLEROSIS

Some risk factors implicated in Multiple Sclerosis include environmental exposure, genetics, gender, age, lack of exposure to sunlight, less exposure to parasites, and other factors not yet identified.

1. Environmental Exposure:

   Environmental exposures have led to the postulation that the cause of MS is related to a virus or viral exposure, especially in childhood. In addition, industrial exposures or other toxic influences have often been considered but not proven. No specific toxic exposure has been convincingly incriminated.

   A number of infectious agents have been linked to the etiology of Multiple Sclerosis. Those have included canine distemper, measles, corona virus, HTLV1, HTLV6, Chlamydia, and Epstein Barr virus (EBV). Molecular mimicry may play an important role (7). Currently, Herpes virus 6 (8), Chlamydia, and Epstein Barr virus are the leading candidates for potential infectious agents. Efforts to incriminate Chlamydia and HHV6 have been mixed. However, substantial evidence is accumulating to the link the association of Multiple Sclerosis with Epstein Barr virus (9, 10, 11). Epstein Barr virus (EBV) has been previous linked to Burkitt's lymphoma and Hodgkin's lymphoma as well as primary CNS lymphoma, nasopharyngeal carcinoma, post-transplant lymphoproliferative diseases, and gastric cancer. EBV is a neurotrophic virus that has been isolated from the brain and spinal fluid, primarily from B-cells. It remains in the body in a latent state and has been identified as the cause of infectious mononucleosis that usually affects adolescence and young adults. Type 1 EBV is the predominate strain in developed countries. Antibodies to EBV virus are

more common in Multiple Sclerosis patients than the general population, although as many as 90% of the general population have EBV antibodies. The EBV antibodies titers are higher during MS relapses and MS patients are more likely to have had mononucleosis than the general population. EBV antibodies have been identified in oligoclonal bands in spinal fluid of patients with MS. Children with MS are more likely to be antibody positive for EBV virus. Elevated EBV titers associated with HLA DR15 haplotype increase the risk for MS even more. (12, 13)

Another environmental exposure issue is lack of Vitamin D and sunlight, which increase the risk of Multiple Sclerosis (14, 15,16, 17). Vitamin D has immunomodulatory activity and lower levels of vitamin D in the blood are more likely found in areas of less sunlight exposure. Studies have found that nurses who took more than 400 IU of supplemental vitamin D a day were less likely to get Multiple Sclerosis. A Defense Department study showed that higher levels of vitamin D in the blood were associated with a lower risk of Multiple Sclerosis. Therefore, Vitamin D and sunlight may have an effect on reducing the risk of developing Multiple Sclerosis. Nevertheless, these findings have not led to general recommendations of supplementing vitamin D for patients who have already contracted the disease. However, research continues in the area.

The relationship between parasitic diseases and Multiple Sclerosis is intriguing. Traditionally, underdeveloped countries have had a low risk of Multiple Sclerosis and a high risk of parasitic diseases. Parasitic diseases have a known immunomodulating effect. MS patients who also have parasitic diseases are likely to have a milder form of the disease (18). An MS treatment trial using parasites is underway (Fleming J. U of Wisconsin, 2008)

2. Genetics and Multiple Sclerosis:
While Multiple Sclerosis is not considered a specific hereditary disease, the risk of Multiple Sclerosis is higher in close relatives than in controlled populations (19, 20). The risk of Multiple Sclerosis in the general population in the USA is approx. 0.1 per 1000. In close family relatives the risk is 1-5%; in identical twins the rate is approximately 30% compared to like-sex fraternal twins, which is 2-5%. In a Canadian study, genetic factors were considered the primary association for familial cluster cases, versus environmental factors. MRI studies have shown that 4% of relatives of patients with sporadic

MS and 10% of relatives of patients with familial MS have asymptomatic brain lesions resembling Multiple Sclerosis. However, these findings do not necessarily indicate clinical Multiple Sclerosis in these patients. Clustering of autoimmune disease in females with high risk for MS has been described (21).

The strongest genetic influence of Multiple Sclerosis appears to lie in the HLA-DRB1 gene, located on chromosome 6. The HLA Class II DR2, DR3, and DR4 haplotypes are over represented in Multiple Sclerosis. A polygenetic inheritance in Multiple Sclerosis with a number of genes contributes to the risk factors in Multiple Sclerosis. However, only chromosome 6 haplotypes have been consistently linked to Multiple Sclerosis. Recently, IL2 and IL7R polymorphisms have also been directly linked to Multiple Sclerosis (22). Therefore, the search for the associated genes in Multiple Sclerosis is narrowing.

Some evidence also shows that there may be genetic influence in the course of Multiple Sclerosis and the response to therapy. Some research suggests that the APOE4 gene is associated with a more aggressive Multiple Sclerosis (23). In addition, some groups, such as African Americans, may not respond as well to current interferon betas compared to other ethnic groups (24).

In summary, there seems to be a clear genetic link to the risk of Multiple Sclerosis. However, except for identical twins, the risk appears to be less than 5% in relatives of MS patients.

3. Gender Differences in Multiple Sclerosis:
Women are at greater risk for Multiple Sclerosis than men and that ratio may to be increasing. Women also have an increased risk for other autoimmune disease such as lupus, rheumatoid arthritis, and Sjögren syndrome. The increased risk may be related to the influence of sex hormones on the immune system. As early as 1969, birth control pills were shown to have an ameliorating effect on experimental autoimmune encephalomyelitis (EAE) in rodents (25). More recently, Estriol, a natural occurring estrogen, has been shown to have a beneficial effect in Multiple Sclerosis in pilot studies (26, 27). Pregnancy reduces the exacerbation rate in Multiple Sclerosis during pregnancy. The risk of MS attacks in the last trimester of pregnancy declines by 70%. However, there was a 70% increase in exacerbation rate during the first 3 months post-partum. These changes are presumably related to the immunomodulating effects of hormones.

Breastfeeding does not appear to increase the risk of post-partum exacerbations. MS does not seem to have an effect on reproductive functions. Some studies have indicated that symptoms of MS and MRI activities are associated with hormonal fluctuations during the menstrual period (28, 29). Hormonal replacement therapy and contraceptives have not been proven to reduce MS exacerbations.

The FDA approved immunomodulating therapies of Interferon Betas, Glatiramer Acetate, Mitoxantrone, and Natalizumab are not recommended if pregnancy is contemplated. If an MS patient becomes pregnant while on one of these therapies, it is recommended that they stop the therapy until after the pregnancy is completed. Interferon beta is an abortifacient, but has not been demonstrated to increase the risk of teratogenesity. Glatiramer Acetate has not been associated with either abortions or fetal malformations. Nonetheless, caution is advised for all MS therapies.

IV. PATHOLOGY OF MULTIPLE SCLEROSIS

Multiple Sclerosis damage is associated with or results from immune dysregulation (2). This complex subject is not completely understood. An acute attack of MS is thought to begin with antigen activated T-cells in the peripheral blood system. These activated T-cells cross the blood-brain barrier and initiate a series of immunologic events involving cytokines, monocytes, plasma cells, macrophages, microglia, astrocytes, and chemokines. The activated T-cells in the presence of antigen presenting cells (APC) initiate a series of events where activated macrophages produce myelin toxic substances such as nitric oxide, free radicals, and pro-inflammatory cytokines such as interferon gamma and TNF alpha. As a result, myelin, axons, and neurons are damaged.

Immunologic events both up-regulate and down-regulate the immune system in a complex series of interactions during a Multiple Sclerosis relapse. T cells, B cells, T-regulatory cells, IL17 cells, and macrophages interact to up or down regulate the immune system and through cytokines (pro and anti-inflammatory) and chemokines. Based on these complex interrelated processes, current treatment goals include efforts to promote anti-inflammatory cytokines producing cells, T-regulatory cells, and brain derived neurotrophic factors, while reducing pro-inflammatory cytokines producing cells, IL 17 cells, and nitric oxide production.

Four specific immunopathological patterns are described (30, 31). Pattern I involves a T-cell and macrophage interaction. Pattern II appears to be related to antibody-mediated lesions associated with deposition of immunoglobulin and complement activation. Both patterns I & II are associated with partial oligodendrocytes survival and remyelination. Pattern III is a diffuse oligodendrogliopathy with apoptosis of oligodendrocytes and a preferential loss of myelin associated glycoprotein protein (MAG). Type III resembles the diffuse pathology as might be seen in hypoxia or diffuse viral or toxic encephalitis. In pattern IV, the primary event appears to be oligodendrocyte degeneration.

Pattern II pathology was seen in 58% of cases compared to pattern III in 26%, pattern I in 15%, and pattern IV in 1% of cases studied. The patterns were exclusive in any individual patient, i.e. the pattern of pathology was the same in all lesions from any individual patients, indicating there may be four distinct pathogenic subgroups.

Patterns I and II represent autoimmune demyelination, either T-cell/macrophage associated or antibody/complement associated. Patterns III and IV involve oligodendrocyte damage primarily with less of an apparent immunology bases. Patterns I and II are associated with remyelination, but not patterns III and IV.

Barnett and Prineas offer an alternative explanation in that a primary injury to oligodendrocytes may represent the initial lesions in RRMS patients (32). They postulate that MS may not be primarily an autoimmune disease and that inflammation may be secondary to damage of oligodendrocytes. They are not convinced that four separate immunogenic subtypes of multiple sclerosis exist.

Remyelination may be extensive in MS (33). Remyelination can be related to the survival of oligodendrocytes or from stem cell-type differentiation. In addition, T-cells can also release anti-inflammatory cytokines such as interleukin 4 and 10, as well as brain derived neurotropic factor (BNDF), which may promote repair and remyelination.

Axonal injury and loss is well documented in multiple sclerosis (34, 35, 36). Dark spots or "Black holes" in T-1 MRI are indicative of axonal damage or loss. Inflammation is associated with axonal loss as well as myelin damage. Neurotoxic substance such as nitrous oxide, can damage both axons and myelin. In pattern II immunopathology, antibodies and compliment also damage axons as well as myelin. However, non-inflammatory chronic lesions

also show axonal loss, which may indicate that subtle inflammation occurs even in late secondary progressive MS (SPMS) or primary progressive MS (PPMS). Other factors may play a role in MS lesion development and progression.

Late pathology may result from early damage. Earlier demyelination, which is associated with repair, may leave the damaged cells susceptible to eventual programmed death or apoptosis after several years. Axons that are relatively intact, but that have lost their protective myelin cover, may be more susceptible to local environmental influences and further damage. Early transected axons may undergo Wallerian degeneration (antegrade from the site of the initial myelin damage). Damage to the axon can increase intranodal calcium, which leads to impaired axon transport and further disruption of axonal function.

Gray matter pathology can be present in very early multiple sclerosis (37, 38). Current MRI technology usually does not usually detect gray matter abnormalities. However, utilizing higher MRI magnets, some gray matter lesions are extensive and can involve the entire cortical gray matter thickness. Cortical lesions affect both myelin and neurons. Monocytes are rarely seen in cortical lesions. Cortical lesions are more likely seen in progressive types of multiple sclerosis than in RRMS. Demyelination in the gray matter may be extensive. Cortical lesions may explain some of the cognition dysfunction as well as the poor correlation between the clinical examination and the white matter lesion load on MRI.

Normal appearing white matter may not normal in MS (39). By newer imaging techniques, diffuse white matter changes are seen even in areas where the routine MRI is normal. This may be secondary to wallerian degeneration or other silent mechanisms of damage

Degenerative changes in the CNS are prominent in later stages of MS. The rate of progression in MS may not be related exclusively to relapses or inflammation as seen by the MRI. While immunomodulating therapies have a marked affect on inflammation, they have less effect on progressive types of MS. Progressive axonal loss may occur in areas without widespread white matter lesions. Magnetic resonance spectroscopy reveals a decrease in n-acetyl aspartate (NAA) in gray and white matter, which suggests primarily neuronal and axonal degeneration (40, 41).

In summary, at least two mechanisms of damage are noted in the CNS. In addition to the inflammatory lesions, a separate neurodegeneration process

exists. Damage in the progressive MS disease types may be related to separate degenerative process or an intrinsic CNS inflammatory process without associated blood-brain-barrier abnormalities. In other words, instead of the activation of the immune system occurring in the periphery, the destructive process might be compartmentalized to the central nervous system.

V. CLINICAL SUBTYPES IN MULTIPLE SCLEROSIS

Types of multiple sclerosis include relapsing/remitting MS disease (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and progressive relapsing MS (PRMS) (42). A newly defined early MS type is called clinically isolated syndrome (CIS). CIS is the earliest clinical manifestation of RRMS, although damage may precede this first event. This diagnosis along with specific MRI damage allows for treatments to commence earlier in patients who are destined to get clinically definite RRMS, but have not had a second attack.

Clinically Isolated Syndrome (CIS) is defined as the onset of the first acute clinical demyelinating event with MRI evidence of subclinical demyelination not related to the clinical symptoms (43, 44). These patients are considered to be at very high risk for clinically definite multiple sclerosis and are likely to benefit from treatment before the second clinical episode. Other causes of demyelinating pathologies must be excluded such as those listed on Table A. Patients with clinically isolated syndrome and a T-2 lesion load greater that 1.23 cc have a 90% chance of developing clinically definite MS (CDMS) with in five years. 52% of these patients will have an Expanded Disability Status Scale (EDSS) greater than 3 at five years. Patients with normal MRIs with clinically isolated syndrome have less than 20% chance of developing clinically definite MS. Patients with two or more MRI lesions unrelated to the clinical event have an 85% chance of developing clinically definite MS by two years (45).

Relapsing/Remitting MS (RRMS) is the most common type of MS. Relapses are defined as new or recurrent clinical signs or symptoms lasting greater than 24 hours. These episodes may take months to resolve. They are followed by either partial or complete remissions. In relapsing-remitting MS, the patient remains stable between attacks. However, relapses may lead to residual deficits over time (46)

Secondary Progressive Disease (SPMS) is defined in patients, who initiated their MS symptoms with RRMS but, after a period of time, have progression between attacks. Later, they have progression without evidence

of clinical attacks. Approximately 50% of untreated RRMS patients will develop SPMS within 10 years, and 90% may develop SPMS after 25 years (47, 48). SPMS is described as a slow, insidious progressive neurologic deterioration with or without relapses, following RRMS.

Primary Progressive MS (PPMS) is found in approximately 10% of MS patients and is characterized as a slowly progressive deterioration without relapsing or remissions from the onset of neurological symptoms. Patients with PPMS tend to have the onset in an older age group and have prominent spinal cord symptoms leading to progressive weakness, sensory loss, and spasticity as well as bowel, bladder, and sexual dysfunction over a period of several years.

Progressive Relapsing MS (PRMS) is relatively rare (5%). In PRMS, patients start with progressive MS but will have occasional exacerbations. Patients continue to deteriorate between relapses.

In a cross sectional analysis of one MS population, 55% of patients had RRMS, 31% SPMS, 9% PPMS and 5% PRMS.

Benign or Mild MS: The definition of benign MS has been controversial. Some studies have shown that patients with "benign MS" after 10 years will continue to deteriorate (49). In one study, only 20% maintained their true benign status after another 10 years of follow-up. Factors favorable to forecast benign MS include RRMS onset before age 40, fewer areas of CNS involvement on MRI, optic neuritis, sensory and brain stem symptoms, female gender, and infrequent relapses. Unfavorable prognostic factors include onset after age 40, multiple areas of CNS involvement including motor, cerebellar and sphincter involvement, male gender and frequent relapses early in the disease. The percentage of patients that have sustained "benign MS" is debated but is likely around 10%, if patients are untreated.

The existence of "Burned Out" MS is a controversial issue. However, some patients with severe disability stabilize, usually after age 50 or 60.

VI. DIAGNOSIS OF MULTIPLE SCLEROSIS

1. Lesions in Time and Space:

The diagnosis of MS is usually determined by a detailed neurologic history and examination, which indicate "multiple lesions in time and space." In other words, multiple areas of the central nervous system are involved and damage occurs at different times. Lesions can be documented by clinical findings, such as a second confirmed attack, or

by MRI findings of subclinical demyelinating lesions. Initially these new subclinical lesions were defined by a second MRI at least three months after the clinically isolated syndrome (McDonald criteria) (50). Recently, the McDonald criteria have undergone revision to include new T-2 lesions at one month after CIS, to indicate multiple sclerosis if other MS mimickers have been eliminated (51). Also, spinal cord lesions are included in the latest criteria. Even newer criteria are being developed to suggest that treatment immediately following a CIS is reasonable.

Early clinical signs of multiple sclerosis may include visual loss, fatigue, numbness, parasthesias, weakness, visual disturbances such as double vision or an intranuclear opthalmoplegia, trigeminal neuralgia, facial nerve paralysis, cerebral ataxia, neuropathic pain (including L'Hermitte's sign), or even cognitive dysfunction.

2. Imaging in Multiple Sclerosis:

After a thorough history and examination, an MRI may reveal multiple subclinical lesions, which involve the periventricular white matter, subcortical area, brain stem, cerebellum, or spinal cord. Hyperintense lesions on the T-2 MRI are the most common early lesions. In additional, contrast enhancing (GAD) lesions are often seen early in many MS patients on T-1 MRI images. The enhancement may take several forms from a mild enhancement to an intense ring enhancement pattern. Higher dosed contrast material and higher magnet strength may increase the diagnostic accuracy. T-1 hypo-intense lesions, or "black holes", are thought to correlate with axonal loss, but a recent study has shown that "black holes" may not lead to persistent hypo-intensities on a T-1 MRI (52). Increasing T2 lesion volume loss is correlated with increased risk of SPMS and increased disability over a 20-year period (53)

Cerebral atrophy on MRI decreases brain volume and increases the ventricular size. Quantifying atrophy is often one of the MRI criteria in clinical trials. However, in routine clinical practice, cerebral atrophy on MRI may not be obvious.

Spinal cord MRI abnormalities are detectable in most patients with MS in clinical research evaluations (54).

New MRI technology has not been incorporated in most clinical settings but is becoming more available. For example, magnetic

resonance spectroscopy (MRS) allows one to measure various tissue metabolites such as n-Acetylaspartate (NAA), a marker for axons and neurons. Flare MRI is incorporated in most MRI centers, which increases the sensitivity for identifying and quantifying MS lesions. Functional MRI relates to blood oxygen level dependent signals to the brain during activation while completing complex task. Diffusion tensor imaging measures the diffusion of water as an indication of tissue damage. Magnetization transfer imaging is another research tool used to increase sensitivity for detecting brain damage and repair.

3. Other Tests in Multiple Sclerosis:
Cerebral spinal fluid (CSF) analysis is a recommended diagnostic test by many neurologists. Before the advent of the MRI, it was a mainstay for ancillary MS testing. CSF protein is usually normal, as is glucose. Cell counts usually do not exceed 10 to 20 white blood cells per cc in MS. In MS the cerebral spinal fluid will often indicate an increase IGG production in the spinal fluid as well as showing oligoclonal bands within the IGG range. Serum values of immunoglobulins need to be obtained at the same time as the CSF. Routine spinal fluid evaluations also are performed to rule out infection, neoplastic disease or other central nervous system disorders.

Evoked potentials measure the speed of impulse within the central nervous system from the sensory pathways of the extremities, as well as visual and auditory brain stem pathways. Visual evoked potential abnormalities are most consistently seen in MS or optic neuritis.

Cognitive testing is not used routinely in most clinics but is found to be abnormal in many patients, even with clinically isolated syndrome. User friendly and computer based cognitive testing are being developed (55, 56, 57).

Other evaluations done in multiple sclerosis patients involve measuring disability, usually with the (EDDS) or the MS Functional Composite Scale (MSFCS), or the Scripps scale. These evaluations are usually utilized to measure serial disability scores in clinical trials.

Other tests are usually included to rule out possibilities of other diseases, which may mimic multiple sclerosis, shown listed on Table A. The most common screening tests include a complete blood count (CBC), thyroid studies, anti-nuclear antibody testing, syphilis serology, vitamin B-12 levels, folic acid levels, lime titers in high-risk areas and

erythrocyte sedimentation rate. Other special tests for the MS mimics are also available.

Optical Coherence Tomography (OCT) is an emerging clinical trial evaluation that measures infrared light reflected from the retina (58). OCT measures the thickness and integrity of the retinal nerve fiber layer. Since these nerve cells have no myelin, one can get a direct view of the axon and axonal damage. An abnormal nerve fiber layer indicates loss of axons in Multiple Sclerosis patients. OCT may become recognized as a test to follow specific damage to axons in the central nervous system. OCT is now being used in several clinical trials to test its validity in measuring progressive damage to axons in Multiple Sclerosis.

Table A:

Differential Diagnosis of Multiple Sclerosis	
• Acute disseminated myelitis (ADEM)	• Adrenoleukodystrophies
• Neuromyelitis optica (Devic)	• Lyme disease
• Collagen vascular disease (SLE)	• Syphilis
• CADASIL	• TB, other CNS infections
• Thyroid disease	• Sarcoidosis
• Hypoglycemia	• CNS malignancy
• Vitamin deficiencies (B12)	• CNS embolic disease
• Sjögren syndrome	• AVM
• Behçet disease	• AIDS
• Myasthenia gravis	• PML
• Spinocerebellar degeneration	• Migraine headache
	• Psychosomatic

VII. DIFFERENTIAL DIAGNOSES OF MULTIPLE SCLEROSIS

The differential diagnoses of MS are in Table A. They include metabolic, neoplastic, vascular, inflammatory, granulomatous, infectious, and psychosomatic conditions (59, 60, 61, 62, 63, 64). Acute Disseminated

Encephalomyelitis (ADEM) and Neuromyelitis Optica (NMO) are two conditions that can be easily confused with Multiple Sclerosis.

Acute Disseminated Encephalomyelitis (ADEM) can be difficult to distinguish from multiple sclerosis clinically isolated syndrome (65). ADEM may be seen more frequently in children, the elderly, or after an infection or vaccination. However, ADEM can occur without an antecedent event. It is usually monophasic but can be recurrent. Seizures and encephalopathy are more common than in RRMS. Spinal fluid protein and white cells may be elevated but there is a less likelihood of oligoclonal bands in the spinal fluid. ADEM is treated with IV steroids without MS disease modifying therapies. The long-term prognosis is usually favorable, if recovery occurs.

Neuromyelitis optica (NMO) (DEVIC'S Disease) can be confused with multiple sclerosis (66). The gender predilection in NMO is more female to male in an approximately ratio of 10:1. There is less ethnic predilection compared to MS. In fact, NMO can be seen throughout the world. Distinguishing features of NMO include an optic neuritis and a transverse myelitis occurring together or within a matter of several months. White blood cell counts may exceed 50 per cc in the cerebrospinal fluid (CSF). Polymorphonuclear white cells may also be detected in the CSF. Oligoclonal banding is usually negative in the CSF. The spinal cord MRIs may show longitudinally extensive lesions greater than 3 spinal segments with central necrotic lesions in the spinal cord. Some cerebral lesions are permitted in the diagnosis. An Aquaporin-4 antibody or NMO antibody is found in approximately 70% of the cases, indicating this may be an antibody-mediated disease.

In Asia, an optica spinal form of MS is reported. Also, this has been reported in Latin America. The female to male ratio is approximately 3 to 1. The brain MRI may be normal or show typical MS lesions, and spinal cord lesions can be of variable length. Oligoclonal bands are seen in approximately 30% of the cases, and NMO antibody is found in over 50% of the patients, especially if long cord spinal lesions are present (67). The specific relationship to NMO and optica-spinal MS is under investigation.

VIII. DISEASE MODIFYING THERAPIES IN MS

Before the release of Betaseron in 1993, there was no widely accepted or FDA approved treatment to alter the long-term disease course. Corticosteroids, especially intravenously at very high doses (1,000 mg per day) for 3 to 10 days, were utilized for patients with moderate to severe

exacerbations of MS. No evidence showed that this treatment altered the long-term prognosis of the patient.

Four disease-modifying therapies (DMT's) have now been approved by the FDA as first line therapies in multiple sclerosis. They are: Betaseron (Interferon B-1b, 1993), Avonex (Interferon B-1a, I.M., 1996) Copaxone (Glatiramer Acetate, SC, 1996) Rebif (Interferon B-1a, Subcutaneous, 2002). Mitoxantrone (Novantrone, 2000), an immunosuppressant anti neoplastic agent, is indicated for worsening MS, and Natalizumab (Tysabri, 2004), a monoclonal antibody (anti VLA-4), is approved for relapsing MS but is currently used primarily as a "rescue therapy", when other drugs have produced suboptimal responses or shown significant toxicity.

1. Interferon Betas (Betaseron, Avonex, Rebif):
   Interferon Betas have anti-inflammatory effects by suppressing pro-inflammatory T-cells and cytokines such as interferon gamma as well as reducing blood-brain-barrier permeability, which inhibit activated lymphocytes from migrating into the brain.

   Betaseron was the first Interferon Beta approved by the FDA after it was shown to reduce exacerbation rates by one-third and MRI lesions by more than 80% in relapsing/remitting MS (68). In secondary progressive MS, one study from Europe demonstrated reduced relapses, progression of disability, and MRI lesions (69). It was approved for the treatment of SPMS in Europe and Canada. A North American trial in SPMS showed some of the same positive effects, but did not show an effect on disability (70). In the USA, Betaseron is approved for relapsing forms of MS, which includes patients with secondary progressive disease who are still having relapses.

   In a recent CIS trial, Betaseron reduced the risk for clinically definite MS by 55% after two years compared to placebo treatment. It also decreased the risk of progression of disability by 40% at the end of three years in patients who received continuous Betaseron treatment versus those who got delayed Betaseron treatment (45). The delayed group was treated with Betaseron after they had a second episode, or after two years, whichever came first.

   Interferon Beta 1-a is available in two preparations – Avonex and Rebif, which are similar but given at different frequency doses and routes of administration. Avonex is given intramuscular once weekly at 30 mg and is approved by the FDA for relapsing forms of MS. The pivotal trial showed an effect on the exacerbation rate and disability

progression. It is also approved in CIS to reduce the risk of clinically definite MS at two years (71). A follow-up study at five years shows continued benefit in those taking Avonex for CIS (72).

Rebif is usually given in the USA as a 44 mg dose subcutaneously three times a week. The Pivotal Trial showed a positive effect on relapses, MRI, and disability (73). In a head-to-head trial with Avonex, the FDA deemed it clinically superior to Avonex and therefore it was approved for relapsing forms of MS (74, 75). This is the first example of an orphan drug therapy being FDA approved because of therapeutic superiority over a previously approved orphan drug.

Adverse events from Interferon Beta include flu-like side effects, which can be minimized with dose escalation and prophylactic analgesics such as ibuprofen, acetaminophen, or aspirin. Injection site reactions are another potential problem with subcutaneous interferons (Betaseron and Rebif). However, auto injectors and better injection techniques have minimized these problems considerably. Depression may occur and should be evaluated by the treating physician on a regular basis. Increase in liver abnormalities and decrease in white blood cell counts, as well as thyroid abnormalities are also occasionally seen in interferon therapies. Blood tests are followed over the course of treatment. Injection site pain is another potential problem.

Neutralizing antibodies (NAbs) (76, 77) are detected in Interferon treated patients. Their significance is debated. The American Academy of Neurology does not recommend routine testing. Antibodies to Betaseron are more frequent, but are usually of lower titer and more transient. Rebif has less likelihood of antibodies than Betaseron, but may be of a higher titer and more persistent. Avonex has the lowest titer of interferon antibodies, with only about 5% of patients having neutralizing antibodies on Avonex. The association of high titered and persistent NAbs with reduced efficacy is likely (77). One large study comparing NAbs in MS patients on three continents found no correlation with NAbs and efficacy.

2. Glatiramer Acetate (Copaxone):
   A random sequence of four amino acids within the myelin basic protein structure, Glatiramer Acetate (GA) is approved for Relapsing/Remitting MS. It has been shown to positively affect the relapse rate and the MRI. The mechanism of action reveals that it reduces proinflammatory T-cells and cytokines and converts pro-inflammatory Th1- cells to anti-

inflammatory Th2-cells, which can migrate into CNS and produce brain-derived nerve growth factor (BDNF) (78, 79). BDNF may have a neuro-protective affect. Recently, Copaxone has also been shown to act on antigen presenting cells (APC) as well (80).

Given subcutaneously, 20 mg per day, GA side effects include transient injection site pain, skin redness, and lipoatrophy. An infrequent adverse event is a post injection systemic reaction, which is manifest by chest tightness, pain, flushing, anxiety, and shortness of breath, usually lasting for only a few seconds to a few minutes, without sequelae. Binding antibodies in Glatiramer Acetate have been detected but neutralizing antibodies have not been consistently demonstrated.

Preliminary data (Comi, AAN 2008) has shown effectiveness of GA in CIS. GA has yet to be approved for CIS by the FDA. In a pilot study, doubling the dose of GA to 40 mgm per day was more effective than 20 mgm in RRMS (81). A larger trial is underway. A study in PPMS was not successful, although a post hoc analysis indicated a possible effect in males. GA is not FDA approved for PPMS.

3. Long-term Data from Immunomodulating Therapies:
   Encouraging long-term data has been presented. Betaseron (16 years), Copaxone (10 years), Avonex (8 years), and Rebif (8 years) have all demonstrated that patients who stay on therapy continue to show beneficial effect. The scientific rigor of this data has been challenged since patients who stop therapy may be lost to follow-up. However, a recent Betaseron study was able to track approximately 90% of the patients from the pivotal trial after 16 years, which increases the validity of the long-term data. All long-term data demonstrates the benefits of staying on therapy continually. Long-term safety has also been demonstrated.

4. Head-to-Head Class I Trials:
   Two published reports of Class 1 head-to-head trial data are available. The first was the INCOMIN trial of Betaseron versus Avonex, which demonstrated clinical (Class III data) and MRI (Class I data) superiority of Betaseron over Avonex at two years (82). In an extension study, a small group of patients who were doing well on Betaseron were randomized to stay on Betaseron or switch to Avonex. Those who switched to Avonex had greater deterioration (83).

Therefore, switching drug therapy is not recommended, if patients are responding well and are not experiencing significant adverse events.

The second head-to-head trial (Class I) was the EVIDNCE trial, which trial compared Rebif versus Avonex. EVIDENCE trial showed clinical and MRI superiority of Rebif over Avonex at 24 and 48 weeks (84).

Two recently completely completed head-to-head trials have not been published. They compared Rebif versus Copaxone (REGARD) (ECTRIMS 2007, Michol D.) and Betaseron versus Copaxone (BEYOND) (press release 2007). No differences in the relapse rate were noted between Glatiramer Acetate and these Interferons, although the Interferons demonstrated superiority on some MRI testing. The annualized relapse rate for all three drugs was much better than predicted, likely due to earlier treatment. Further analysis awaits publication. An ongoing study comparing Copaxone versus Avonex versus a combination (COMBI-Rx trial) has not been completed.

5. Mitoxantrone (Novantrone):
   Mitoxantrone is a chemotherapeutic agent used to treat neoplastic disease. MS clinical trials of Mitoxantrone have lead to the FDA approval of Mitoxantrone for "worsening MS". The recommended dosage is 12 mg per meter square every three months, not to exceed 140 mg per meter square total dose. This limitation is to avoid cardiotoxicity, which may be permanent. Amenorrhea and the risk of secondary leukemia with Mitoxantrone are also potential adverse events. Mitoxantrone is usually used as a rescue therapy for patients who have not responded adequately to the immunomodulating therapies discussed earlier.

6. Natalizumab (Tysabri):
   Natalizumab is a monoclonal antibody (anti-VLA-4), which reduces the transmigration of lymphocytes across the blood-brain-barrier. In the Pivotal trial against placebo, a 68% reduction in relapse rate and an 85% reduction in active MRI lesions, as well as a 42% reduction in disability was noted (85). After FDA approval, two cases of Progressive Multifocal Leukoencephalopathy (PML) were reported (86, 87). One case was fatal. At that point, the drug was voluntarily withdrawn from the market. A third case of PML, which was also fatal, was found in a non-MS Trial. After a thorough safety evaluation, Natalizumab was re-approved with added monitoring. It is mainly

used as a rescue therapy for patients who have a suboptimal response to the immunomodulating therapies. More safety data may modify its utilization. Currently over 20,000 patients have gone through the safety monitoring programs for Natalizumab. To date no new cases of PML have been detected. It is recommended that Natalizumab only be used as monotherapy for MS, since both PML cases in MS were also on Interferon B-1a, intramuscularly. Recently, two patients were reported to have developed Melanoma while taking Tysabri (88). Also, liver toxicity has been noted. Since the re-release, not enough long-term data is available to determine Natalizumab's ultimate safety profile.

IX. Comprehensive Team Care, Rehabilitation, and Symptom Management

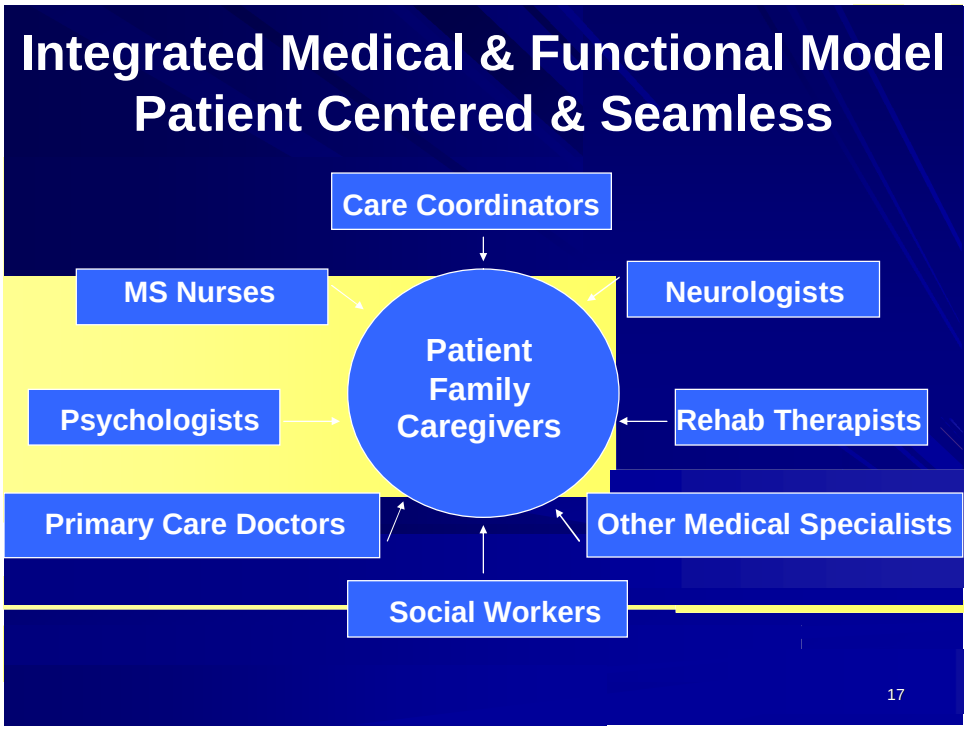
Since the introduction of disease modifying therapies beginning in 1993, the long-term benefits have become obvious to most MS experts. Patients with relapsing forms of MS are being helped substantially by reducing attacks and reducing the progression of disability. However, none of these treatments "cure" the disease. Therefore, the need for aggressive rehabilitation and symptom management care remain high. In recent years, numerous studies have evaluated the effectiveness of Multiple Sclerosis rehabilitation in both the inpatient and outpatient setting (89, 90, 91, 92). The effort to maintain the highest function and quality of life, despite progressive disease, is a major challenge facing MS patients. Also, no FDA approved treatments are available for primary progressive MS. Therefore, rehabilitation is the mainstay of therapy.

1. Comprehensive MS Team Care:

   In addition to disease modifying therapies, comprehensive team care for rehabilitation and symptom management is the "gold standard" for caring for Multiple Sclerosis patients (Figure A). The Multiple Sclerosis healthcare team works to maximize quality of life and independence in the community for the patients. The MS "medical model" approach utilizes healthcare professionals' to provide direct care to reduce tissue damage and symptoms. This approach is combined with a "functional model" of care where the healthcare professionals function as educators and coordinators of care, and the patient takes a more active role in the decisions that affects their well-being (Table B). This care team provides knowledgeable, comprehensive, and timely care while educating patients, family, and caregivers, providing information needed to understand their condition and available community resources. Examples of patients' needs include "best practice" healthcare, emotional support, family support, employment counseling, equipment and aids, modification in the home, work and transportation,

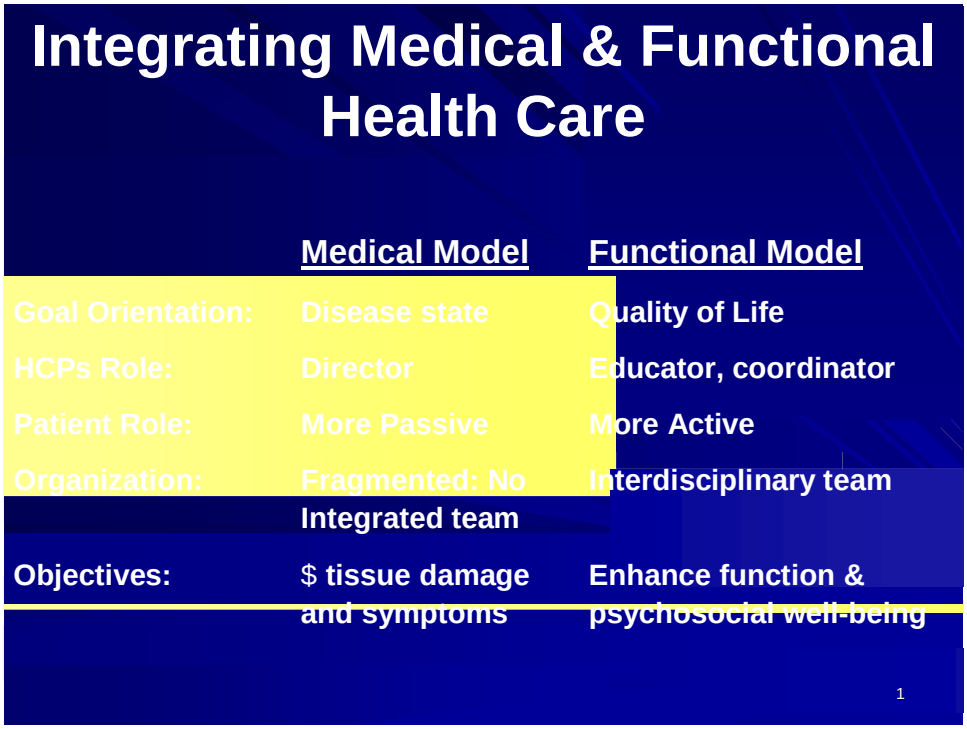
insurance guidance, disability guidance, legal guidance, transportation and others. Mobility and activity levels, as well as supporting family, friends, caregivers, and the patient are addressed. The teams strive for functional improvement and safety while helping the patients adapt and cope with their Multiple Sclerosis. The goals of the functional model are to enhance patient function, and to improve psychosocial well being and quality of life.

Figure A:



An integrated comprehensive MS team care model includes neurologists, primary care doctors, MS nurses, other medical specialists, rehabilitation therapists, psychologists, social workers, health educators, care coordinators, the patient's family, and their caregivers (Table C). The aim is a seamless patient-centered combination of a medical and functional model of care (Table B).

Table B:



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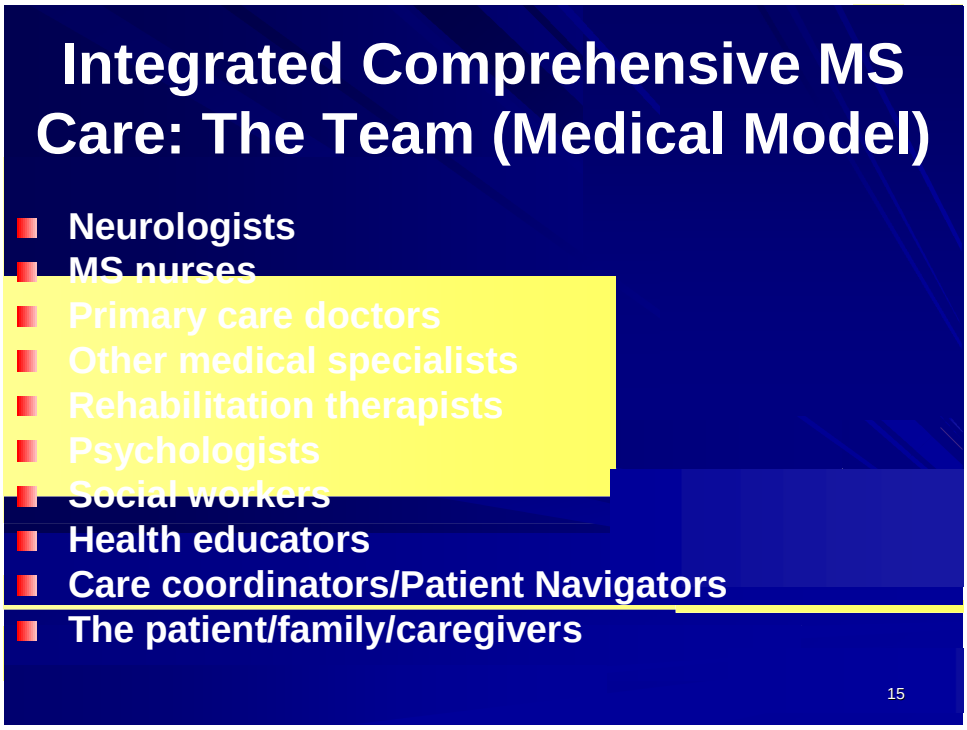

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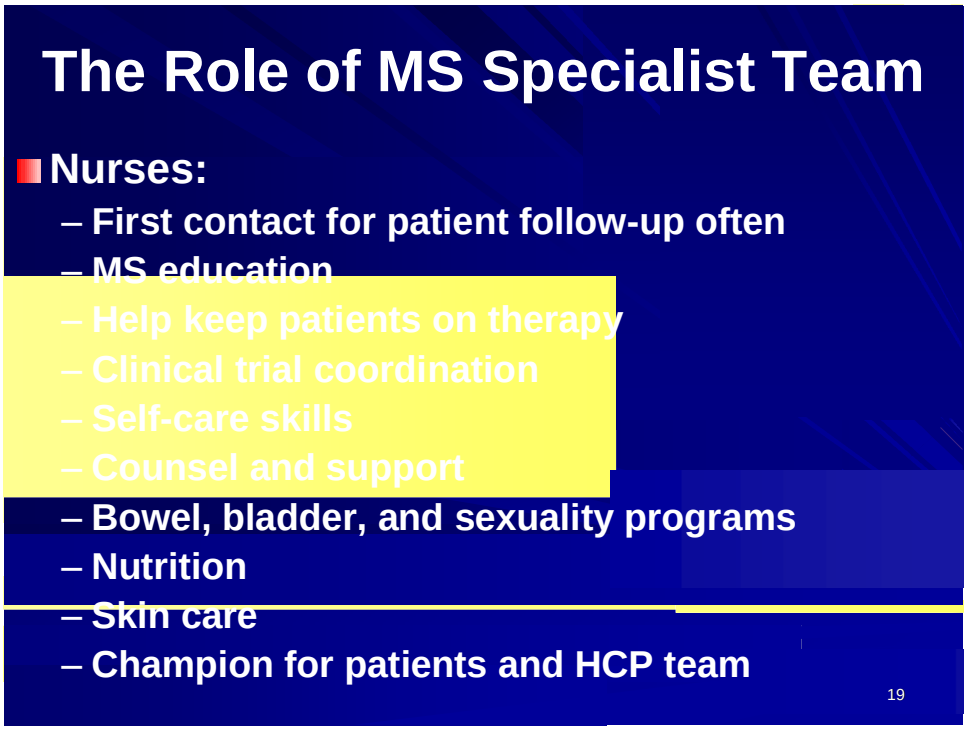

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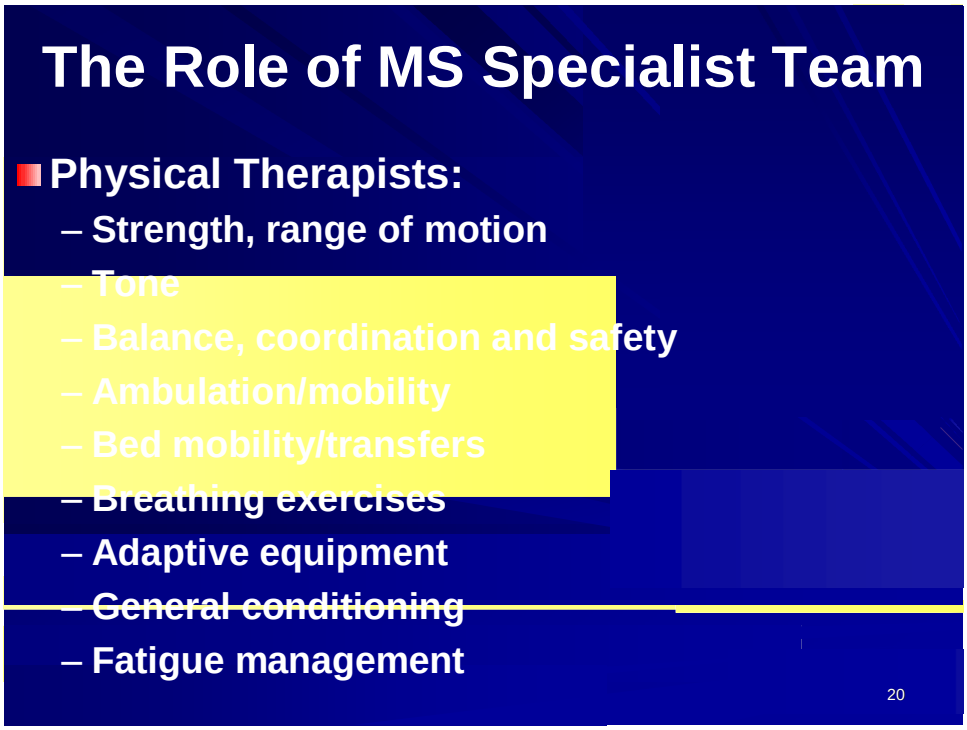

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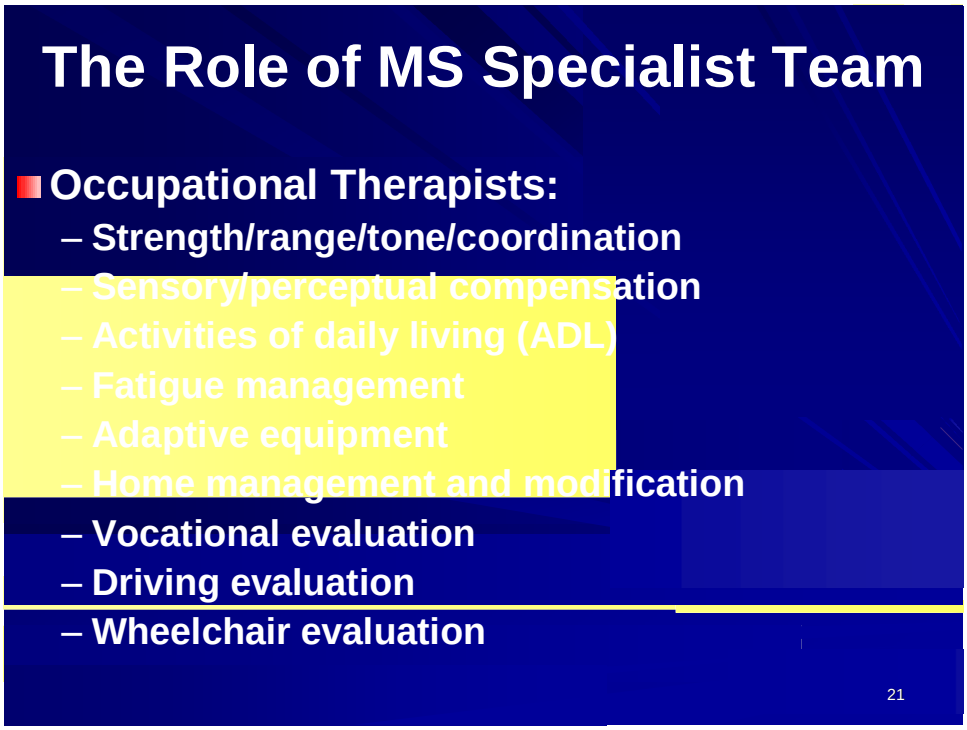

Table H:

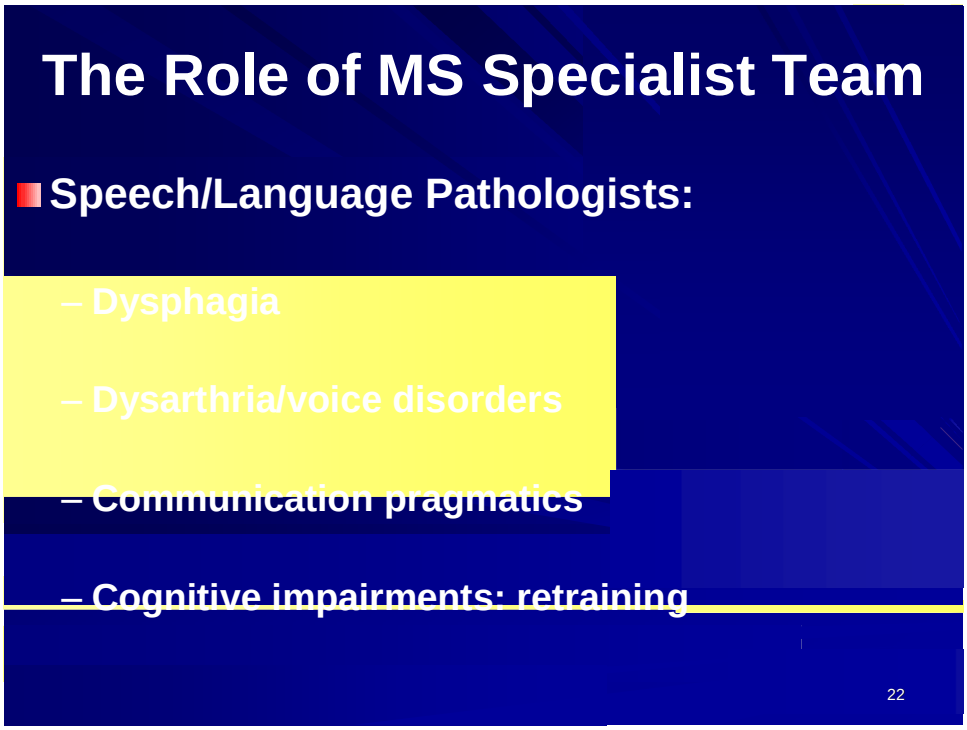

Table I:

Table J:

Tables C-J are examples of the role of the various MS specialty team members. As one can see from the variety of interventions from each of the healthcare professionals, an integrated comprehensive approach can cover most of the patient's medical and functional issues.

Integrating western medicine with complimentary and alternative medicine can be a major support to people with Multiple Sclerosis. However, MS patients can become victimized by some care providers, especially those that promote items that "enhance immune function." Multiple Sclerosis patients already have an up-regulated immune system. Therefore, products that increase immune system activity may actually be harmful to MS patients. The textbook Dietary Supplements and Multiple Sclerosis: A Health Professional's Guide or Complementary and Alternative Medicine and Multiple Sclerosis is recommended reading.

Caregiver support cannot be underestimated for Multiple Sclerosis patients. Fifty million family caregivers are in the US. The risk of anxiety, stress, and depression in caregivers has been called a national crisis where over 50% of caregivers suffer significantly. In fact, 50% of caregivers feel their health has deteriorated within the first six months of assuming their role. Caregivers' immunologic dysfunction continues for at least three years after their role ends (93). Caregivers need information about MS and available resources as much as patients. Psychosocial and emotional support for caregivers is critical. Respite care, which provides caregivers independent time and space, can be an important break for caregivers. An interdisciplinary approach to the disease provides help for caregivers and family members as well as MS patients.

Coordination of the various aspects of care "through the system" is a major challenge in Multiple Sclerosis. In cancer, the concept of a patient navigator to provide support and referrals to needed resources is gaining support. Voluntary Health Organizations for MS such as the National MS Society (NMSS), The MS Association of American (MSAA), The MS Foundation (MSF), the Heuga Foundation, and others provide some of these resources. A care coordinator or patient navigator helps to identify financial, home, health, transportation and other resources. They can coordinate clinical trial opportunities and can work with insurance companies and employers to reduce non-reimbursed care. They can help patients, families, and caregivers to navigate the healthcare system independently, resulting in less

dependency on the caregivers. They provide timely and compassionate help at a time of need. Unfortunately, other members of the MS comprehensive healthcare team are often too overcommitted to provide this added responsibility.

In summary, the comprehensive care team integrates the medical and functional healthcare models with professionals that understand that maintaining a high quality of life is a complex challenge necessitating interdisciplinary teamwork.

2. Disease Management & Rehabilitation:
The ideal long-term management of MS patients resides in the interdisciplinary rehabilitation model using a team approach to patients. Most physicians treating MS patients are troubled by a fragmented healthcare system for people with chronic disabilities. This fragmentation, miscommunication, and lack of collaboration is problematic for the MS patient care. The management of MS patients involves, not only diagnosis and medical management, but includes preventive maintenance by addressing family issues, caregivers, employment issues, and avocational issues. Education and care coordination are key to successful long-term disease management. Patient self-responsibility and empowerment are intregal componenets of disease management. The systematic use of patient advocacy groups in the community (NMSS, MSAA, MSF, and other organizations) increase in the quality of life of the MS patient (94, 95, 96).

The specific components of disease management include prevention, diagnosis, acute medical treatment, treatment of MS excerbations and combined complications, long-term medical treatment, rehabilitation, psychosocial adaptation, community integration, and end-of-life issues. The "best practice" approach to the MS patient starts with a better doctor–patient communication system and the integration of healthcare providers and services. As team care concepts increasingly become part of the management strategy of MS patients, the patient's quality of life will benefit greatly.

Basic and clinical trial research results have provided positive disease modifying outcomes. However, rehabilitation to minimize the functional loss remains critically important. The concept of "maximum rehabilitation potential" is a perpetual challenge in MS care because the issues for the MS patient continually changes and are life long.

Should rehabilitation start only when the patient has significant disability? Some doctors believe, erroniously, that MS patients do not benefit from active rehabilitation early, or that those with severe disabilities cannot benefit from rehabilitation. In fact, active rehabilitation interventions must start early soon after the diagnosis. The issues of adaptation, wellness, exercise, nutrition, energy conservation, psychosocial equilibrium, stress management, and education are part of the postdiagnosis treatment plan. Family involvement cannot be overemphasized: for example, divorce rates decrease in comprehensive care centers that can focus on family issues.

Rehabilitation plays a role to maximize function and to create safe environments, as well as to prevent secondary disabilities and medical complications. This facilitates improved independence and quaility of life in the community with decreased cost and burden of care.

The maintenance rehabilitation concept for MS patients was pioneered by Dr. Randall Schapiro, Minnesota. His active ongoing rehabilitation interventions successfully increase function and decrease complications over a long period of time.

3. Symptom Management:

Almost any neurologic symptom can be associated with MS, depending on the location and scope of lesions within the central nervous system. The following is a brief description and therapeutic recommendations for the most common of MS symptoms. The textbook Managing the Symptoms of Multiple Sclerosis (2007) Demos, is recommended reading.

1. Fatigue

Fatigue is the most common symptom in MS and requires a combination of rehabilitation and medical management (97). Heat often exacerbates fatigue. However, this may be temporarily relieved by cooling via cooling vests, sucking on ice chips, and cool baths (98). Fatigue counseling to maximize the patient's ability to function on a daily basis can be very helpful. For example, most MS patients experience fatigue in the late afternoon. Therefore, important daily activities are often done in the morning, so that the patient can rest in a cooler environment in the late afternoon. Often, a 30-minute rest period can reduce fatigue significantly.

Exercise and conditioning programs are important activties for patients with MS, which can reduce fatigue. Increased strength and physical fitness improves the MS patient' mobility and function. These programs must be individualized for each patient (99).

Medications play a role in the treatment of MS fatigue as well. Amantadine (Symmetrel®) or the selective serotonin reuptake inhibitors (SSRIs) may be given initially. However, modafinil (Provigil®) is frequently the first line treatment to help MS fatigue (100). CNS stimulants such as methylphenidate (Ritalin®), and dexedrine sulfate (Dexedrine®) are usually second-line treatments because of the risk of side effects, habituation, and tolerance. An experimental treatment, 4-aminopyridine has been used by patients but is still under investigation. Seizures may be associated with 4-aminopyridine. A sustained released formulation (Fampridine SR) is undergoing Phase III testing.

2. Spasticity

Spasticity management requires a combination of rehabilitation and medications. Stretching exercises and cooling often relieve mild spasticity. Baclofen (Lioresal®) or tizanidine (Zanaflex®) is usually the initial medication for spasticity. These medications must be initiated with slowly increasing doses because of the tendency to produce drowsiness and fatigue in some patients. Many patients tolerate these medications beyond the common or usualrecommended dose. Intrathecal baclofen is under utilized, because it involves an intrathecal pump. However, it can be very helpful in selected patients who do not respond to oral medications (101, 102). Diazepam (Valium®), Clonzapan (Klonipin), gabapentine (Neurontin), dopamine agents and sodium dantrolene (Dantrium®) are aslo used sometimes by neurologists. Motor point blocks, botulium toxin (botox) injections, and ablative procedures are also used in selected circumstances (103).

3. Weakness and Mobility

Weakness is a difficult problem. Attempts to strengthen the affected muscles sometimes have limited success. However, complementary muscles may be strengthened. Combined with rehabilitation, this increased muscle strength may help

overcome the weaker muscles. Difficulty with mobility and ambulation can create additional hardships for MS patients. The approach to the patient with mobility difficulties is similar to other conditions with reduced mobility encountered by the rehabilitation team. Assistive technology such as ankle–foot orthoses (AFO's), canes, scooters, and wheelchairs can reduce fatigue and increase mobility. Many MS patients delay use of these aids. Recent studies with 4-aminopyridine (Fampridine SR) has shown effectiveness in increasing strength and endurance. While not FDA approved, a Phase III trial is underway.

4. Vertigo, Dizziness, Cerebellar Incoordination, and Tremor:

   Vertigo, dizziness, cerebellar incoordination, and tremor are difficult to treat. Balancing exercises and vestibular stimulation therapy may be helpful. Safety issues are a major concern because some MS patients may fall because of imbalance. Medications are usually not very helpful. Vertigo may respond temporarily to transdermal scopolamine, meclizine (Antivert®), diphenhydramine (Benadryl®), and dimenhydrinate (Dramamine®). Cerebellar tremors are also very difficult to treat in MS patients. Clonazepam (Klonopin®), propanolol, Primidione, Busprione, Isoniazod, Ondagatram, and some sedative drugs have been shown to help tremors somewhat. A weighted walker and wrist weights may be helpful. Stereotactic brain stimulation can be considered in selected patients with refractory tremors (103, 104).

5. Paroxysmal Disorders:

   Some of the most frequently neglected symptoms in MS are paroxysmal disorders. Paroxysmal muscle spasm, pain, sensory symptoms, ataxia, and dysarthria are often not recognized. If healthcare professionals are aware that up to ten percent of MS patients experience paroxysmal disorders, they can be alerted to treat earlier. Paroxysmal disorders are temporary signs or symptoms that occur suddenly and last from seconds to several minutes. The clinician is urged to identify patients who are having "spells" of neurologic dysfunction. Trigeminal neuralgia, L'hermittes phenomenon, and tonic spinal cord seizures with tonic spasms are the most easily recognized paroxysmal

disorders in MS. Anticonvulsants are the first-line therapies for paroxysmal disorders. Gabapentin (Neurontin®) is the most frequently used treatment. Pregabalin (Lyrcia) is now available with a similar mode of action. Carbamazepine (Tegretol®), phenytoin (Dilantin®), and other anticonvulsants are other potential treatments.

6. Pain:

In the past, pain was thought to be an unusual symptom in MS patients. However, studies have shown pain to be present in as many as 75 percent of MS patients (105). The pain is usually one of two varieties. The first is central neurogenic pain, which is often described as burning, hot, painful, dysesethesia with numbness and tingling, deep, and "indescribable." Anticonvulsants, such as gabapentin (Neurontin), are first line therapies (106). Pregabalin (Lyrcia) and Duloxetine (Cymbalta) may also be helpful. The second type is musculoskeletal pain, which occurs frequently in MS because of abnormal postures, muscle spasms, and contractures. These patients are treated like other neuromuscular pain patients in rehabilitation: stretching, range of motion, active exercises, cooling and removal of pain-precipitating factors are the mainstays of treatment. Headache, including migraine headaches, are often seen in MS. Other treatments for pain, such as biofeedback and accupunture can be helpful in some patients.

7. Depression and other affective states:

Depression is seen in most MS patients at some time during the course of the illness. Therefore, psychotherapy and counseling to deal with adaptation and coping are important. Early intervention can help prevent later disruptions. Family counseling is also an integral part of better understanding the disease. When depression becomes manifest, psychotherapy and medications are often used concurrently. Tricyclic antidepressants (TCA's) were the mainstay of MS depression treatment for many years. However, their anticholinergic side effects made many MS symptoms worse. Blurred vision, cognitive blunting, dry mouth, constipation, and urinary retention are some of the problems with tricyclic antidepressants. Therefore, the SSRI's and non-SSRI's such as Effexor (Venlafaxine), Trazodone (Desyrel), Nefazodone

(Serzone®), Bupropion (Wellbutrin®), Duloxetine (Cymbalta) and many other drugs are also used in the medical management of moderate depression. Careful selection and monitoring of anti-depressants are important. Depression can be associated with anxiety and/or bipolar states, which require added attention. The drug treatment of depression need not be life long, especially if there is adequate psychological support. Bipolar disease and mania are also seen in MS.

8. Cognitive Dysfunction:

Cognition dysfunction previously was not thought to be a major part of MS symptomatology. Now we realize that cognitive dysfunction is frequent (>50%), may occur early and may be unrecognized for a long period of time. Therefore, cognitive testing might be helpful early in the disease course. Depression, fatigue, and medications for other MS symptoms may worsen cognitive dysfunction. The medical treatment for cognitive dysfunction has not been adequately studied. Anticholinesterase inhibitors and other "Alzheimer drugs" are often tried in MS cognitive dysfunction. The results of small studies have been mixed (56, 57). However, cognitive retraining helps patients adapt and increases the quality-of-life issues in patients with cognitive problems. Immunomodulating therapy has also been shown to have favorable results to reduce progression of impaired cognition.

9. Bladder Dysfunction:

Bladder problems are among the most common MS symptoms, causing social isolation and a reduced quality of life (107). The evaluation of bladder dysfunction starts with a detailed history and bladder evaluation including assess most of a post-void residual volume and evaluation of bladder emptying by ultrasound, if indicated. More formal bladder dysfunction testing using urodynamics may be performed by urologists. The treatment for bladder dysfunction starts with education and counseling. Volume and timing of fluid intake is extremely important. Drinking more fluid especially at night may lead to urine leakage or frank incontinence. However, fluid deprivation can lead to dehydration, bladder infection, stone formation, constipation, and other side effects such as dry mouth, dizziness, and nausea. For Nocturia, evening fluid restriction,

anticholinergic agents, and desmopressin given by nasal spray at bedtime can be useful.

Rehabilitation of bladder voiding and incontinence problems begin with timed voiding and ultrasound scans to assess voiding patterns and post void residual bladder volume. The goals are continence and avoiding over distending the bladder beyond 400 cc's. Management of the large, hypotonic bladder is challenging. Bethanechol (Urecholine®) is the only agent available to stimulate Detrusor bladder contractions. Results are variable. Intermittent catheterization is often the best treatment for patients who have urinary retention.

A dyssynergic bladder, where both the bladder wall and the urinary sphincter contract at the same time can cause urinary retention and reflux of urine to the kidneys. Baclofen (Lioresal®) and alpha-blockers may help the dyssynergic bladder. Medication for a small spastic bladder usually begins with Tolterodine tartrate (Detrol®), because it has the least anticholinergic side effects. Oxybutynin (Ditropan XL®) can be given once a day with fewer anticholinergic side effects than regular Oxybutynin. Many other anticholinergic drugs are also available. Alpha-blockers inhibit the urethral internal sphincter contraction with resultant decreased bladder outflow resistance. Available alpha-blockers include Flomax (Tamsulosin Hydrochloride), Terazosin (Hytrin®) and Phenoxybenzamine (Dibenzyline®) Alpha-blockers may cause orthostatic hypotension, and follow-up blood pressure assessments are important.

10. Bowel Dysfunction

Bowel dysfunction usually means constipation, but diarrhea and incontinence also occur (107). Medications for other MS symptoms, which are complicated by dehydration, can play a significant role in aggravating constipation. The first step in treating bowel dysfunction is an assessment of the patients' bowel habits and time of day including frequency of bowel movements, laxative medication, and episodes of incontinence. Patients are trained to establish a regular pattern of bowel elimination.

A high-fiber diet and hydration are the cornerstones to treatment of most bowel dysfunction. The gastrocolic reflex,

especially after breakfast, can be utilized if the patient adequately prepares for a bowel movement at that time. A warm beverage may also help stimulate a bowel movement.

Stool softeners and bulk agents may also be helpful. Chemical stimulant cathartics (laxatives) for bowel movements can lose their effectiveness over time because of habituation. A rectal suppository administered after the preferred meal can be useful. A glycerin suppository, which contains no medication, is preferred over the stimulant suppositories such as Bisacodyl (Ducolax) ®. Enemas are effective, but should be saved for failures with the preceding treatments. Digital stimulation can also be effective if other treatments fail.

11. Sexual Dysfunction

Physicians and patients historically seem to be joined in a conspiracy not to discuss or treat most sexual dysfunction (108, 109). Sexual dysfunction is common in both men and women. Sexual dysfunction in women may be as prevalent as in men. However, erectile dysfunction seems to be the center of attention of most treatment efforts. Both men and women may have altered libidos, altered genital sensation, decreased frequency, and intensity of orgasms, and/or pain during sexual intercourse. Vaginal dryness and pain are common complaints in women. Sometimes, sexual intercourse may stimulate massive muscle spasms or pain. Adductor muscle spasms may hamper intercourse. Urinary incontinence may accompany intercourse.

The management of sexual dysfunction begins with education and counseling about the specific pathophysiology of sexual dysfunction. If sexual intercourse is extremely problematic, sexual activities can occur in many forms that do not require sexual intercourse. Intimacy is a special connection that is not necessarily tied to intercourse. Communication is often the key to intimacy.

The medical treatments for fatigue, depression, bladder dysfunction, bowel dysfunction, and muscle spasms are important considerations in the treatment of sexual dysfunction. For women lubrication, estrogen creams and vibrators may be helpful. Sildenafil citrate (Viagra), Vardenalfil (Levitra) & Tadalafil (Cialis) have been very effective for erectile

dysfunction (ED) in some males. One additional problem associated with these medications is that patients may focus on the act of sexual intercourse as the ultimate in sexuality. However, communication and intimacy may actually play a greater role in quality of life in the long run.

12. Dysphagia

Dysphagia occurs in 20 to 25 percent of MS patients (109). Patients may have a delay in swallowing, where food enters the pharynx before the pharyngeal motor response has been initiated. This leaves the airway open, which leads to aspiration and possibly pneumonia. The motility of food through the pharynx may also lead to inefficient swallowing and aspiration. Reduced tongue movement, incoordination, and poor lip closure or facial tone may also decrease swallowing. Esophageal peristalsis dysfunction is theoretically possible in MS, although very few studies have been published.

The treatment of dysphagia is difficult, but a speech and language pathologist can provide treatments to improve dysphagia. Surgical procedures to prevent aspiration have not been very successful in MS patients. Dysphagia is also related to fatigue: for example, some MS patients take a long time to finish a meal. Chewing becomes difficult and, by the end of the meal, fatigue may produce coughing, regurgitation of food, and aspiration. Therefore, it is recommended that patients having problems with dysphagia have more frequent but smaller meals to prevent fatigue.

13. Dysarthria

Dysarthria is very complex in MS and may involve spasticity, weakness, or ataxic incoordination of the muscles of the lip, tongue, mandible, soft palate, vocal cords, and diaphragm. A speech and language pathologist can be helpful in the evaluation and treatment of dysarthria. Dysarthria is thought to occur in between 25 and 50 percent of MS patients. The medical treatment of dysarthria involves the treatment of fatigue and spasticity as well as attempts to treat ataxia and tremor.

X. POTENTIALNEW MULTIPLE SCLEROSIS THERAPIES IN TRIALS

1. Novel Oral Therapies in Clinical Trials:
   There are several oral therapies that are being tested with encouraging results and preliminary studies (110).

   Cladribine is a small non-peptide molecule that is cytotoxic to lymphocytes and monocytes (111) that is used in leukemia therapy. In one MS study it was given orally 20 days the first year and 10 days the second year. It is currently being tested versus placebo and as an induction agent before interferon beta therapy. Parental Cladribine was used several years ago and was shown to have a positive affect on relapses and MRI but not on progression of disease in patients who had progressive MS. In current trials, it is used orally in relapsing/remitting MS patients.

   Fingolimod (FTY720), a Sphingosine receptor modulator, blocks lymphocytes from leaving the lymph nodes and therefore prohibits them from entering the central nervous system (112). Fingolimod is given orally daily. A 24 months study showed Fingolimod rapidly reduced the relapse rate as well as having a marked affect on MRI lesions. Adverse events included Bradycardia, increased blood pressure, airway obstruction, macular edema, and infections. Other positive effects, such as neuroprotection, have been noted in EAE.

   Fumaric Acid Ester (Fumarate BG-12) is another oral agent with anti-inflammatory and possibly neuro-protective properties (113). It is used in psoriasis. In a Phase 2B study in MS patients, BG-12 showed a 69% reduction in the formation of new gadolinium enhanced lesions, and a 32% reduction in relapse rate over a 48-week period. The toxicity profile was favorable.

   Laquinimod is an immunomodulating agent that converts pro-inflammatory TH-1 cells to anti-inflammatory TH-2 cells (114). A Phase 2 trial in RRMS demonstrated that MRI activity was reduced by 40% and the annual relapse data was also positive. Laquinimod was derived from Linomide, which was tested in MS previously and found to be effective but with significant adverse events. Laquinimod has an improved safety profile.

   Teriflunomide is an oral immunomodulator primarily affecting T-cell synthesis (115). It is an active metabolite of Leflunomide, which is currently approved for rheumatoid arthritis. The drug inhibits new RNA and DNA synthesis. In a Phase 2 trial, a marked reduction in new MRI

activity was noted in nine months. Treatment was well tolerated. Studies adding Teriflunomide to patients taking Interferon and Copaxone are in progress.

2. Monoclonal Antibodies: (116)

Alemtuzumab (Campath) is a monoclonal antibody directed against the CD-52 receptor on T-cells and monocytes (117). It induces long-term T-cell depletion and it is currently indicated for B-cell leukemia. In a study comparing Alemtuzumab versus Rebif, a reduction in the Alemtuzumab group was noted for relapses and sustained disability over a 36 month period, even though Alemtuzumab was given only at baseline and year one (5 days and 3 days respectively). Over 50% of Campath patients improved in this trial, suggesting the possibility of reduced neurodegeneration or increased neuroprotection. In another study, Alemtuzumab produced a dramatic reduction in the annualized relapse rate. Adverse events include idiopathic thrombocytopenia purpura (ITP), which produced one fatality, as well as Graves Disease (about 8%), infusion reactions and infections. A phase III trial is underway.

Rituximab (Rituxan) is a monoclonal antibody to CD-20, which induces B-cell depletion. In a relapsing/remitting MS study, two infusions of Rituximab were given and the patients were followed for 48 weeks versus placebo. All clinical and MRI outcomes favored Rituximab over placebo (118). Rituximab has been associated with serious adverse events including Progressive Multifocal Leukoencephalopathy (PML) in non-MS patients. A trial in PPMS failed to show clinical efficacy over placebo (press release, 2008).

Rituximab has also been studied in Neuromyelitis Optica (NMO) (DEVICS Disease) (119). Ten (10) patients who were doing poorly on current therapy were given Rituximab and the relapse reduced from 3.7 to 0.57 over a nine-month period. 70% of these patients were NMO antibody positive.

Daclizumab is a monoclonal antibody that binds to the receptor of the inflammatory cytokine interleukin 2 (IL2), which results in a decrease in an IL2 mediated stimulation of T-cell function. It is used for Renal Transplants. In Interferon beta treated MS patients who had continual disease activity, two recent studies have shown that daclizumab was effective in reducing MRI lesions and relapses and/or are improving EDSS scores. Adverse events were not serious but included decreased platelet counts, infections, and infusion reactions (120).

3. Other Therapies for Multiple Sclerosis:

MBP82-98 is a synthetic peptide encompassing myelin basic protein (MBP) peptides 82 to 98, which are considered the immunogenic sites of MBP. High dose tolerance is the mechanism of action. The drug is given intravenously every six months to HLA DR2, and DR4 patients. This is the first emerging drug to specifically target genetic subtypes. In a preliminary study, MBP82-98 delayed progression in secondary progressive MS (SPMS) versus placebo from 18 to 78 months (121). Trials are in progress in both SPMS and RRMS. The side effect profile shows that it is well tolerated.

BHT-3009 is a plasmid DNA "vaccine", which encodes the entire molecule of myelin basic protein and induces tolerance, which turns off the immune system. In a 13 week study versus placebo, the treated group had decreased MRI lesions, decreased myelin reactive T-cells and decreased myelin antibodies in the spinal fluid. BHT-3009 was well-tolerated (122).

Bone Marrow Transplant is under evaluation in specialty centers (123). For active relapsing MS, a new study has been encouraging, but adverse events, including death are still being reported (Freedman M., ECTRIMS 2007)

Embryonic stem cells and remyelination research are in early phases of research.

Atorvastatin (Lipitor) and Simvastatin (Zocor) are oral statins currently being tested in MS (124). Zocor 80 mg a day was shown to reduce MRI enhanced lesions in an uncontrolled study (Vollmer, AAN 2005). A controversy exists whether statins may interfere with the interferon mechanism of action (Birnbaum- AAN 2007, Reder-AAN 2007). The latest two studies did not show a specific interference (Sorenson, ECTRIMS 2007), but the controversy remains. The potential mechanism of statin interference with interferons is not an issue with Copaxone. Other trials with statins are in progress

Minocycline is a tetracycline type antibiotic, which decreases matrix metalloproteinase and decreases the transmigration of lymphocytes across the blood-brain-barrier. It has been shown to be effective in experimental autoimmune encephalitis (EAE) in animals. It also decreases a neurotoxin,

nitric oxide, in the CNS. Pilot studies with Minocycline have found an effect on decreasing enhancing lesions and relapse rates (125, 126).

Estriol is an oral estrogen, which has anti-inflammatory effects and potential neuroprotective properties. Increased Estriol production is thought to be one of the mechanisms by which MS disease activity is reduced during pregnancy. A pilot study showed a reduction in enhancing lesions. A study utilizing Copaxone with and without Estriol in relapsing/remitting MS showed a more robust effect on MRI and relapse rate with the combination therapy versus Copaxone alone (127, 128).

Fluoxetine (Prozac) is an SSRI anti-depressant, which has an immunomodulating effect by decreasing inflammation. It decreases lesions in experimental autoimmune encephalitis. Also, Fluoxetine is a sodium channel blocker and has been shown to increase brain derived nerve factor (BDNF) in the CNS. In a small trial, it reduced MRI lesions and increased n-Acetylaspartate, an axonal marker, on magnetic resonance spectroscopy (Mostert, ECTRIMS 2007). These data are considered preliminary.

NeuroVax, a T-cell vaccine, is comprised of three T-cell receptor peptides. NeuroVax induces T suppressor cells, which have been found effective in animal models of EAE. Clinical trials are forthcoming (Bourdette, AAN 2006) (129).

Erythropoietin has encouraging preliminary data as a disease-modifying agent (130).

Other Potential Disease Modifying Therapies in Multiple Sclerosis:
Aziathiaprine (Imuran), Pulse steroids, Cyclophosphamide (Cytoxan), intravenous immunoglobulins (IVIG), Methotrexate, Plasma Exchange (131), and Micophenolate (CellCept) are currently in use in MS patients by some neurologists. They are not FDA approved.

4. Potential Symptom Management Treatments in Clinical Trials:
Fampridine SR is a sustained release formula of 4 amino-pyridine (4AP). Fampridine SR has shown positive effects on walking speed and endurance as well as strength (132). This sustained release formulation is designed to reduce the risk of seizures, which has been problematic with 4AP. A phase III clinical trial is underway.

Zenvia, formerly Neurodex, is a drug being tested to treat pseudobulbar affect, which is characterized by sudden and unpredictable episodes of laughing, crying, and other displays of emotion. It is a combination of dextromethorphan and low dose quinidine. Preliminary trials are encouraging. (133)

Modafinil (Provigil), (100) a treatment used by many neurologists for MS fatigue, is now being investigated for its effect on cognition.

Cannabis (Sativer) drug (134, 135) is used in Canada and the United Kingdom for symptomatic treatment in Multiple Sclerosis, including pain, bladder symptoms, and spasticity. In addition, cannabis may have immunomodulator and neuroprotective effects, but more data is needed. A recent study showed deleterious effects on cognition in MS with cannabis.

Botulinum Toxin Type A has been effective in treating overactive bladder symptoms, as well as muscle spasticity in MS (136).

Low dose Naltrexone (LDN), an opioid receptor blocker, is currently being tested in MS patients in trials in the USA and Italy. A higher dose of LDN (50 mgm) is currently approved for alcohol and opioid addiction. Results in MS have not been published.

Vitamin D is being evaluated for possible effectiveness in MS. Reduced Vitamin D and sunlight exposure have been linked to an increased risk of MS (55).

XI. COMPARING MULTIPLE SCLEROSIS AND SPINAL CORD INJURY ISSUES

The most obvious difference between MS and SCI is the natural history of the disorder. MS patients tend to progress over time, whereas SCI patients tend to stabilize or get better. However, other differences are important to recognize. MS patients tend to be older than SCI patients. MS patients tend to come from higher socioeconomic backgrounds and are more likely to be college educated. Childbearing issues and genetics are often more relevant in MS. A major goal in MS is to find treatments to prevent damage over time, whereas SCI damage prevention management is currently confined to the immediate post-injury phase. Because of the location of many MS lesions above the spinal cord level, more problems with cognition, vision and eye movement, speech and

swallowing disturbances, paroxysmal symptoms, cerebellar tremors and incoordination are likely.

Most MS symtoms are treated with rehabilitation techniques as well as medication (137, 138, 139). Much of the disability in MS is related to spinal cord involvement; therefore, some rehabilitation issues in MS are similar to those in SCI. However, there are many key differences in the treatment of the symptoms of MS versus SCI. Rehabilitation Medicine physicians are often the principal physician care providers for SCI, whereas Neurologists are more often the principal physician care providers for MS. Their backgrounds and orientation to disease management can be different, although that difference has been narrowing in the last several years.

Reimbursement for rehabilitation in SCI is somewhat less difficult to obtain than long-term rehabilitation in MS. Although it is obvious that SCI patients need rehabilitation, the benefit of rehabilitation in MS is less utilized, in spite of numerous recent articles demonstrating efficacy.

XII. CONCLUSION

This chapter previews some of the complexities in the diagnosis, pathogenesis, disease courses, and treatments of MS symptoms. Disease modifying therapies, especially when initiated early, have favorably altered the short and long-term prognosis. Emerging therapies may facilitate treatment even more. However, dramatic efficacy results may be tempered by the adverse event profiles. Clinical trials will help establish future approved therapies. The integrated, comprehensive treatment approach among rehabilitation therapists, the physicians, and other members of the healthcare team is an important aspect to successful long-term management of MS patients.

The disease management approach in MS provides education, self-management, and empowerment opportunities for the patient. This not only helps the patient but also helps the caregiver and healthcare professionals involved in the treatment. A well-designed system of care accomplishes the ultimate goal of a higher quality of life for MS patients. Symptom management is often underutilized but can increase functioning in most MS patients.

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