MULTIPLE SCLEROSIS: IMPLICATIONS FOR PRACTICE

By

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Abstract

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Multiple Sclerosis (MS) is an immune-mediated disorder affecting the myelin sheaths of the central nervous system. People with MS live for decades with disease-related disabilities despite the fact they have normal life spans. The disease has no known prevention and no cures, but the list of treatments continues to grow.

Multiple Sclerosis typically strikes between ages 15 and 50 with peak onset around age 30. Women are three times as likely to be affected as men. Between 250,000 and 350,000 people in the United States have MS.

This article focuses on how practitioners can learn to recognize the essential features of MS, and to assist with diagnosis and treatment. Using the theoretical framework of the Health Belief Model (HBM), the manuscript will explain who is affected and how, what benefits and barriers are to the individual and practitioner toward making an accurate diagnosis, and the role of self-efficacy in assisting illness management and treatment of accurate, effective treatment.

The pathologic process of MS involves the formation of Central Nervous System multiple lesions called plaques. The plaques cause inflammation and demyelination of the myelin sheath and the formation of permanent scar tissue. Multiple Sclerosis has a highly variable course and a long-term nature.
Multiple Sclerosis is a clinically determined diagnosis of exclusion. There are no tests, which are specific for MS, and no single test is 100% conclusive. Based on sensitivity and specificity the most clinically appropriate plan is to take a carefully detailed history and physical and look objectively at the clinical presentation of the patient.

Treatment can be addressed in four ways: acute exacerbations of symptoms, long-term symptom management, and treatment to slow disease progression and alternative types of treatment. One of the best treatment modalities for Multiple Sclerosis has developed from Interferons. Treatment with Interferons assumes a viral pathogenesis in MS. Several alternative therapies have been shown to be beneficial to Multiple Sclerosis patients. Nutritional therapy, massage, reflexology, magnetic field therapy, neural therapy, and psychological counseling have all been used as alternative treatments.

This article, focuses on how practitioners can learn to recognize the essential clinical laboratory and physiological features, to diagnose, and to treat Multiple Sclerosis. Current pathophysiology, diagnostic criteria and treatment approaches are described.
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Introduction

Multiple Sclerosis (MS) is an immune-mediated disorder affecting the myelin sheaths of the central nervous system (Smiroldo, 1999). People with MS may live for decades with disease related disabilities despite the fact they have normal life spans. The disease has no known prevention and no cures, but the list of treatments continues to grow. This article focuses on how practitioners can learn to recognize the features of MS that are essential to making an accurate and timely diagnosis and to proper illness treatment. Using the theoretical framework of the Health Belief Model (HBM) (Becker, 1974), the manuscript will explain who is affected and how, what benefits and barriers are to the individual and practitioner toward making an accurate diagnosis, and the role of self-efficacy in assisting illness management and treatment.

The Health Belief Model (HBM) originated around 1950 and is regarded as the beginning of systematic, theory-based research in health behavior (Becker, 1974). The HBM was originally developed to explain and predict health behavior. It focused on the relationship among health behaviors, practices, and utilization of health services. The HBM has been revised to include general health motivation for the purpose of distinguishing illness and sick-role behavior from health behavior (Becker, 1974).

People are more likely to seek care from a provider, if they perceive a susceptibility or threat to disease. Awareness of disease susceptibility and a perception of threat are influenced by different cues to action such as education level, the incidence and severity of symptoms, and by health-related media information. People are more likely to take action in the form of a treatment, if they perceive it to be beneficial in reducing severity of disease.
The HBM was selected as an organizing framework because it offers a conceptual heuristic for understanding the barriers to seeking a timely diagnosis of MS and people’s motivation to utilize health services. MS is an insidious disease process. The initial symptoms are often ambiguous—a sore joint or throat, headaches, fatigue—and can be attributed to many conditions other than a serious illness. People may delay seeking health care until a critical incident such as falling, loss of vision, memory lapses—raises their perception of threat and susceptibility. Moreover, the ambiguous nature of the presenting symptoms often makes it difficult, if not impossible, to make an initial diagnosis. Referrals to multiple specialists are common and people with suspected MS may become confused, frightened, angry, depressed, discouraged, and fatigued as health providers search for a diagnosis. The HBM addresses many of these issues: health seeking behavior and the delay in seeking treatment, factors that affect the perception of symptom severity, motivation to seek a diagnostic confirmation and to follow-thru with dozens of diagnostic tests, and health provider’s reluctance to treat people in the absence of a definitive diagnosis.

The diagnosis of Multiple Sclerosis carries with it a sense of fear related to pain, discomfort, financial burdens, loss of work, difficulties with family, and susceptibility to future conditions. The diagnosis itself is a barrier for the provider, as well as the person. Once a diagnosis is certain, barriers to treatment exist in the form of expense, inconvenience, embarrassment and pain. The likelihood that a given action toward treatment will come with the individual perceiving the benefits of early treatment and overcoming barriers.
Classification of Multiple Sclerosis

Multiple Sclerosis typically strikes young adults between ages 15 and 50 with peak onset around age 30. Women are three times as likely to be affected as men. Between 250,000 and 350,000 people in the United States have MS (Halper, 1998). MS is a primarily a Caucasian disease which occurs in temperate zones (Smiraldo, 1999). Climatic factors such as pollution, solar radiation, temperature, rainfall, humidity, have all been investigated; however, the only consistent effect appears to be due to latitude. MS is in general a disease of temperate climates with a population prevalence that decreases with decreasing latitude. High incidence rates are found in Scandinavia, Iceland, and the British Isles (about one in 1000). Even within the United States, distinctions exist in the prevalence of MS between populations living north and south of the 37th parallel (Hogancamp et al., 1997).

The geographic distribution of MS may alternatively be related to the degree of sunlight exposure catalyzing the production of the hormonally active form of vitamin D or vitamin D₃. Exposure to UV light may have a protective effect in MS. In Switzerland for example, MS risk increases at low altitude and decreases at high altitude. In addition to its role in calcium homeostasis and bone metabolism, vitamin D₃ possesses both anti-inflammatory and immunomodulatory properties (Cippitelli, 1998).

Multiple Sclerosis has a highly variable course and a long-term nature. The disease can be characterized in four groups by clinical pattern and are clearly defined by Lublin (1996). The first is Relapsing-Remitting (RR) MS, which is defined by episodes of acute worsening of the person’s neurological function followed by a variable degree of recovery, with a stable course between attacks. The periods between attacks do not have
obvious physical progression. The second group is Primary-Progressive (PP) MS, which is a gradual continuously worsening baseline of functioning with minor fluctuations, but no distinct relapses. The third clinical group, Secondary-Progressive, is the point at which the Relapsing-Remitting group begins to progress with or without occasional relapses, minor remissions, and plateaus. The fourth group as defined by Lublin is Progressive-Relapsing (PR) MS. In this case, the disease is progressive from the beginning and continues to have acute relapses with or without full recovery, but there is continued progression even between the relapses.

Multiple Sclerosis can also follow a benign course defined as minimal disability after disease duration of greater than 10 years. The benign course of MS was researched by Koopmans, Li, Grochowski, Cutler, and Paty (1989). They compared 32 people with benign MS and 32 people with the Chronic-Progressive Multiple Sclerosis (CPMS). The people were matched for age, sex, and disease duration. Computer-assisted quantitation of magnetic resonance images revealed a higher mean lesion load in Chronic-Progressive Multiple Sclerosis (CPMS); however, in approximately 20% of people with benign MS, the lesion load was higher than that in the people with CPMS. People with CPMS had a higher number of infratentorial lesions, yet similar numbers of supratentorial lesions, when compared with people with benign MS. The degree of confluency of lesions and the clinical expression of infratentorial lesions were typically higher in people with the CPMS. Benign MS was characterized by a lower degree of confluency and a higher number of asymptomatic infratentorial lesions. Thus, magnetic resonance imaging shows characteristic differences in magnetic resonance-detected changes between people with MS with different clinical courses.
**Pathophysiology**

The pathologic process of MS involves the formation of central nervous system multiple lesions called plaques. Plaques cause inflammation and demyelination of myelin sheaths and the formation of permanent scar tissue (Smiroldo, 1999). Scar tissue that forms decreases electrical nerve conduction in the CNS. MS is noted for the presence of T-cell predominant perivascular inflammation in the brain’s white matter. (Smiroldo, 1999).

Natural killer (NK) cells, which are important in innate immunity and also exert many immunomodulatory activities (Horwitz et al., 1997), might play a role in the immunopathogenesis of Multiple Sclerosis (Manschauer et al., 1995). The active inflammatory lesions of MS are associated with release of an array of additional cytokines (i.e., interleukin-12, interleukin-15, tumor necrosis factor-alpha, type 1 interferons, and chemokines). These cytokines may serve not only to activate NK cells, but also to upregulate ligands on the target cells, such as the intracellular adhesion molecules (ICAMs), CD48, and CD58, that promote their interaction with susceptibility to NK-mediated injury (Lanier, 2000). Kastrukoff et al., 1998 studied 34 Relapsing-Remitting Multiple Sclerosis patients for two years correlating NK cell functional activity (FA) and phenotype. The researchers found significant correlations between reductions in NK cell functional activity and the development of active lesions on MRI. The mean NK cell functional activity among MS persons is approximately 20% specific release lower than among their age/sex matched controls (P<0.001). A significant number of the active lesions are preceded by a reduction in NK functional activity, as represented by 80% of people. The results suggest that Relapsing-Remitting MS patients with a higher
mean NK functional activity are at greater risk of developing active lesions (Kastrukoff et al., 1998). This study demonstrated NK cells having some involvement in the immunopathogenesis of people with Relapsing-Remitting MS, however, the role is still unclear. NK cell functional activity might later be replaced by T-cell mediated autoimmunity or this research may only be applicable to some populations of Relapsing-Remitting MS.

Trapp et al., (1998) researched postmortem lesions in Multiple Sclerosis and discovered that axonal transection is a consistent consequence of demyelination. Axonal transection is irreversible and found most abundantly in areas of inflammation. The greatest degree of axonal transection occurred in areas of active demyelination and inflammation. The researchers considered it most likely that demyelinated axons are vulnerable to inflammatory environments and that axonal transection is caused by proteolytic enzymes, cytokines, oxidative products, and free radicals produced by activated immune and glial cells (Hohlfeld, 1997). The axonal transection may be the reason that neurologic impairment is irreversible (Trapp et al., 1998).

Serial Magnetic Resonance (MR) Imaging studies have added much to our understanding of the natural history and pathophysiology of the disease. Blood-brain barrier breakdown is a consistent early feature of new lesion development in Relapsing-Remitting and Secondary-Progressive Multiple Sclerosis, and this usually correlates with active inflammation and myelin breakdown.

A number of the acute MR changes are reversible, but chronic persistent abnormalities in a number of MR parameters, such as reduced N-acetyl aspartate, low magnetization transfer ratios, atrophy and T1-hypointensity, suggest the presence of
demyelination and/or axonal degeneration in many chronic lesions. The presence and extent of T2-weighted MRI abnormalities at first presentation with a clinically isolated syndrome suggestive of demyelination strongly predicts the risk of developing Clinically Definite Multiple Sclerosis in the next few years (Miller, Grossman, Reingold, & McFarland, 1998).

The pathologic process is active in people with Relapsing-Remitting MS. Cumulative irreversible tissue injury occurring during this stage of the disease determines later progression to Secondary-Progressive MS. The underlying pathological process during Relapsing-Remitting MS is poorly reflected by clinical symptoms, however, and it is for this reason that clinical features in people with Relapsing-Remitting MS are such poor predictors of subsequent disability progression (Rudick et al., 1999).

Approximately, 50-75% of people with Relapsing-Remitting MS have one or more gadolinium enhancing lesion (GAD+) on a random cranial MRI scan (Simon, 1997). Early treatment has a robust rationale both in prevention of irreversible pathological changes and in reducing clinical and MRI activity with favorable prognostic implications (Comi, Colombo, & Martinelli, 2000). The early reduction of relapse rate, as well as of the extent of pathological lesions should be the strategy for people particularly in the first phases of the disease (Comi, Colombo, & Martinelli, 2000).

Clinical Presentation

The clinical features of Multiple Sclerosis can range from weakness and clumsiness to numbness, visual disturbances, and even emotional and intellectual changes. Clinical signs can demonstrate as fatigue, depression, pain, bowel and bladder dysfunction, impaired mobility, spasticity, speech and swallowing difficulties, and
tremors. The presentation of MS depends on which nerve fibers are involved in demyelination. People can either experience cycles of relapse and remission or progression to severe debilitation.

Alteration in vision is often the first feature symptom for many people. An optic lesion may cause diminished visual acuity, blind spots, or a decrease in brightness. Optic neuritis occurs in approximately 17% of MS attacks. Symptoms of optic neuritis may be blurred vision, vision loss in one central spot (scotoma), depth perception loss, or diminished night vision. Vision problems may be exacerbated by tension, eyestrain, and fatigue. An optic neuritis attack generally peaks within a few days and typically resolves fully or partially within two to six weeks of initial occurrence (Rosner & Ross, 1987).

People may present with a positive L’hermitte’s sign. L’hermitte’s sign is a sensation of electric shock running up and down the spine/back associated with compression of the cervical spinal cord and frequently weakness.

Any of the above clinical features may or may not bring a person in to see a health care provider. If a person with these symptoms believes that he or she has a susceptibility or threat to disease and may benefit from seeking treatment, then he or she will present to a health care provider. If the person with neurological symptoms is able to deny the seriousness, he/she will do so until he/she has no other choice. In many cases, seeking health care will depend on what barriers can be overcome (ie., lack of money, knowledge, time), as well as what cues to action are influencing the individual (ie., resources, media).
Case One

AD, a 46-year old male, presented to the ER by ambulance after a motor vehicle accident. The patient stated his vision became blurry and he felt as if he was revolving around himself before he hit the telephone pole. AD was also having left sided weakness and numbness, urinary incontinence, and extreme fatigue.

A careful history indicated that he had been having neurological symptoms for over ten years. AD related that he had difficulty with a stumbling gait, changes in visual acuity, and heat intolerance for many years. At times he could not hold objects in his hands, had significant tremors, and severe exhaustion. He recently began having arthralgia bilaterally and has had experienced several falls. He denied changes in speech, and memory.

AD had a heart rate of 89, blood pressure of 135/74, and a respiratory rate of 19. Neurological Exam of Cranial Nerve II, showed sharp disks of normal color, funduscopic examination was normal, Cranial Nerves III, IV, and VI with small inappropriate saccades interrupting fixation. Pendular nystagmus was noted bilaterally. The remainder of cranial nerve exam was normal except for decreased hearing on the right, and numbness in the left face, which extended down into the entire left side. The Weber test revealed greater conductance to the left. Rinne’s test revealed air greater than bone bilaterally. The palate elevated well. Swallow appeared to be intact. Tongue movements were slowed, but tongue power appeared to be intact.

The motor examination revealed relatively normal strength in the upper extremities throughout. Visible dysdiadochokinesis was noted in the left arm with finger-nose ataxia. Mild tingling was noted in both legs with moderate spasticity. Deep tendon
reflexes were normal and symmetrical in both arms. Exaggerated response at the ankles and the knees was noted. The heel-knee-shin test showed ataxia.

The sensory exam revealed decreased sensitivity to light touch and decreased proprioception sensation on the left diffusely. AD had vibration sense absent to lower distal extremities. Romberg’s was positive. Gait ataxia was noted with unsteadiness. Ambulation index was 8.0 seconds for 25 feet.

A MRI scan revealed a multifocal white matter disease. Areas of increased T2 signal in both cerebral hemispheres. A spinal tap revealed the presence of oligoclonal bands in CSF, supporting the diagnosis is Secondary-Progressive Multiple Sclerosis.

Treatment for AD began with a neurology consult to a Multiple Sclerosis specialist. He began injection of Copolymer 1 (Copaxone) immediately to slow progression and disability.

Differential Diagnosis

Multiple Sclerosis is a clinically determined diagnosis of exclusion. There are no tests, which are specific for MS, and no single test is 100% conclusive. A complete medical history, neurological examination, and current status of health will be are necessary needed to confirm a diagnosis.

Laboratory data should be gathered to rule out alternative conditions. Nutritional deficiencies should be evaluated. Vitamin E levels should be drawn because a Vitamin E deficiency can lead to neurologic disorders characterized by ataxia, areflexia, gaze disturbances, loss of proprioception and vibratory sensation. A Vitamin B12 level should be drawn, because a deficiency can lead to anemia presenting with symptoms such as weakness, numbness, tingling, and loss of vibratory sensation (Jacobs et al., 1996). A
CBC with manual differential should be drawn. The WBC count will help in ruling out infectious processes. An endocrine panel should be evaluated to include TSH levels, PTH levels and cortisol levels. The provider should evaluate the possibility of Lyme disease based on geographic area, season, and patient history. The labs to draw for Lyme disease are Immunofluorescence assay (IFA) or immunosorbent assay (ELISA) to detect specific antibodies to B burgdorferi in serum. The provider should identify risk factors and perform PAP smear to test for syphilis. Neuroimaging will identify the presence of multifocal CNS white matter lesions. If neuroimaging is not able to confirm a lesion, then evoked potential testing is useful for diagnosis of a clinically silent lesion.

The differential diagnosis can be approached in two ways. The most important signs are clinical presentation. If a person presents with several of the common symptoms with a history of the symptoms lasting greater than 24 hours, reoccurring at least a month later and neurologic exam abnormalities, then an MRI would be indicated. MRI criteria for diagnosing MS is at least two lesions and two of the following: Lesions abutting the lateral ventricles, lesions with diameter greater than 5 mm, and lesions present in the posterior fossa (Offenbacker, Fazekas, & Schmidt, 1993). If symptoms were vaguer, without neurologic involvement, then one should proceed with lab tests and a lumbar puncture for CSF analysis.

The diagnosis of MS falls into four different classes as indicated by Poser, Paty, Scheinberg et al., in 1983. In a person aged 10-59, who has had two attacks at least one month apart and who on clinical examination has evidence of two separate CNS lesions can be diagnosed as having Clinically Definite Multiple Sclerosis (CDMS). People with two attacks and clinical evidence of one lesion also have CDMS. Two attacks and signs
not documented and only one current sign, commonly associated with MS, have Clinically Probable Multiple Sclerosis (CPMS). People with one attack, clinical evidence of a lesion, and new lesions developing also have CPMS. One attack with clinical evidence of a lesion is not diagnostic for MS. One attack, clinical evidence of one lesion, CSF oligoclonal bands with new lesions developing is Laboratory Supported Definite Multiple Sclerosis (LSDMS) (Poser et al., 1983).

**Diagnostic Testing**

The diagnosis of Multiple Sclerosis is constituted by three primary diagnostic tests, neurological exam findings and clinical observations. The three primary diagnosistic tests are Magnetic Resonance Imaging (MRI), Lumbar puncture (LP) and Evoked responses. An MRI demonstrating the presence of areas of demyelination in the Central Nervous System (CNS) would contribute to a MS diagnosis. The second test, a LP is used to evaluate for the presence of oligoclonal bands and/or elevated IgG index in the cerebral spinal fluid. Lastly, Evoked Potential Tests (EVPs) are used to evaluate nerve pathways for a conduction delay.

**Sensitivity/Specificity**

Disease progression and irreversible disability in Multiple Sclerosis results from incomplete recovery from relapses, but most importantly from insidious disease progression. Although magnetic resonance imaging parameters, such as new lesion rate and gadolinium enhancement, reflect inflammation and disease activity, they have no bearing on disease progression. Until now the T2 lesion load or disease burden has been relied upon for reflecting inflammation and disease activity, despite its poor relationship with disability measures (Stevenson & Miller, 1999).
Based on the sensitivity and specificity, the most clinically appropriate plan is to take a carefully detailed history and physical and look objectively at the clinical presentation of the person. The most definitive diagnosis can be made with MRI, so if clinical judgment points to MS, proceed with imaging. If the person presents with vague symptoms then proceed with the cost effective route of ruling out alternative diagnoses.

**Cost Effectiveness**

The cost for Magnetic Resonance Imaging (MRI) of the brain and head is $1,052.00 (Inland Imaging, Spokane, WA). If a contrast agent is used the cost increases to $1,262.00 (Inland Imaging, Spokane, WA). The expected time frame for receiving test results is one to two days. If multiple lesions are discovered on MRI, diagnosis can be made without further testing.

If only a single lesion is discovered on MRI, further testing should be done. If a lumbar puncture were performed, the cost would be $67.86 for oligial banding of cerebral spinal fluid, plus physician cost of procedure.

If labs are used to rule out alternative diagnosis following clinical presentation and history, the costs may be significantly less. The cost of labs will be cheaper, but depending on the clinical presentation a judgment call has to be made on which route will be more definitive.

**Pharmacologic Treatment**

Treatment can be addressed in four ways: acute exacerbations of symptoms, symptom management, and treatment to slow disease progression and alternative treatment. Acute exacerbations of symptoms are usually treated with high dose corticosteroids. A typical dose given in the outpatient setting is intravenous
methylprednisolone 1 gram for three to seven days. The person is given oral prednisone 60-80mg to be tapered over the next two to three weeks (Aminoff, 2000).

Symptoms are managed with individual drugs to improve quality of life. Five different drugs are used in treatment of spastic muscle: Tizanidine (Zanaflex), baclofen (Lioresal), gabapentin (Neurontin), diazepam (Valium) and dantrolene (Dantrium). The fatigue is treated with Pemoline (Cylert), fluoxetine (Prozac), selegiline (Eldepryl), amphetamines, and caffeine. Tremors are treated with clonazepam (Klonpin), propranolol (Inderal), diazepam (Valium), and Isoniazid (INH). Specific pain such as trigeminal neuralgia is treated with baclofen (Lioresal), carbamazepine (Tegretol), valproic acid (Depakote), phenytoin (Dilantin), and gabapentin (Neurontin) (Kaplan, 1999).

Treatment to slow disease progression may be monitored by a tool called the Kurtzke Expanded Disability Status Scale (EDSS). It is based upon findings of the standard neurologic examination, which are grouped into eight functional systems. The systems include visual functions, cerebral or mental functions, sensory functions, bowel and bladder functions, brain stem functions, cerebellar functions, and pyramidal functions, as well as other functions. A person with an EDSS of 3.5 may be able to walk without any problems, but may have moderate decreases in touch sensation and moderate urinary retention. A person with an EDSS of 6.0 may need the assistance of a cane to walk the distance of a block and may have marked decreases in visual fields and touch sensation. The major drawback of the EDSS is that it emphasizes gait impairment and ignores disability that results from other impairments such as upper limb problems or memory loss (Kalb, 1996).
One of the best treatment modalities for Multiple Sclerosis has developed from Interferons. Interferons are small proteins separated by nucleated cells in response to viral infection or other appropriate stimuli, and are thought to act principally on other cells in their vicinity. Interferon-alpha and Interferon-beta have been the most promising (Polman, Miller, Thompson, & McDonald, 1999). Treatment with Interferons assumes a viral pathogenesis in MS.

Interferon beta-1b (IFNB) (Betaseron) was approved in 1993. The IFNB Multiple Sclerosis Study Group (1995) studied the effectiveness of treating MS with Interferon-beta1b. The population consisted of 372 people with Clinically Definite or Laboratory-Supported MS of short duration. The participants were from 11 participating centers formed over five years. The Multicenter, blinded, randomized, and controlled study comparing two different dose strengths of Betaseron. The sample population was divided into three groups of low dose, high dose, and placebo. The primary outcome was the relapse rate. Compared with placebo, treatment with the higher dose reduced the relapse rate by 31%, increased the time to first relapse and the proportion of patients who were relapse free, and reduced by about 50% the number of patients who had moderate and severe relapses. There was no significant difference in changes in EDSS scores between treatment groups. The people in the placebo group had a mean increase of 17% in the total T2 lesion load MRI at three years, compared with a mean decrease of 6% in those on high dose IFNB. In addition, there was a significant reduction in disease activity as measured by the analysis of new or enlarging lesions on serial MRI (The IFNB Multiple Sclerosis Study Group, 1995). This study supports the use of IFN-beta1b in limiting
progression of disease, but does not prove a treatment effect. More people and longer follow up are needed to evaluate the role of IFNB in preventing disability.

Kastrukoff et al., (1999) researched the effect of treatment with Interferon beta-1b on natural killer cell function and phenotype in Relapsing-Remitting MS persons. The researchers wanted to find the relationship to disease activity and assess it clinically and with serial MRI evaluations. People were divided into three-treatment groups; placebo, high dose eight MIU, and low dose one point six MIU. Interferon B-1b has also been used with intravenous methylprednisolone and was found to further reduce tissue damage and promote lesion recovery in Relapsing-Remitting MS persons. The side effects related to Interferon beta-1b are flu-like symptoms, injection site reactions, mild anemia, leukopenia thrombocytopenia, and liver function abnormalities (Richert et al. 2001).

Interferon beta-1a (Rebif) was approved for Relapsing-Remitting MS in 1996. The Prevention of Relapses and Disability Study Group (1998) undertook a double blind, placebo-controlled intervention study to determine the effects of subcutaneous interferon beta-1a for the treatment of Relapsing-Remitting MS. The participants included 560 people from 22 different centers in nine countries over a two year period. Participants were randomly assigned to one of three interferon therapy groups; low dose, high dose, or placebo. The low and high dose groups demonstrated a reduction in relapse rate from that with placebo (27-33%). The number of T2 active lesions on the biannual scans was significantly lower (67% and 78%) in the low dose and high dose groups than in the placebo group (p<0.0001). Rebif was well tolerated; the only adverse effects found were injection site reactions, flu-like symptoms, and asymptomatic lymphopenia (PRISMS, 1998). This study demonstrated that Rebif has a good safety profile and that it can offer
some clinical benefits, however, the long-term effects on lesion development are not yet known.

A recent study by Comi et al., (2001) showed that initiating treatment with weekly intramuscular interferon beta-1a (Avonex) dose at the time of a first isolated demyelinating event was beneficial for people with brain lesions on MRI. The study reported the effect of low-dose interferon beta-1a (Avonex) on the occurrence of relapses in high-risk people after first presentation with unifocal or multifocal neurologic events. Eligible people had had a first episode of neurological dysfunction suggesting MS within the previous three months and had strongly suggestive brain MRI findings. People were randomly assigned interferon beta-1a or placebo once weekly for two years. Neurological and clinical assessments were done every six months and brain MRI every 12 months. Three hundred and nine people were deemed eligible and randomized into the study. Fewer people developed Clinically Definite MS in the interferon group than in the placebo group (52/154 [34%] vs. 69/154 [45%]; \( p = 0.047 \)). The time at which 30% of people had converted to clinically definite MS was 569 days in the interferon group and 252 days in the placebo group \( (p = 0.034) \). The annual relapse rates were 0.33 and 0.43 \( (p = 0.045) \). The number of new T2-weighted MRI lesions and the increase in lesion burden were significantly lower with active treatment \( (p < 0.001) \). This study confirms that interferon beta-1a (Avonex) treatment at an early stage of MS has significant positive effects on clinical and MRI outcomes (Comi et al., 2001).

Interferon-Alpha 2a was investigated by Myhr et al., (1999) in a randomized controlled pilot study design. The study had 97 people randomized to receive subcutaneous injections of placebo, low dose, and high dose Interferon-alpha 2a (IFN-
alpha 2a. IFN-alpha 2a treatment resulted in fewer new MRI lesions during the treatment period (p<0.003). The probability of no new lesions during treatment was greater than 2.5 times higher with high dose than with placebo (p<0.005). The median number of lesions at the end of treatment was lower with IFN-alpha 2a treatment than with placebo (p=0.030). The results demonstrated Interferon alpha 2a treatment significantly reduced disease activity as measured by gadolinium-enhanced MRI; however, the efficacy disappeared within six months after discontinuing treatment. No treatment effect was found on exacerbation rate or progression of disability. The adverse effects are headache, flu-like symptoms, fever, rigors, myalgia, and pain. Since the drug was able to reduce disease activity temporarily, perhaps further study will prove it to be a useful treatment.

Natural human interferon beta (n-hIFN beta) to reduce MS activity was investigated in 60 people with Relapsing-Remitting MS. People were randomized to receive either 33 micrograms of n-hIFN beta by subcutaneous route, three times per week, on alternate days, during one year, or no treatment during the first six months and then switched to the same treatment for the following six months. MRI and clinical parameters were used to monitor disease activity monthly. An intergroup analysis during the first six months of the study showed fewer active lesions and lower exacerbation rate in the treatment group than in the control group. Similarly, there were more exacerbation-free patients in the treatment group during this time. When switched to treatment, the control group showed a significant reduction in the number of active lesions (p = 0.00001) and the exacerbation rate decreased by half. Exacerbation-free persons more than doubled (p = 0.006) and the median time to first exacerbation was
significantly prolonged (96 vs > 180 days; p = 0.019). Treatment was extended for 12 additional months at a dose of 22 micrograms, once a week and disease activity persisted under control in 88% of patients. Treatment with n-hIFN beta was well tolerated, adverse events being mild and self-limiting. Several were analyzed for anti-IFN beta antibodies and neutralizing activity was found in 12% of the people after two years. The results of this phase II study show, that n-hIFN beta promotes a significant reduction of disease activity in Relapsing-Remitting MS as shown by both MRI and clinical variables, and that the treatment is well tolerated, with low antigenicity (Fernández et al., 1999).

Treatment for Relapsing-remitting Multiple Sclerosis with Copolymer 1 has been researched by Johnson et al., (1995). Copolymer 1 is also known as Copaxone, an acetate salt composed of four amino acids. The purpose of the study was to compare tolerance and therapeutic impact of daily subcutaneous injections over two years. The results demonstrated that Copolymer 1 significantly reduced the relapse rate in Relapsing-Remitting MS persons. In a study of 251 relapsing MS persons, Copaxone significantly reduced the relapse rate by 29% at two years and 32% at 35 months, with the most pronounced effects seen in people with less severe disability. Copolymer 1 was generally well tolerated with only injection site irritation. The researchers suggest that the only way to know if Copolymer 1 is any better than previous research on Interferon B-1b or if they can be used together, is to find new information on the natural history of MS, improve protocol design, and complete more studies. (The copolymer 1 Multiple Sclerosis Study Group, 1995).

Cladribine was studied by Rice, Filippi, and Comi (2000) for safety and efficacy in two different doses for progressive MS. The 159 study subjects, with a median
baseline EDSS score of 6.0, were randomly assigned to receive placebo or cladribine 0.07 mg/kg/day for five consecutive days every four weeks for either two or six cycles, followed by placebo, for a total of eight cycles. Thirty percent had Primary-Progressive PPMS and 70% had Secondary-Progressive SPMS. EDSS and Scripps Neurologic Rating Scale (SNRS) scores were assessed bi-monthly and MRI was performed every 6 months. The primary outcome measure was disability (mean change in EDSS). Mean changes in disability did not differ among the groups at the end of the 12-month double-blind phase. Both cladribine treatments were superior to placebo for the proportion of people having gadolinium-enhanced T1 lesions and for the mean volume and number of such lesions (p < or = 0.003). Differences were statistically significant at the six month evaluation time, with < or =90% reduction in volume and number of enhanced T1 lesions, which was maintained through final evaluation. This effect segregated largely with the SPMS group.

The T2 burden of disease showed a modest improvement in cladribine treated patients and worsened in placebo-treated persons. Most adverse events were mild or moderate in severity and not treatment limiting. No significant treatment effects were found for cladribine in terms of changes in EDSS or SNRS scores. Both doses of cladribine produced and sustained significant reductions in the presence, number, and volume of gadolinium-enhanced T1 brain lesions on MRI, and cladribine 2.1 mg/kg reduced the accumulation of T2 lesion load. Cladribine at doses up to 2.1 mg/kg was generally safe and well tolerated.

Novantrone (Mitoxantrone) is an antineoplastic agent approved for treating people with Secondary-Progressive MS. Novantrone is an immunosuppressive and
immunomodulating agent. It requires administration only once in three months, which is not only convenient for the person, but also cost-effective. The duration of therapy is usually limited to two to three years due to concern for possible cardiotoxicity (Jain, 2000). The role of mitoxantrone in escalating treatment of people with frequent and severe relapses and with rapid progression of disability is less clear. A retrospective analysis of 15 people with severe relapsing-remitting and secondary progressive MS was treated open-labeled with mitoxantrone. The people received mitoxantrone over a period of at least 12 months, with a single dose monthly for the first three months. Thereafter, infusions were repeated every 3 months. The annual relapse rate could be significantly reduced from 3.0 +/- 1.5 in the year before therapy to 0.5 +/- 0.5 during therapy. Stabilization was seen in 60% of people, while 27% showed an improvement of disability. The treatment was well tolerated with only minor side effects (Cursiefen, Flachenecker, Rieckmann, Toyka, 1999).

Many of the pharmacological treatments involving injections are very difficult for the person with MS. The side effects of daily injections, motivation to continue injections in the presence of pain, edema, and parathesia at injection site can be overwhelming. Motivation to continue injecting despite the side effects and often extreme costs, when feeling normal is difficult.

**Alternative treatments**

Several alternative therapies have been shown to be beneficial to people with Multiple Sclerosis. Nutritional therapy, massage, reflexology, magnetic field therapy, neural therapy, and psychological counseling have all been used as alternative treatments. These treatments are often not supported by clinical trials, but instead testimonials.
Neural therapy was used by Gibson (1999) in a double blind, placebo-controlled randomized study of 61 people. Neural therapy is a modified form of acupuncture in which an injection is given of small amounts of local anesthetic without adrenalin into specific trigger points in the ankles and around the greatest circumference of the skull. The results demonstrated 65 % of the people in the pilot and 76 % of the people in the double-blind trial benefited from the treatment. On the long-term follow-up of two to three and a half years more than 50 % of the patients continued to show improvement. Neural therapy was shown to be effective for immediate and long-term benefits, especially since it is nontoxic and inexpensive.

An intervention study using fish oil was conducted by Nordvik, Myhr, Nyland, and Bjerve (2000). The study consisted of 16 people diagnosed with Relapsing-Remitting MS in the last 12 months. The people were followed for two years and had a significant reduction in the mean annual exacerbation rate and the mean EDSS. The mean annual exacerbation rate for the two years was 0.06 (p>0.001). The mean EDSS score declined to 1.62 after the second year with 69% of people improving. Two persons had an exacerbation during the two years and also had a history of smoking >20 cigarettes per day. The researchers alluded to a possible connection between oxidative stress and disease activity.

The findings suggest that fish oil supplementation given together with vitamins and dietary advice can improve clinical outcome in people with newly diagnosed MS. The findings are difficult to apply since the study was open, uncontrolled, and on a small sample of people.
A pilot study using music therapy was completed by Wiens, Reimer, and Guyn (1999). The design was a randomized and controlled pilot study. The purpose of the music therapy is to improve respiratory muscle strength in people with advance MS by emphasizing diaphragmatic breathing and coordination of breathing and speech to instrumental music. A hand held battery powered device to measure mouth pressures measured the expiratory muscle tone. Respiratory muscle weakness is a major concern, since it can contribute to stasis of secretions, pneumonia, and a decrease in activities-of-daily living. Participants included 28 people with MS and 21 people without. The group with MS received music therapy and the other group attended music appreciation classes. The results demonstrated that music therapy was not statistically effective in improving the respiratory muscle strength of the people with advanced MS. The experimental group did have an improvement in expiratory muscle tone, whereas the control group showed only deterioration. Despite the lack of statistical significance this pilot study continues to build on prior research.

In recent years, thousands of MS persons have reported significant symptom relief through the alternative practice of bee venom therapy (BVT). For centuries BVT has been practiced in many eastern countries, including China, Japan, and Korea. The therapy involves repeated stings from honeybees to various parts of the body (MSAA, 2001).

BVT is being studied at Georgetown University Medical Center in Washington, DC by the Multiple Sclerosis Association of America (MSAA). It will be the first human scientific study under FDA-approved guidelines of honeybee (Apis melittin) venom therapy. The purpose of the study is to examine the safety and tolerance of honeybee
venom extracts as a possible therapy for people with progressive MS. Progressive MS persons are receiving two injections per week of honeybee venom extract for one year. Each study participant is undergoing monthly evaluations for safety and tolerance of the treatment. The study will determine dose-response relationships by giving known quantities of honeybee venom in calculated increasing doses. This study is only the beginning of scientific research on BVT and will need additional clinical research with double blind studies. BVT could prove to be a safe, alternative treatment for progressive MS persons (MSAA, 2001).

Physical rehabilitation was researched by Solari et al., (1999) in a single-blind, controlled, randomized on-going study. The purpose was to determine the efficacy of an inpatient physical rehabilitation program in clinically definite, out of exacerbation MS persons. The results demonstrated no changes in impairment in either group. The physical rehabilitation resulted in an improvement in disability and had a positive impact on mental components of health-related quality-of-life perception at three and nine weeks.

A meta-analysis of current occupational therapy related treatments was completed by Baker and Tujcke-Degnen in 2001. Their research found that occupational therapy-related treatments were effective in treating deficits associated with MS, particularly for outcomes in capacity, ability, and task related activities. The researchers note that further rigorous research is needed to fully understand its effectiveness.

The participants in the above treatment studies perceive their disease as serious and threatening to them. The people believe that by treating the disease they will have a
benefit of less exacerbations, disease progression, and disability. They were able to overcome barriers to action and begin dealing with their illness.

Case two

DM, a 35 year old female, presented for evaluation of numbness in her right arm, with subsequent numbness descending down the right leg causing an altered gait. She also complained of an electric shock sensation down her extremities when she flexed her neck. DM stated she had extreme fatigue and some vague vision changes for one week, which she attributed to being run down.

DM had a heart rate of 72, blood pressure of 126/64, and a respiratory rate of 22. Funduscopic examination revealed optic disk pallor, bilaterally. Retroocular movements were within normal limits. No nystagmus was noted. Saccadic and pursuit movements were normal. All other cranial nerves were intact.

Motor examination indicated paresis in the upper right extremity. Deep tendon reflexes were increased in the right upper and lower extremities. The person had a positive Romberg sign and mild ataxic gait. L’hermitte’s sign was positive.

Sensory examination revealed moderate vibratory sense loss in the distal upper right extremity, and a severe loss in the lower right extremity. Pin prick was intact. Proprioception was depressed in the fingers and toes of the right side of the body.

Diagnostics demonstrated CSF findings of a high IgG synthesis rate within the CNS and the presence of four-five oligoclonal bands. The MRI studies showed one enhancing white matter lesion and new developing lesions. The diagnosis was Clinically Probably Relapsing-Remitting Multiple Sclerosis.
The person was treated with 500 mg intravenous methylprednisolone for 3 days on an outpatient basis and then tapered on oral prednisone. She tolerated the treatment well and had marked improvement in her numbness, gait, and electric shock sensation. She was referred for a neurologist consult and treatment options.

**Application of Health Belief Model**

The Health Belief Model (HBM) is helpful for developing messages that are likely to persuade individuals to make healthy decisions. The practitioner can further look to the HBM to determine the barriers to a diagnosis and develop a concept of self-efficacy of the provider for guiding patients through the treatments of Multiple Sclerosis.

In case study one, AD, had been having neurological symptoms for over ten years and yet did not see a healthcare provider until forced to by a critical event, in this case a motor vehicle accident. Optic neuritis with vertigo was compounded by his left-sided weakness and numbness, urinary incontinence, and extreme fatigue. Significant findings that would alarm many people such as the inability to hold objects in their hands, significant tremors, and severe exhaustion, did not cause AD to seek health care.

AD was able to deny the possibility of having an adverse condition due to his socio-economics and knowledge level. Maybe at some point he considered the difficulties that would arise if he had a particular disease; however, he did not perceive the susceptibility or the seriousness of his condition. This prevented him from seeking a diagnosis and ultimately ten years of untreated demyelination of neurons. He also had barriers preventing him seeking action such as a “busy life style” and “lack of adequate health insurance”.

Case study two, DM, had a different perception of her illness than AD. She presented to a provider right away for evaluation of right arm and leg numbness, Lhermitte’s sign, extreme fatigue, and some vague vision changes. She had a high index of suspicion that she had an adverse condition. Some modifying factors contribute to her susceptibility such as her sex, age, personality, socioeconomic, and knowledge level. DM had external cues to action influencing her such as newspaper articles on MS and education from a friend with similar symptoms. DM had always received good medical care in the past and had reason to believe that presenting to a provider during the first episode of neurological symptoms would benefit her in some way.

**Summary**

Because Multiple Sclerosis is a diagnosis of exclusion, it can take some period of time before an adequate evidence of disease is apparent to the provider. Factors like not perceiving susceptibility, affect the health care provider, as well as the patient. It is important to recognize the symptoms, complete diagnostic testing, and begin treatment, as soon as possible to prevent further damage. Since MS is a disease characterized by relapsing and remitting, it is easy to believe when there are no symptoms, there is no pathology. This is simply not true, since the demyelination is a continuous process.

This article reviewed MS through application of the Health Belief Model and described how the patient and provider are affected. The pathologic process and clinical presentation was discussed to guide the health care provider. The process of determining a diagnosis and preparing the patient for various tests was listed. Treatment options in traditional medicine and alternative practices were provided with research results.
The Health Belief Model helps the clinical health care provider to understand what the person with suspicious symptoms may be feeling and why. It is easy for a person to ignore pains and deny vision problems if they fear the diagnosis of MS. As a health care provider it is important to recognize people that are in delay of care, have lack of motivation to seek care or be treated, and improper utilization of medical services. If the health care provider is not able to overcome the barriers to diagnosis MS then it is the MS person that suffers for the delay in treatment.

Even though Multiple Sclerosis does not yet have a cure, the odds of a longer life with less relapses, disability, and disease progression are now possible. The pathology is becoming increasingly better understood and with that treatment will become better. New research is coming out frequently, making the hopes of a cure more promising.

Multiple Sclerosis has always been an important pathology to me personally. I have taken care of many patients with MS, as well as had close friends who have been living with the disease for years. Extensive research is underway with new drugs and modifying treatments, which will one day, change the course and prognosis of MS.
TABLE 1: Health Belief Model*

<table>
<thead>
<tr>
<th>Concept</th>
<th>Definition</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perceived</td>
<td>One's opinion of chances of getting a condition</td>
<td>Define population(s) at risk, risk levels; personalize risk based on a person's features or behavior; heighten perceived susceptibility if too low.</td>
</tr>
<tr>
<td>Susceptibility</td>
<td></td>
<td>Specify consequences of the risk and the condition.</td>
</tr>
<tr>
<td>Perceived</td>
<td>One's opinion of how serious a condition and its sequelae are</td>
<td>Define action to take; how, where, when; clarify the positive effects to be expected.</td>
</tr>
<tr>
<td>Severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceived</td>
<td>One's opinion of the efficacy of the advised action to reduce risk or seriousness of impact</td>
<td>Identify and reduce barriers through reassurance, incentives, and assistance.</td>
</tr>
<tr>
<td>Benefits</td>
<td>One's opinion of the tangible and psychological costs of the advised action</td>
<td></td>
</tr>
<tr>
<td>Perceived</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barriers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cues to Action</td>
<td>Strategies to activate &quot;readiness&quot;</td>
<td>Provide how-to information, promote awareness, reminders.</td>
</tr>
<tr>
<td>Self-Efficacy</td>
<td>Confidence in one's ability to take action</td>
<td>Provide training, guidance in performing action.</td>
</tr>
</tbody>
</table>

Becker, 1974
TABLE 2: Differential Diagnosis

<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
<th>Labs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B-12 deficiency</td>
<td>Decreased Vitamin B-12 level</td>
</tr>
<tr>
<td>Vitamin E deficiency</td>
<td>Decreased Vitamin E level</td>
</tr>
<tr>
<td>Infectious process, Anemia</td>
<td>CBC with Manual differential</td>
</tr>
<tr>
<td>Hypothyroid, Hypoparathyroidism,</td>
<td>Endocrine panel (decreased TSH, decreased PTH</td>
</tr>
<tr>
<td>Lyme Disease</td>
<td>IFA or ELISA to detect specific antibodies to B burgdorferi in serum</td>
</tr>
<tr>
<td>Allgrove’s syndrome,</td>
<td>Decreased Cortisol level</td>
</tr>
<tr>
<td>Adrenoleukodystrophy</td>
<td>History of viral infection, MRI</td>
</tr>
<tr>
<td>Postinfectious Encephalomyelitis</td>
<td>RPR</td>
</tr>
<tr>
<td>Tertiary Syphilis</td>
<td></td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>CSF for oligoclonal bands and elevated IgG, MRI, EVT</td>
</tr>
<tr>
<td>Primary Central Nervous System Vasculitis</td>
<td>Elevated protein in CSF, Elevated sedimentation rate</td>
</tr>
<tr>
<td>Systematic Lupus Erythematosus</td>
<td>Elevated WBC, hematuria on UA, elevated sedimentation rate</td>
</tr>
<tr>
<td>Tropical Spastic Paraparesis</td>
<td>History of time in Caribbean Sea Basin, MRI</td>
</tr>
<tr>
<td>Sarcoidosis and Sjogren’s Syndrome</td>
<td>MRI, Chest x-ray, oligoclonal bands and elevated IgG in CSF</td>
</tr>
<tr>
<td>Leukodystrophies of Adulthood</td>
<td>MRI</td>
</tr>
<tr>
<td>Olivopontocerebellar degeneration,</td>
<td>MRI, CSF</td>
</tr>
</tbody>
</table>

NOTE: complete blood count (CBC), thyroid stimulating hormone (TSH), parathyroid hormone (PTH), immunofluorescence assay (IFA), immunosorbent assay (ELISA), Neuroimaging (MRI), Rapid plasma regain (RPR), Cerebral Spinal Fluid (CSF), evoked potential testing (EVT), urinary analysis (UA), white blood cell (WBC)
<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Patient Preparation</th>
<th>Patient Teaching</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>Remove watches, tapes, credit cards, jewelry, anything with metal, no pacemaker patient, or patients with metal implants, void before procedure can take up to an hour</td>
<td>No risk of radiation. Patient is on a moving pallet, which is pushed into large cylinder containing a magnet. Patient may have some anxiety related to claustrophobia and will hear a variety of noises. MRI may be with or without contrast. If contrast is used patient will have to drink the dye and have it inserted intravenously. Patient will need to drink increased H2O intake to flush from body</td>
</tr>
<tr>
<td>CBC with manual differential</td>
<td>Prepare for blood draw</td>
<td>This test will identify an increased WBC indicating infection, types of anemia, blood loss, and lead poisoning</td>
</tr>
<tr>
<td>Vitamin E level</td>
<td>Prepare for blood draw</td>
<td>This test can identify a diet restricted in saturated fat</td>
</tr>
<tr>
<td>Vitamin B12 level</td>
<td>Prepare for blood draw</td>
<td>A deficiency may be caused by pregnancy, oral contraceptives, lack of animal protein, and alcohol abuse</td>
</tr>
<tr>
<td>TSH</td>
<td>Prepare for blood draw</td>
<td>This test will identify hypo and hyperthyroid</td>
</tr>
<tr>
<td>PTH intact</td>
<td>Prepare for blood draw</td>
<td>This test is to evaluate for hypercalcemia, parathyroid function, and calcium metabolism</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Prepare for blood draw. Levels should be drawn in the morning with patient at rest after fasting. Dilantin will interfere with the test</td>
<td>This test can identify a pituitary tumor, other malignant tumors, long-term corticosteroid use, Addison's disease, AIDS</td>
</tr>
<tr>
<td>Test</td>
<td>Procedure</td>
<td>Notes</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>----------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Lyme disease IFA or ELISA</td>
<td>Prepare for blood draw</td>
<td>Lyme disease is characterized by fever, migratory arthralgias, arthritis, neurological complications, and carditis.</td>
</tr>
<tr>
<td>RPR</td>
<td>Prepare for pelvic exam. Serum must be expressed from the base of a lesion</td>
<td>Tests are positive 3-4 weeks after exposure. If syphilis is not detected early it can spread causing neurological problems, blindness, death, and can be passed to a fetus.</td>
</tr>
<tr>
<td>Oligoclonal Banding CSF</td>
<td>Prepare for lumbar puncture by positioning, informing, and relaxing. Signed consent must be taken from patient. Local anesthetic will be used on site</td>
<td>Oligoclonal bands on CSF are typical, but not pathognomonic for MS. Patient will be maintained supine for few hours to avoid headache.</td>
</tr>
<tr>
<td>EVT</td>
<td>Prepare for the placement of small electrodes on the head to monitor brain waves</td>
<td>Evoked potentials measure the time required by the brain to receive and process nerve messages.</td>
</tr>
</tbody>
</table>

NOTE: complete blood count (CBC), thyroid stimulating hormone (TSH), parathyroid hormone (PTH), immunofluorescence assay (IFA), immunosorbent assay (ELISA), neuroimaging (MRI), rapid plasma regain (RPR), cerebral spinal fluid (CSF), evoked potential testing (EVT), white blood cell (WBC), acquired immune deficiency (AIDS)
Table 4: Sensitivity and Specificity

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Sensitivity and Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>100% specific and sensitive to lesions in CNS</td>
</tr>
<tr>
<td>CBC with manual differential</td>
<td>100% specific and sensitive to decreased or increased CBC</td>
</tr>
<tr>
<td>Vitamin E level</td>
<td>100% specific and sensitive to decreased or increased PTH</td>
</tr>
<tr>
<td>Vitamin B12 level</td>
<td>100% specific and sensitive to decreased or increased B12</td>
</tr>
<tr>
<td>TSH</td>
<td>100% specific and sensitive to decreased or increased TSH</td>
</tr>
<tr>
<td>PTH Intact</td>
<td>100% specific and sensitive to decreased or increased PTH</td>
</tr>
<tr>
<td>Cortisol</td>
<td>100% specific and sensitive to decreased or increased cortisol</td>
</tr>
<tr>
<td>Lyme disease IFA, ELISA</td>
<td>Sensitivity is 40-60 % and can be nonspecific</td>
</tr>
<tr>
<td>Syphilis RPR</td>
<td>It is more sensitive than VDRL 93% of patients with primary syphilis have positive tests</td>
</tr>
<tr>
<td>Oligoclonal Banding CSF</td>
<td>90% sensitivity for MS, but not specific</td>
</tr>
</tbody>
</table>

NOTE: complete blood count (CBC), thyroid stimulating hormone (TSH), parathyroid hormone (PTH), immunofluorescence assay (IFA), immunosorbent assay (ELISA), neuroimaging (MRI), rapid plasma regain (RPR), cerebral spinal fluid (CSF), evoked potential testing (EVT), white blood cell (WBC), Veneral disease research laboratory (VDRL)
Table 5: Labs and costs

<table>
<thead>
<tr>
<th>Lab</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood draw fee</td>
<td>$16.65</td>
</tr>
<tr>
<td>CBC with manual differential</td>
<td>$23.70</td>
</tr>
<tr>
<td>Vitamin E level</td>
<td>$55.55</td>
</tr>
<tr>
<td>Vitamin B-12 level</td>
<td>$65.00</td>
</tr>
<tr>
<td>TSH level</td>
<td>$39.00</td>
</tr>
<tr>
<td>PTH Intact</td>
<td>$188.85</td>
</tr>
<tr>
<td>Cortisol Level</td>
<td>$62.90</td>
</tr>
<tr>
<td>Lyme Disease (if in risk group) IFA, ELISA</td>
<td>$63.20</td>
</tr>
<tr>
<td>Syphilis RPR (If in risk group)</td>
<td>$9.60</td>
</tr>
<tr>
<td>Oglial Banding CSF</td>
<td>$67.86</td>
</tr>
<tr>
<td>Total</td>
<td>$451.65</td>
</tr>
</tbody>
</table>

NOTE: complete blood count (CBC), thyroid stimulating hormone (TSH), parathyroid hormone (PTH), immunofluorescence assay (IFA), immunosorbent assay (ELISA), rapid plasma regain (RPR), cerebral spinal fluid (CSF), white blood cell (WBC)
Figure 1: Diagnosis and Treatment Algorithm for Multiple Sclerosis

H & P exam key points of presentation:
- Patient presenting with weakness, numbness, tingling, or unsteadiness in a limb
- Patient presenting with spastic paraparesis, retrobulbar neuritis, diplopia, disequilibrium
- Patient presenting with sphincter disturbance, urinary urgency or hesitancy

H & P QUESTIONS
- Is patient < age 55?
- Does Pt have any close relatives with MS?
- Does Pt live in temperate climate?

LABS
- CBC with Manual diff
- Vitamin E level
- Vitamin B12 level
- TSH
- PTH Intact
- Cortisol
- Lyme disease
- Syphilis RPP

IMAGING
- MRI of brain or cervical cord to demonstrate multiplicity of lesions
- MRI with myelopathy alone can exclude a congenital or acquired surgically treatable lesion
- Diagnosis of MS can be made if evidence of multiple lesions in CNS

If all negative continue with congenital or acquired imaging studies, lumbar puncture, or monocular visual stimulation

If MRI is negative for lesions then Multiple Sclerosis is ruled out
References


