TAKE HOME MESSAGES

1. Multiple sclerosis is an inflammatory disease of the central nervous system that initially affects CNS myelin but concurrently also results in axonal degeneration.

2. The course of the disease is highly variable and does not necessarily lead to major disability. However, truly “benign MS” is a clinical rarity.

3. Permanent CNS damage occurs early in the disease due to loss of axons and associated glial scarring. Thus early treatment of MS, even in the absence of any disability, is necessary.

4. Much disease activity can occur “silently” without immediate clinical consequences. Yet such “silent” disease can, over time, lead to scarring and brain atrophy. It is thus important to closely monitor patients, even those who are clinically stable.

5. MS may not be one disease but a syndrome with multiple genetic and environmental factors involved in its pathogenesis.

6. Long term immune modulating treatments are now available to reduce the presumed autoimmune attack on CNS myelin, and are capable of changing the course of disease. Such treatments are most effective early in the course of the disease.

I Definitions

A. Myelin: Myelin is a trilaminar proteolipid composed of proteins, phospholipids, cholesterol, cerebrosides, and sulfatides. Hydrophilic protein monolayers comprise myelin’s inside and the outside surfaces with a hydrophobic lipid layer in the middle. There are two forms of myelin. One is in the central nervous system, the other in the peripheral nervous system. While similar chemically, they differ antigenically and only rarely do immune reactions against one form of myelin cross-react with the other.

i. Oligodendrocytes: Oligodendrocytes produce myelin in the central nervous system. This myelin is anatomically and biochemically slightly different from peripheral nervous system myelin. A single oligodendrocyte myelinates up to 12 to 15 axons. Thus, the death of one oligodendrocyte can cause widespread axonal dysfunction.

B. Schwann Cell: This is the cell producing myelin in the peripheral nervous system. A single Schwann cell produces myelin only for a single axon.

C. Dysmyelination: In this condition abnormal myelin is formed. As a result, myelin breaks down. Such conditions usually affect infants and children. Examples of dysmyelinating neurologic diseases are metachromatic leukodystrophy, adrenal leukodystrophy and phenylketonuria.

D. Demyelination: In this condition apparently normal myelin is destroyed while axons are relatively spared. Demyelination is a relatively nonspecific reaction of the central nervous system to a variety of stresses. Some causes of demyelination are toxic metabolic causes (e.g., hexachlorophene toxicity), nutritional causes (e.g., vitamin B12 deficiency) and chronic viral infections (e.g., progressive multifocal leukoencephalopathy). Immune or allergic reactions can also produce demyelination. The prototypic disease for this is multiple sclerosis (MS). While myelin is the initial target of the disease process in MS, demyelinated axons are very susceptible to the toxic cytokines generated in these areas and are destroyed early in the disease. Such changes are irreversible.
E. **Plaques:** The demyelinated and scarred regions of white matter that are the hallmark of MS. They consist of areas almost devoid of myelin and axons and are comprised predominantly of astrocytes. They are the end stage of the destructive inflammatory process and are irreversible. Not all inflammation in MS leads to plaques. Some remyelination can be seen in areas of milder inflammation (“shadow plaques”).

II. **Basic Concepts**

i. Multiple sclerosis is the prototypical and by far the most common demyelinating disease. The demyelination occurs only in the CNS, i.e., brain and spinal cord. The pathological hallmark of the disease is inflammatory, multifocal demyelination.

1. Any white matter region can be affected, but some areas are preferentially involved such as the periventricular white matter and the corpus callosum. In rare instances demyelination may be limited to the optic nerves and spinal cord (Devic’s Disease).

2. MS is predominantly a disease of young adults between the ages of 18 and 50. It may occur earlier or later but this is unusual. In relapsing remitting MS there is a preponderance of the disease in women with a female: male ratio of 2-3:1.

ii. Pathologically, the demyelination of MS appears to be caused by immunological mechanisms directed at myelin and oligodendrocytes.

1. Demyelination may be the end stage of the pathophysiologic process. The earliest abnormality noted in regions of demyelination is an infiltration of the perivenular (i.e., around veins) white matter by inflammatory cells, mainly T cells. T cells then migrate into the surrounding white matter, followed by migration of B cells and macrophages. As noted above, this occurs in a multifocal fashion throughout the central nervous system. As a result of demyelination, axons also are destroyed, leading to neuronal changes too. In response to the inflammation at the site of demyelination, there is a proliferation of astrocytes and the formation of dense glial scars (plaques).

iii. Demyelination causes neurological symptoms by altering conduction in CNS axons and by destruction of axons.

1. Demyelination results in metabolic abnormalities of axons, causing greatly reduced nerve conduction velocities and eventually conduction blocks. These alterations in conduction increase with increases in core body temperature. Thus, with fevers, hot ambient temperatures, or exertion, persons with MS can experience a reappearance or worsening of previous neurologic symptoms. Such changes are not true relapses but “pseudoexacerbations” and can rapidly reverse as body temperature decreases.

II. **Histories**

**Case 1**

A 37-year-old woman is referred to her neurologist because of pain in the right half of her face. The pain began abruptly one week prior to consultation. It is characterized as a sharp, electric,
shooting sensation which radiates from her lip into her cheek. It can be precipitated by chewing, or touching the lip.

Past medical history reveals that at age 18, the patient had a one week episode of numbness in both hands associated with an uncomfortable “buzzing” sensation when she flexed her neck. She was diagnosed as having a “stress reaction”. Five years prior to her present symptoms, the patient had a two week episode of numbness and tingling in both lower extremities which ascended to the mid thoracic region. This occurred three months after the birth of her second child. Symptoms were attributed to “post partum depression”.

On physical examination, the patient has disconjugate gaze on looking laterally to either side, with bilateral loss of adduction. This is associated with brisk nystagmus in the abducting eyes. There is mildly decreased light touch sensation in the second division of the right trigeminal nerve. Station and gait, motor testing and cerebellar function are normal bilaterally. Deep tendon reflexes are hyperactive throughout. There are bilateral Babinski responses.

Case 2

The patient is a 49-year-old gentleman referred to his neurologist because of increasing difficulties with walking.

Very gradually, over the ensuing five years, the patient noted increasing difficulties with walking manifested by dragging of his right foot. At first this was noticeable only when jogging. Recently it became noticeable when walking distances as short as one half mile. Associated with the dragging of his right foot are feelings of numbness in both lower extremities, described as “burning and prickling sensations”. These ascend to the thighs bilaterally and are relieved with rest. In addition, the patient notes increasing difficulties with bladder urgency, frequency and urge incontinence. Sexual impotence has been present for 16 months.

Past medical history is noncontributory. There is a strong family history of multiple sclerosis. The patient’s mother as well as a maternal aunt both have this illness.

On physical examination, cranial nerve testing reveals optic disc pallor on the left. There is mild intermittent head tremor. Extraocular movement examination reveals brisk vertical nystagmus on upward gaze. Station and gait examination reveals a moderate broadening of the patient’s base with stiffness and circumduction of the right leg. The patient is able to walk on heels and toes but is unable to tandem walk. On Romberg testing, the patient falls to the right. Motor examination reveals a mild, spastic catch in the right upper extremity with normal strength in both upper extremities. Tone is moderately increased in the right lower extremity with spasticity. It is mildly increased in the left lower extremity, also with spasticity. Hip flexor strength is 4/5 on the right and 5/5 on the left. Hamstring function is normal bilaterally. On cerebellar testing, there is mild dysmetria in the left upper and lower extremities. Deep tendon reflexes are brisk throughout with 8 or 9 beats of right ankle clonus and two to three beats of left ankle clonus. There are bilateral Babinski responses.

III. Clinical Concepts

A. The symptoms of MS reflect the multifocal nature of the pathologic changes.

1. Symptoms: Because MS is multifocal, a large number of symptoms may occur. Especially common symptoms are:
   a. Sensory symptoms, e.g. paresthesias and dysesthesias
   b. Cerebellar dysfunction with intention tremor and ataxia
   c. Pyramidal tract dysfunction with spasticity and weakness
   d. Cranial nerve symptoms with decreased visual acuity (optic nerves) or diplopia (oculomotor pathway),
e. Bowel, bladder and sexual dysfunction.
f. Fatigue

2. While pain is not common in multiple sclerosis, it can occur if demyelination of the trigeminal nerve or spinothalamic tracts are present. The latter abnormality may be associated with painful, burning dysesthesias (causalgia).

3. Signs: Mirroring the symptoms of MS are a wide variety of neurologic abnormalities on physical examination. No physical finding per se is pathognomonic of multiple sclerosis. Evidence of corticospinal tract dysfunction in the form of hyperreflexia and Babinski responses is very common as is cerebellar dysfunction with ataxia, dysmetria and dysarthria. Spinothalamic tract abnormalities with numbness and tingling are very frequent. Extraocular movement abnormalities in the forms of internuclear ophthalmoplegia, nystagmus or irregular tracking saccades, may be present along with evidence of optic atrophy (pallor of the optic disk on funduscopic exam). Many of the above signs may be present without associated symptoms (for example optic nerve pallor may be present without changes in vision).

B. Symptoms and signs of multiple sclerosis may appear abruptly (acute exacerbations) or very gradually (chronic progressive course) and may improve spontaneously (remissions).

1. The ‘triggers” for exacerbations are not known but infections are the best documented triggers, presumably due to activation of the immune system, resulting in increased inflammation and demyelination. The post-partum period also is associated with a higher frequency of relapses. Remissions may be due to:
   a. areas of abnormal myelin healing prior to actual demyelination and axonal loss.
   b. Remyelination.
   c. Alternate areas of the brain assuming the function of the demyelinated region (brain plasticity).

2. Multiple sclerosis is very pleomorphic disease, in terms of the temporal pattern of the disease, and there is no “typical” course. Some patients may have sufficiently mild symptoms as to go undiagnosed during life. Instances have been reported of patients dying of other causes who had the pathologic changes of multiple sclerosis with no antecedent history. This is very rare. Most patients will either have a relapsing-remitting course (80%) while about 20% will have a gradually progressive course from onset, without attacks or remissions (Primary Progressive MS). In relapsing-remitting MS, patients will note the fairly sudden onset of neurologic symptoms which may persist for days to months. Symptoms may gradually subside to varying degrees but some may not resolve completely. Patients with primary progressive MS usually note a gradual onset of neurologic symptoms that progressively increases over time with no evidence of remission. A small number of patients will have a combination of exacerbating, remitting and chronic progressive symptoms. About 40-50% of patients with an initially relapsing-remitting course will experience a change in the pattern of their disease to one of gradual progression (Secondary Progressive MS). The reason for this change is not known.
C. Demyelination can occur “silently,” without symptoms. Detection of these silent lesions are of great diagnostic value.

1. Multifocal abnormalities may be seen with CT scan, MRI scan and with evoked response testing. If findings suggestive of multifocal demyelination are found in patients presenting with their first time neurologic episode, this helps in establishing the diagnosis of MS. Many patients in apparent clinical remission will have “silent” demyelination, with progressive accumulation of lesions on MRI in the absence of changes by history or exam. The long term effects of continued demyelination, even if clinically silent, are increasing scarring and loss of brain tissue with resulting atrophy. Eventually more subtle neurologic symptoms may arise such as increasing cognitive impairment and increasing fatigue.

B. Multiple sclerosis is not an inevitably paralyzing disease.

1. In over two thirds of individuals, only mild to moderate disability will be present after 20 to 30 years of disease. The severe paralyzing form of the disease is, fortunately, relatively uncommon. Factors suggesting a milder course of disease are younger age of onset and the predominance of sensory symptoms. Factors increasing the likelihood of severe disease are an older age of onset, the early presence of motor symptoms, and lack of complete remission between attacks. However, patients with truly “benign MS” are very rare and can only be diagnosed in retrospect. Thus, all cases of active MS should be considered potentially disabling and should be considered for treatment.

IV. Diagnosis and Diagnostic Tests

A. The diagnosis of multiple sclerosis is a clinical diagnosis, with laboratory tests assisting in confirming the diagnosis of a progressive, multifocal, inflammatory disease of the central nervous system. In addition other disease causing similar changes must be excluded. Symptoms alone are not sufficient to make a diagnosis of MS. There must be objective evidence, either on exam or on laboratory studies, for a progressive, multifocal, inflammatory disease of the central nervous system. As a corollary, “spots” alone on MRI, in the absence of clinically supportive data, are not sufficient to diagnose MS.

1. There is no single diagnostic test that is pathognomonic for multiple sclerosis.

2. The essential diagnostic tools are the history and the physical examination. They must indicate the presence of progressive central nervous system dysfunction that is disseminated in time and space. As noted above, symptoms alone are not sufficient to diagnose MS.

3. Since demyelination can occur on a subclinical level, laboratory tests are useful in demonstrating evidence of subclinical, multifocal CNS dysfunction.

4. Electrophysiological tests that can show abnormal CNS nerve conduction are:
   a. Visual evoked responses. These are used to show neurophysiologic evidence of optic nerve dysfunction.
   b. Brainstem auditory evoked responses demonstrate the presence of abnormalities of brainstem auditory pathways
   c. Somatosensory evoked responses can demonstrate evidence of dysfunction of central nervous system sensory pathways.
2. Imaging techniques that can show plaques are CT scanning and MRI scanning. MRI is greatly superior to CT scanning in this regard and CT scans are no longer routinely used to evaluate patients with MS. Injection of magnetic contrast medium, such as gadolinium, at the time of MRI is also of great value in showing areas of blood-brain barrier breakdown that can indicate sites of acute inflammation. However, many conditions can cause “spots” on MRI and demyelination cannot be diagnosed unequivocally with either CT or MRI. Some other conditions that can cause multifocal CNS spots are trauma, brain infarcts, migraines, infections, and neoplastic disease. Thus, “spots” alone cannot make a diagnosis of MS. Nevertheless, in the appropriate clinical setting, the demonstration of multifocal lesions in the white matter of the brain and spinal cord, with associated contrast enhancement of some of the lesions, may indicate areas of inflammation and demyelination and can corroborate a diagnosis of MS.

B. An immune abnormality in cerebrospinal fluid is found in multiple sclerosis.

1. Examination of the CSF is of great importance. The abnormalities most frequently found in patients with MS indicate the presence of a low grade, chronic inflammatory process in the CNS. Such changes are not pathognomonic for the disease, and can be seen in other chronic inflammatory CNS conditions such as CNS Lyme Disease and chronic viral infections. However, if other causes for these abnormalities can be eliminated, the diagnosis of multiple sclerosis is strengthened. The specific inflammatory changes noted are:

   a. A mild to moderate pleocytosis, predominantly of lymphocytes. Numbers are almost always less than 50 cells per mm$^3$.
   b. Oligoclonal banding of CSF immunoglobulins using the PAGE technique.
   c. An elevated spinal fluid gamma globulin or IgG index.
   d. An elevated IgG synthesis rate.
   e. Least valuable is the myelin basic protein level.

The longer a person has MS, the greater the likelihood of having these changes (>90%). Conversely, in patients with early MS, the CSF may be normal.

V. Epidemiology of MS

A. The geographic and racial distributed of MS is not uniform.

1. MS is not distributed uniformly throughout the world. It is found predominantly in northern and southern temperate zones. Within these zones there are particular high risk areas. Minnesota is one such high risk zone. If one lives in a high risk area but leaves that area before age 13, one acquires the risk of the area to which one moves. If one leaves a particular risk area after age 13, one takes with him the risk of that area. This observation suggests that an early environmental exposure is an important determining factor for the development of the disease. Such a factor may be an infectious agent such as a virus. Indeed, epidemics of the disease have been reported in conjunction with the appearance of foreigners into a geographically secluded region.
2. MS is rare in certain racial groups. These include African blacks, Native Americans and Gypsies. The relative resistance of these groups to MS may result from an absence of particular susceptibility genes in these populations.

VI. Pathogenesis

A. The etiology of MS is unknown. Viral and immunologic factors or some combination of the two are important. An underlying genetic predisposition is also reported. Some evidence for these views is given below:

Genetics:

1. 75-80% percent of cases of multiple sclerosis are sporadic, with no other family members effected. However, if taken to the level of first cousins, up to 25% percent of MS occurs in multiple generations. In addition there is a high concordance rate for MS in identical twins (25-40%). Clinically, there does not appear to be any difference between familial and nonfamilial MS.

2. HLA phenotyping of MS patients has revealed a preponderance of particular phenotypes in these patients. The clustering is especially prominent for certain HLA-D and DR phenotypes. Thus, MS patients of Northern European extraction have a very high frequency of DR-2 antigens. Different DR antigen phenotype clusters have been noted in other groups of MS patients such as Italians and Japanese. Such clustering of particular DR antigen phenotypes in MS patients suggests that certain “MS susceptibility genes” are located in or near the group of major histocompatibility genes. Most data indicate that multiple genes are involved in determining susceptibility to MS.

3. Viral: Multiple sclerosis has been postulated to be the result of a persistent viral infection of the central nervous system. For unknown reasons the virus either suddenly reappears, causing destruction of oligodendrocytes with associated demyelination or alters myelin antigens such that they become targets of immune attack. There are several human and experimental animal diseases exist that demonstrate such a pattern.

4. Immune: Another theory states that MS is an autoimmune disease, with associated immunologic attack on central nervous system myelin. This occurs periodically for reasons that are not clear, resulting in multifocal regions of demyelination. Again, there are experimental and human diseases that result from autoimmune demyelination, supporting this hypothesis in MS.

5. A combination of these two theories best explains the pathogenesis of MS. A persistent viral infection may alter the immune response or myelin antigens in such a way as to result in an autoimmune attack on central nervous system myelin.

VII. Treatments

A. There is no cure for MS but there are many effective treatments. Treatments can be divided into two categories, those directed at the underlying disease process and those directed towards alleviating symptoms.
1. Since an immune reactivity to myelin antigens may be fundamental to the etiology of MS, various medications aimed at suppressing immune function are used. In the past 10 years several new treatments have been brought to market that can significantly alter the course of the 80% of MS patients with relapsing-remitting MS. These are the beta-interferons (Avonex, Betaseron, and Rebif) and the non-interferon, glatiramer acetate (Copaxone). Recently the chemotherapeutic agent mitoxantrone (Novantrone) was approved by the FDA for treatment of severe relapsing remitting MS and secondary progressive MS. There are no proven treatments for patients with primary progressive MS.

2. The are other treatments, such as cyclophosphamide, methotrexate, intravenous IgG, and azathioprine that are used but are not definitively proven to be effective and so must be considered relatively experimental. Even more experimental are protocols aimed at decreasing the activity of particular populations of T cells. These include the use of monoclonal antibodies specific for either helper T cells or T cells in general. Such therapies would be preferable to more generalized immune suppressants.

3. Since MS is an inflammatory disease, corticosteroids are used to treat acute attacks with the intent of shortening the duration of an attack and to minimizing the formation of glial scars. Either oral corticosteroids in the form of prednisone, or intravenous steroids, in the form of high dose methylprednisolone, are used in most instances. Continuous, long term corticosteroids do not alter the course of the disease and have no role in the management of MS patients. Pulse corticosteroids may have an effect and are being studied.

4. A large number of symptomatic therapies are available to treat MS. Thus, patients with spasticity may be helped by antispasticity drugs such as benzodiazepines, baclofen, and tizanidine. Patients with spastic bladder and bladder urgency and frequency may be helped by anticholinergics (such as oxybutynin and amitriptyline) which reduce bladder detrusor tone. Emotional lability is alleviated with tricyclic drugs. Fatigue is lessened with amantadine or modafinil. Stool softeners help the constipation. Physical therapy and conditioning are essential in maximizing a person’s physical abilities.

5. Since multiple sclerosis often is a spontaneously remitting disease with a variable course, therapeutic trials of new agents must involve a double blind controlled protocol with sufficiently large number of patients followed for a sufficiently long periods of time to prove their effectiveness.

VIII. **Summary**

MS is the prototypical and most common demyelinating disease of the CNS. It is characterized by multifocal involvement of the CNS white matter. In 80% of individuals it is characterized by a relapsing-remitting course with exacerbations and remissions. In half of these individuals the course can change to one of secondary chronic progression. Most patients with MS do not experience severe disability. The diagnosis of MS is, to a large extent, one of exclusion, with a need to establish the presence of a multifocal, progressive, inflammatory central nervous system
disease that cannot be explained by other disease processes. There are effective treatments available that are aimed at modulating the activities of the immune system and at decreasing the rate of disability. Treatment must be initiated early in the course of disease to minimize the accumulation of scar tissue and other irreversible changes in the CNS. There are many ways to symptomatically manage MS, resulting in better quality of life for these individuals.

**Recapitulation of Principles (or “take home lessons”):**

1. Multiple sclerosis is an inflammatory disease of the central nervous system that initially effects CNS myelin but concurrently also results in axonal degeneration.
2. The course of the disease is highly variable and does not necessarily lead to major disability. However, truly “benign MS” is a clinical rarity.
3. Permanent CNS damage occurs early in the disease due to loss of axons and associated glial scarring. Thus early treatment of active MS, even in the absence of any disability, is necessary.
4. Much disease activity can occur “silently” without immediate clinical consequences. Yet such “silent” disease can, over time, lead to scarring and brain atrophy. It is thus important to closely monitor patients, even those who are clinically stable.
5. MS may not be one disease but a syndrome with multiple genetic and environmental factors involved in its pathogenesis.
6. Long term immune modulating treatments are now available to reduce the presumed autoimmune attack on CNS myelin, and are capable of changing the course of disease. Such treatments are most effective early in the course of the disease.

**IX. References**


**X. SAMPLE EXAM QUESTIONS**

A 28-year-old pediatric resident developed severe back pain over several days, with retention of urine and weakness in the lower extremities. On examination he had normal mentation and cranial nerve function. Motor, sensory and reflex examinations were normal in the upper extremities. There was weakness of both lower extremities, with brisk reflexes and extensor plantar responses bilaterally. There was complete loss of pinprick sensation in a band around the mid-trunk. Vibration and proprioception were normal at the fingers and toes.

1. Given the motor examination, which of the following sites is most likely involved in the patient’s disorder?
   a. Thoracic cord
   b. Medulla
   c. Bilateral cerebral hemispheres
   d. Anterior horn cells
   e. Polyradiculopathy

On year later, the same man developed a peri orbital headache that increase over a period of days to become quite unbearable. Associated with the pain, he had loss of visual acuity in temporal and nasal fields of the right eye.

2. The visual defect in this patient localizes to which of the following structures?
   a. Right optic nerve
   b. Right optic tract
   c. Optic chiasm
   d. Left lateral geniculate
   e. Left occipital cortex
3. Assuming normal serological testing, and multiple lesions with high T2-signals on MRI, what can be said about the underlying disease process?
   a. It is an inherited disorder of peripheral and central myelin
   b. It is approximately equally common in all ethnic groups.
   c. There is an infectious etiology in all cases.
   d. It is an acquired disorder of peripheral and central myelin
   e. Less than 10% of cases are familial.