

A PRACTICAL PRIMER

# Multiple Sclerosis for the Physician Assistant

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# Forward

From the time of its seminal description by Charcot in 1868, MS remained principally enigmatic and refractory to treatment until the early 1990s. With the advent of novel treatments to reduce both the clinical and subclinical aspects of the disease process, we have entered a new and more hopeful era of possibilities that promise to transform the traditional rubric of MS from an almost uniformly disabling disease that has exacted its ravages upon the unsuspecting, to a disorder that can be diagnosed with great precision, and subsequently treated with greater and greater efficacy. An enormously important dividend of disease-modifying therapy is the corresponding reduction in the enormous diversity of disease related symptoms and their associated disability.

This book has been prepared for the purpose of equipping the physician assistant (PA) with the fund of knowledge on the diagnostic and multidisciplinary treatment principles that represent a new standard of care for a disorder that for so long has eluded our efforts to halt the perpetuation of physical, intellectual, and even spiritual deterioration. These are families and communities at risk. PAs, given their unique training and alliance with physicians and other members of the care team (nurses, nurse practitioners, social workers, etc.), are endowed with abilities that can be powerfully leveraged on behalf of the MS patient, and the MS care team.

For the last sixteen years, the MS Program and Clinical Center for MS at UT Southwestern Medical Center has long been at the forefront of MS treatment and research, but also has been intimately dedicated to the education of those who participate on the multidisciplinary care team. In particular, our team was awarded funding from the United States Congress in 2001 to establish the first and still sole National MS Treatment Training Program for physicians, nurses and physician extenders. Since its inception, UT Southwestern Medical Center in collaboration with the National Multiple Sclerosis Society has trained in excess of 900 participants who provide care for patients and families with MS.

This Practical Primer on MS is a derivative of our longstanding dedication and exuberance for teaching others about the principles of possibilities; of hope; and of compassionate care.

The serious and dignified management of the MS patient is the primary thrust of this book. My colleagues and I hope it will serve you well in your quest to more optimally serve those with MS who deserve the best you can bring to bear in confronting this most formidably challenging disorder. Today we are equipped with abilities like no other time in history. Standing together with all members of the care team, the PA is on the front line in all aspects of MS care. We hope that you will find our Primer truly practical, cogent, and underscoring of the most important principles that will help you provide care that makes a difference in the management of the MS patient in general, and for those with chronic medical illnesses in general. As a provider of care, the PA can work in alliance with the MS patient to identify new and cutting-edge pathways for progress, like no other time in history. Through this process, it is our hope that the PA will not only represent the agent for hope and promise, but will also be identified by the patient and family as part of the treatment itself.

The person that I admire most for his unparalleled passion for his chosen profession and unending support of mine is my husband Elliot Frohman. He is truly a doctor who considers his MS patients ‘part of the family’. For those of us that have the distinct privilege of his mentorship, a key point to patient care we learn from him is that what you bring to your patients is not solely defined by what you know, or what you can do; most powerfully, you bring yourself!

— Teresa C. Frohman, PA-C; March, 2011

# Acknowledgements

This book has been the result of an enthusiastic collaboration between the National Multiple Sclerosis Society (Society), the Clinical and Scientific Affairs Council of the American Academy of Physician Assistants (AAPA) and most importantly the Multiple Sclerosis specialists in the Department of Neurology and Neurotherapeutics at the University of Texas, Southwestern Medical Center. The content and chapters contained in this work were generated by the specialists in the field under the guidance and leadership of Dr. Elliot Frohman. Teresa Frohman took on the task, not only as an authoritative co-author, but also coordinating the contributions and guiding the production of this work as an editor.

This is an exciting time in the care of patients with MS. We are witnessing an explosion of effective treatments for our patients living with MS. This book was conceived and championed by the Society in recognition of the increasing responsibility and role of physician assistants in the care of patients living with MS. The Society came to the AAPA and specifically solicited the participation to involve the profession in the development of this resource. Thus, representatives of the AAPA, the Society and UT providers met to plan and then give feedback on this work. Once produced, the final form of the book was the result of a edifying and pleasant interaction among the editors.

The editors would like to acknowledge the participation of David Dube, PA-C, from the University of Oklahoma Health Science Center and Kevin Schuer, PA-C, from the University of Kentucky. These PAs care for patients with MS and graciously agreed to provide input on the final drafts of the book. We are grateful to them for their time and sharing their insights on this work.

Admittedly, this work is a snapshot of care provided for our patients with MS. Our aim is to be a significant resource given that there will be shifting treatment paradigms. We plan to revisit this resource as an ongoing project.



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# Introduction

*Teresa Frohman, PA-C*

## CLINICAL PEARLS

- Inflammation is the hallmark of MS and this inflammation is followed by demyelination, tissue scarring (gliotic sclerosis), axonal injury/ transection, and neurodegeneration.
- MS is characterized into four main sub-types:
  1. Relapsing Remitting (RRMS)
  2. Secondary Progressive MS (SPMS)
  3. Primary Progressive MS (PPMS)
  4. Progressive Relapsing MS (PRMS)
- Patients do better when sensory symptoms predominate over motor or cerebellar dysfunction.
- The loss of myelin sheaths surrounding axons results in abnormal patterns or interruption of neural conduction and leads to the clinical signs and symptoms of the MS.

## MULTIPLE SCLEROSIS: WHAT IS IT?

Multiple sclerosis (MS) is the most commonly diagnosed cause of progressive neurological disability in young adults throughout the developed world. Patients typically experience either acute attacks of neurological compromise, or are afflicted by a steadily progressive deterioration in functional capabilities. In the former circumstance attacks arise as exacerbations and can literally produce any neurological symptom with a persistence of at least twenty four hours (but often lasting much longer) followed by a period of partial, and in some cases nearly complete, recovery.

TABLE 1.1: CLINICAL MANIFESTATIONS OF MS

	<i>Symptoms</i>	<i>Progression Features</i>	<i>Interventions</i>
Optic neuritis	Blurred vision Eye pain Color loss Field defects	Acuity loss Visual field loss Reduced reading	Maximize refraction Magnification Corticosteroids plasma exchange
Myelitis	Numbness Pain Dyesthesias Pressure sensations Weakness Ataxia (sensory) Gait dysfunction Neurogenic bladder Neurogenic bowel Sexual dysfunction Spasticity	Sensory disturbances Chronic pain syndromes Weakness Exercise intolerance Poor gait mechanics Foot drop Falling Bladder retention Chronic constipation Anorgasmia Erectile dysfunction Tonic and phasic spasticity Impact on activities of daily living Reduced driving safety	Membrane stabilizers Exercise training Physiotherapy Stretching Orthotic devices Assist devices Anticholinergics Alpha antagonists Fiber, fluid, stimulants Vibrator stimulation Proerectile agents Baclofen/ benzodiazepine
Ocular Motor Vestibular	Double vision Oscillopsia Vertigo Nausea/vomiting Disorientation Gait dysfunction	Double vision Eye strain ( $\pm$ headaches) Poor reading Difficulty driving Falling	Patching/prismatic correction Magnification Driving assessments Assist devices

Paroxysms	Seizures Trigeminal Neuralgia Lhermitte's Focal dystonias Tonic spasms Dysarthria Ataxia Speech arrest Transient Aphasia	Tend to be transient	Membrane stabilizers
Uhthoff's	Virtually any physical or cognitive deficit in MS can be stereotypically and reversibly intensified or exacerbated with infection, heat, prolonged exercise or stress.	This phenomenon becomes more prominent as the disease advances. Uhthoff's phenomenon represents one of the most vexing and disabling aspects of MS and is highly limiting to many patients. It signifies reversible conduction block secondary to demyelination.	Cooling devices Avoid temp extremes 4-aminopyridine Titrate exercise Stress reduction Treat infection Antipyretics when febrile
Cognitive	Slow processing speed Poor multitasking Reduced memory Rarely aphasic syndrome	Reduced work performance Altered activities of living Medication errors Driving accidents Altered communication	Neuro-psychological tests Mental activities Avoid Uhthoff's stimuli Acetylcholinesterase Inhib Memantine Psychostimulant use Modafinil Treat B-12 deficiency Treat hypothyroidism Treat depression Treat anemia

Fatigue	Literally affects all aspects of an MS patient's life. Often related to sleep disturbance, mood dysregulation, Uhthoff's phenomenon, altered properties of physical functions (e.g. faulty gait mechanics, spasticity, etc)	Reduced activities Poor work performance Cognitive compromise Depression Demoralization Altered thinking Reduced walking	Treat depression Evaluate sleep Physiotherapy Exercise training Rest periods Cooling strategies Psychostimulants Modafinil Acetyl-L-carnitine D-Ribose 4-aminopyridine Amantidine Atomoxetine Consider offending drugs
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The pathophysiology of these acute exacerbations is related to the development of inflammation and its consequences within strategic (referred to as eloquent) and often discrete central nervous system (CNS) tract systems. A myriad of hypotheses may explain the mechanisms that contribute to both the predilection and triggering of the multi-phasic inflammatory events that personify MS. Yet much remains to be done in order to fully understand the specific set and sequence of events that produce the disease and its cardinal features.

#### HISTORICAL PERSPECTIVE

MS has been described in medical literature for centuries. St. Ludwina of Schiedam, a Dutch girl who lived in the 14th century, may be the earliest described case of MS. At the age of 16 she was involved in an ice skating accident which was subsequently followed by a relapsing course of highly conspicuous neurological attacks and periods of remission. She later became permanently disabled and died before her sixtieth birthday.

The work of Jean Martin Charcot, a French clinician-investigator and the first Chairman of a Department of Neurology in the 19th century, and colleagues chronicled the longitudinal changes in the disease course and its impact upon clinical disability over the life of patients with MS at the Salpêtrière in Paris. Further, his group performed systematic neuropathological studies on the brain and spinal cord of these patients after their death. They established the two cardinal tenets of neurological practice: 1. *Where is the lesion that is responsible for the resulting clinical signs and symptoms?* (the neuroanatomic approach of lesion localization); and 2. *What is the nature or etiology of this lesion?* Charcot and his collaborators provided the framework upon which progress has been made in our understanding of the relationship between the development of tissue injury in the CNS and its relevance to clinical disability.

The first MS diagnostic criteria was known as Charcot's triad and consisted of scanning speech, intention tremor, and nystagmus. His early work emphasized that MS was multiphasic in producing clinical attacks occurring at different times in a patient's life and affecting distinctly different CNS injury targets (hence the adage '*multiple events in space and time*'). Since the time of Charcot we have witnessed the formulation of expanded and more precise diagnostic criteria (the so-called Schumacher, Poser, and McDonald criteria) that have refined our ability to confirm the diagnosis with greater sensitivity and specificity. Perhaps what has changed most profoundly in the last few decades has been the recognition that the presentation of a clinically isolated demyelinating syndrome (CIS), the first recognizable clinical event, is most typically associated with clear and unmistakable dissemination of ineloquent (i.e. silent or subclinical) brain and/or spinal cord lesions. This suggests that the majority of those evaluated with a CIS already have MS (once conditions that can mimic have been excluded) as their working diagnosis.

Currently the term radiologically isolated syndrome (RIS) is a newer designation for patients who are serendipitously identified when they undergo MRI for other reasons but at which time, classic MS lesions are found.

The normal flow of information in the CNS relies on delicate and precise interconnections of neuronal processes. Most of the axons that make the CNS interconnections are ensheathed with a myelin wrapping that makes signal transmission possible. The loss of myelin sheaths surrounding axons results in abnormal patterns or interruption of neural conduction, and leads to the clinical signs and symptoms of the MS. Inflammation is the hallmark of MS, and this inflammation is followed by demyelination, tissue scarring (gliotic sclerosis), axonal injury/transaction, and neurodegeneration.

### *Inflammation*

MS involves at least two inflammatory processes that are likely interdependent. There are acute and chronic (see below) inflammatory processes that are caused by autoreactivity within the CNS where the body's own immune system attacks itself. In the case of MS, the target of the immune response is myelin. The initial trigger of this autoimmune cascade is unknown at this time. One potential cause involves dysregulation of the immune system with a failure to differentiate between "foreign vs. self", ultimately leading to an immunological attack on myelin within the CNS. A second theory relies on an exposure to an infectious agent that leads to the immune targeting of myelin. Genetic and environmental factors also play significant roles in the disease process. The features of MS pathophysiology are complex and researchers are only beginning to understand how diverse many of the aspects are.

### *Acute Inflammation & Demyelination*

Acute inflammatory processes begin with an increase (upregulation) in adhesion molecules on the endothelium of the brain and spinal cord post capillary veins that allows leukocytes to cross the blood-brain barrier and enter the CNS. Lymphocytes from the circulating peripheral blood are programmed to recognize some epitopes found in myelin and these lymphocytes contribute to the cell infiltrates that are observed in the brain. Once in the CNS these autoreactive lymphocytes activate and

proliferate, triggering a cascade of events resulting in acute inflammatory demyelination within the CNS. Activated T-helper cells (CD4+ and CD8+ cells) recognize antigens within the CNS. These epitopes include components of myelin basic protein proteolipid protein among others (CD8+ is actually the most common all in infiltrate). Cytokines also activate blood-derived microglia (CNS macrophages). The microglia consequently express molecules (class II MHC molecules) and represent myelin antigens to T cells, further priming and perpetuating a pro-inflammatory condition. This cascade of events includes the production of more cytokines (tumor necrosis factor and interferon- $\gamma$ ), chemokines, and other inflammatory mediators, such as nitric oxide, free radicals and superoxide, that reinforce the immune attack on myelin, oligodendrocytes (myelin producing cells), and even the axons themselves.

Autoreactive T-cells and microglia directly attack and damage myelin. This coordinated attack results in the loss of myelin (demyelination) and exposure of the underlying axon. The loss of myelin sheath surrounding axons compromises the transmission of action potentials and leads to abnormal patterns of neural conduction. Ultimately, the clinical signs and symptoms of MS reflect the loss or alteration of axonal conduction.

Oligodendrocytes are also a target of the immune attack in MS. Oligodendrocytes are responsible for the formation and maintenance of myelin around multiple axons. Thus, the destruction of a single oligodendrocyte results in the loss of myelin around several axons, and the loss of many oligodendrocytes limits the ability to repair or regenerate demyelinated areas. Lastly, inflammation is now known to include more than demyelination, as recent studies have found significant axonal pathology. Obviously once an axon is demyelinated, these exposed axons are available and susceptible to damage in this destructive inflammatory environment.

The classic description of MS highlights the changes found in the white matter. Yet there is a growing number of descriptions that characterize changes within the gray matter. The gray matter inflammatory process appears to be different from white matter. Myelin reactive B-cells and their production of myelin specific antibodies play a more prominent role in gray matter inflammation compared to the predominate role of T-cells in white matter inflammation.

### *Gliosis & Plaques*

The classic description of multiple sclerosis derived from observations that plaques, or lesions, are formed in the CNS as a result of the acute inflammation and demyelination. Astrocytes, or astroglia, serve as interstitial cells in the CNS with multiple important functions. These glial cells reside throughout the CNS, but particularly accumulate and proliferate in areas where demyelination and neural damage have occurred. Proliferation of astrocytes leads to the formation of glial scars that surrounds the demyelinated areas. These glial scars act as a barrier to isolate cellular damage and allows for some recovery processes to occur within the barrier. Unfortunately, these same scars prevent neuronal axon extensions, and also likely limit remyelination.

### *Chronic Changes Related Axonal Degeneration*

Long-term changes are seen in addition to the acute inflammatory processes of demyelination. Abnormal increase in the expression of sodium channels within the axon membrane may also contribute to dysfunction axonal function. This increases the entry of sodium across the axon membrane, perhaps as an attempt to re-establish normal conduction. This mal-adaption actually slows nerve conduction and has the potential of blocking conduction. This process appears to be followed by reversal of the sodium-calcium exchanger (i.e., sodium efflux and calcium influx) that can trigger intracellular cascades of calcium-mediated injury and ultimately neuronal degeneration. These chronic changes can culminate in further loss of axons. Ultimately, axonal transections correlate with atrophy within the CNS, and lead to the permanent and irreversible disabilities so well described in MS.

## CLASSIFICATIONS OF MS

MS is characterized into four main sub-types:

- Relapsing Remitting (RRMS)
- Secondary Progressive MS (SPMS)
- Primary Progressive MS (PPMS)
- Progressive Relapsing MS (PRMS)

The initial course of 85–90% of individuals with MS is of the relapsing-remitting subtype (RRMS), characterized by relapses followed by periods of remission. The remissions can be months to years with no new signs of disease activity. Deficits suffered during attacks or exacerbations may either resolve entirely or result in ongoing deficits.

About 65% of patients with RRMS will progress to a new phase of the disease. Exacerbations will be separated by progressive neurologic decline between the acute attacks without any definite periods of remission. This is referred to as Secondary Progressive MS (SPMS). The median time between disease onset and conversion from relapsing-remitting to secondary progressive MS is nineteen years, and disease activity (clinically and radiographically strongly influences the timing of this transition).

In contrast to the patients with relapsing remitting disease, some patients experience a wholly progressive and insidiously changing course of disability from the inception, without any evidence of acute attacks with remission. This would be considered primary progressive MS (PPMS). This primary progressive subtype describes the approximately 10–15% of individuals who never experience a remission after their initial MS symptoms. Progressive relapsing MS (PRMS) describes those individuals who, from onset, have a steady neurologic decline but later exhibit clear superimposed attacks or exacerbations. This is the least common of all subtypes.

## EPIDEMIOLOGY

Multiple sclerosis (MS) is estimated to affect more than 400,000 people in the United States and 2.5 million people worldwide. MS is one of the most disabling neurologic diseases of young adults as it is diagnosed often in those between the ages of 20–50, when people are in the prime productive years of life. However, MS can be a diagnosis in the very young and in those over 65 years as well. MS is much more common in Caucasian women and in those of western European ancestry, and almost absent in certain ethnic groups such as Native Americans and Eskimos.

Prevalence rates for MS differ geographically with a lower distribution in those areas that are closer to the equator, and with increasing frequency in areas above 40° latitude. Studies have demonstrated that migration from a geographic region of higher prevalence of MS to one of lower prevalence may reduce an individual's risk of developing MS in the future. Specifically, the person will take on the prevalence risk of the geographic region (either higher or lower) in which they lived the first 15 years of life.

## GENETICS

The prevalence of MS is approximately 1% of the general population. This risk increases to 2%–4% when a first-degree relative is affected by the disorder. Therefore the risk of developing MS seems to be related to genetics as well as to the environment. What may be a more powerful indicator of genetic predisposition comes from twin studies. In monozygotic twins there is a 30%–40% chance of a twin contracting MS (concordance rate) when the other twin has established MS.

As one can see, MS is a disorder with both genetic and environmental rudiments. Despite this, the vigorous search continues for clues on how different factors interact to either protect against MS or, more urgently, heighten the predilection for developing this autoimmune disorder.

A restricted set of immune response genes may modify the risk of MS, particularly in those who are exposed to some co-factor triggering event (perhaps a viral infection). Thus, MS is more common in family members than in the general population.

#### NATURAL HISTORY

MS is more common in women and Caucasians. MS is more progressive in African Americans. Epidemiologic studies show most patients with MS exhibit progressive neurological deterioration without treatment. Ten years after diagnosis, half of patients use a cane to ambulate, and 15% require a wheelchair. In the same 10 year span approximately half of patients convert to the secondary progressive phase of the disease where there is acceleration of disability and a paucity of effective therapy. A relatively small percentage of patients have a more benign course. Because there are no reliable predictors to indicate which patients will fall into either category, the stratification of patients into high versus low disability groups can only be achieved by retrospective analysis. Therefore from the outset, one is faced with diagnostic uncertainty about who is to be treated and how aggressive treatment should be.

The risk of progression to disability over the first decade may be influenced by several factors. For instance, although MS is more common in women (3:1), men are more likely to have a progressive, even malignant, clinical course. Further, MS relapse rates decrease by an amazing 70% in the third trimester of pregnancy, whereas the risk of exacerbation again increases following delivery of the baby. These observations underscore the principle that hormonal factors figure prominently in the mechanisms of immune modulation and the ultimate expression of MS.

Favorable prognostic factors include infrequent exacerbations in the first year of the disease. Patients do better when sensory symptoms predominate over motor or cerebellar dysfunction. Also, patients progress less when there is good functional recovery from individual neurologic attacks. In longitudinal studies patients with a normal brain MRI at the time of the first clinically isolated inflammatory demyelinating syndrome (CIS) did not accrue significant disability over 14 years of follow up. Alternately, patients with more than ten MRI lesions, or a

change in lesion load within the first year following CIS, were significantly more likely to progress to advanced levels of disability (eg. ambulation with a cane or walker) over the same period of time. Further MS has now been shown to be more ominously progressive in African Americans. Early diagnosis and treatment of MS can reduce the risk of, and mitigate the severity of relapses. Therefore, providers should be well informed to confirm the diagnosis expeditiously and facilitate treatments to forestall the accrual of disability.

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# Neuroimmunology of Multiple Sclerosis

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## CLINICAL PEARLS

- To participate in the inflammation in the central nervous system (CNS) leukocytes must enter circulation, travel to the CNS, and migrate across the blood-brain-barrier (BBB).
- In the absence of inflammation there is little leukocyte trafficking to the CNS.
- Under inflammatory conditions a wide range of cell types, including T cells, B cells, macrophages, and granulocytes, are able to enter the CNS.
- T and B lymphocyte homing to the CNS is indirect as it requires the cells to become activated in the secondary lymphatic tissues prior to entry into the CNS.
- Following activation, T cells express new combinations of selectins, chemokine receptors and integrins allowing them to move into tissues, including the CNS.
- Integrins are large transmembrane proteins that act as cell surface receptors involved in forming tight contact between cells or between cells and the extracellular matrix.
- The integrins VLA-4 and LFA-1 are involved in CNS trafficking.

## INTRODUCTION TO NEUROIMMUNOLOGY OF MS

This chapter illustrates how specific immune cells contribute to the inflammatory cascade of MS, and how other cells may serve to regulate aberrant immune responses. It also clarifies how specific cell types or

molecules have become targets for drug therapy in MS. Over the past two decades tremendous progress has been achieved with respect to the development of pharmacotherapies for patients with relapsing forms of MS. The explosion of information on the immunology of MS in recent years has lead to the approval of more disease modifying drugs than are available in any other branch of neurology, or even general medicine.

#### TRAFFICKING OF T LYMPHOCYTES INTO THE CENTRAL NERVOUS SYSTEM

Cells of the immune system exist in a state of migration. In fact, their function in MS is directly linked to their ability to migrate into the central nervous system (CNS). To participate in the inflammation in the CNS leukocytes must enter circulation, travel to the CNS, and migrate across the blood-brain-barrier (BBB). These processes are controlled by the selectins, integrins, matrix metalloprotease (MMP), chemokine and chemokine receptor families. For each cell the types and levels of receptors expressed determine the extent and timing of migration into the CNS.

CNS trafficking is a highly ordered process. Cells first roll on the surface of the endothelium using selectin proteins. They become activated through chemokine signals and adhere to the endothelial cell surface with integrins. Next the cells secrete MMPs and extravasate through the endothelial cell barrier. Once inside the tissues, the leukocytes follow specific chemokine cues to find the areas of inflammation. Selectin proteins are expressed by leukocytes and by endothelium. P selectin is expressed by the endothelium lining the choroid plexus and the meninges. Activated T cells express the ligand for P selectin. This is thought to allow the T cells to monitor these areas of the brain.

There are approximately 50 known chemokines and 20 receptors. Chemokines are expressed by activated cells like leukocytes and endothelial cells. Chemokine signals are involved in controlling the recruitment of leukocytes and directing their migration within the tissues. A number of chemokines are thought to be involved in MS. Many of these are produced directly by activated T cells. Chemokines can also be released in response to cytokines released by T helper cells such as Th1 and Th17 T cells.

Endothelial cells express integrins and these molecules mediate the firm adhesion of leukocytes on the surface of endothelial cells. Integrins are large transmembrane proteins that act as cell surface receptors involved in forming tight contact between cells or between cells and the extracellular matrix. Integrins play another role in that they facilitate leukocytes to extravasation in addition to their role in stopping leukocytes from rolling in the vascular flow. The functions of integrins are associated with their direct association with the cellular cytoskeleton. The integrins VLA-4 and LFA-1 are involved in CNS trafficking. After stopping on the surface of the endothelium, cells release proteolytic enzymes to disrupt the tight junctions of the BBB. MMP9 is thought to play an important role in opening the BBB and facilitating migration across the endothelial layer.

In the absence of inflammation there is little leukocyte trafficking to the CNS. The major immune cells found in the CSF of healthy persons are T and B cells of a memory or activated phenotype. Under inflammatory conditions a wide range of cell types, including T cells, B cells, macrophages, and granulocytes, are able to enter the CNS. T and B lymphocyte homing to the CNS is indirect as it requires the cells to become activated in the secondary lymphatic tissues prior to entry into the CNS. Resting or naïve T and B lymphocytes continuously migrate between the lymph nodes and circulatory system. Following activation, T cells express new combinations of selectins, chemokine receptors and integrins allowing them to move into tissues, including the CNS.

#### ROLE OF INNATE IMMUNITY IN MS

The function of the innate arm of the immune system is to recognize, control or clear microorganisms to which we are exposed on a daily basis. Cells of the innate immune system include both myeloid and lymphoid cell lineages and both have been associated with MS lesions. Complement and cytokines are soluble non-cellular components of the innate immune system identified in MS. The presence of components of innate immunity within the MS lesions indicates that innate immune responses contribute to the pathogenesis of MS. The following short summary shows each innate immune component and their potential impact on the pathogenesis of MS.

Monocyte/ Macrophages	Hematopoietic monocytes and macrophages are the most abundant phagocytic cells of the innate immune system that infiltrate the MS lesion. Their morphology is very heterogeneous depending on which area of the MS lesion they have infiltrated. Monocytes/macrophages can contribute to neuroinflammation as well as promote neuroprotection in MS.
Microglial Cells	Microglia provide the first-line of defense within the CNS. Microglial cells are phagocytic, and clear debris resulting from inflammation. Upon activation, they can produce several pro-inflammatory cytokines (such as TNF- $\alpha$ ) and reactive oxygen species that are toxic to infectious agents. They may also serve as antigen presenting cells that directly activate T cells.
Dendritic cells	Dendritic cells are potent antigen presenting cells and are considered to be the critical link that bridges the innate and adaptive immune responses. Since the CNS lacks conventional lymphatic circuitry, it is thought that DCs perform their antigen presenting function to directly activate T cells within the perivascular spaces of the CNS. Therefore, DCs in the periphery and within the CNS may contribute to the initiation and perpetuation of immune mechanisms germane to the disease process in MS.
Mast cells	Mast cells release granules that are rich in histamine and other inflammatory mediators. Both mast cells and their mediators have been identified in MS lesions. Tryptase, an enzyme uniquely produced by mast cells, is increased in the CSF of MS patients.
Natural Killer (NK)	Natural Killer (NK) cells recognize and kill virally infected cells and tumor cells, and secrete cytokines including IFN- $\gamma$ , IL-10, IL-5 and IL-13. NK cell numbers are decreased in the CSF and in lesions of MS patients, and cytolytic activity is diminished in comparison to healthy controls. In fact, recent studies suggest that increases in NK cells in pregnant MS patients may contribute to the decreased disease activity observed during pregnancy, and indicate an immunoregulatory role for NK cells in MS.
NK-T	NK-T cells are T cells that express an invariant TCR (Va24JaQVb11) and some features of NK cells. NK-T cells have been identified in MS lesions and are thought to play a regulatory role in MS, but the conclusions of studies investigating NK-T cell numbers and function in MS patients are conflicting.
$\gamma\delta$ T	$\gamma\delta$ T cells are T lymphocytes that express the invariant $\gamma\delta$ T cell receptor and are typically present in high numbers in the epithelium of the gut and are less frequent in the blood. $\gamma\delta$ T cells have been identified in MS lesions but their contribution to the pathogenesis of MS has not yet been elucidated.

Non-cellular components	Nitric Oxide Synthase (NOS) is an inducible enzyme produced by myeloid cells such as monocytes/macrophages, granulocyte and DC, that is used to generate nitric oxide (NO). NO is one of several reactive oxygen and nitrogen intermediates that function as potent antimicrobials. NOS is associated with MS lesions but the role of NOS in MS remains undefined.
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## ROLE OF ADAPTIVE IMMUNITY IN MS

### *CD4+ T cells*

Traditionally T lymphocytes have been suggested to play the critical, if not exclusive, role in the pathogenesis of MS. This suggestion was mostly based on an animal model of MS, experimental autoimmune encephalitis (EAE). This model was conceived eight decades ago by Thomas Rivers and is known to be mediated predominantly by antigen-specific T cells. Specifically, T helper cells, identified by a surface antigen called cluster of differentiation (CD)-4, recognize myelin proteins within the brain and the spinal cord. These CD-4 T-cells play an important pathogenic role. EAE can be transferred to naïve recipient animals by injecting the non-EAE animal with myelin-specific, or myelin reactive, CD4+ T cells.

### *CD8+ T cells*

Recent studies have shown that other immune components such as CD8+ T-cells add to the pathogenesis of MS. CD8+ T cells are sometimes referred to as cytotoxic T cells because they recognize peptide antigens in MHC/HLA Class I molecules (vs. Class II molecules for CD4+T cells). HLA Class I molecules (HLA-A, HLA-B, HLA-C) are expressed on almost all nucleated cells. Therefore CD8+ T cells can interact with a wide array of cell types. CD8+ T cells also interact with “non-classical” Class I molecules, such as HLA-E, which have a more restricted distribution, particularly on activated cells of the immune system. CD8+ T cells have several functions that include clonal proliferation, cytokine and chemokine secretion and modulation of

other immune cell types that are similar to CD4+ T cells. However the major function of CD8+ T cells is their direct cytotoxicity; i.e., direct killing of target cells that express the relevant antigenic peptide in the context of HLA Class I. This function is especially prominent in immune defenses directed in 'search and destroy' missions against cells in the body that are infected with virus or are transformed through neoplastic changes.

In addition to the important role played by CD4+ T cells, CD8+ T cells are now recognized as playing a key role in the pathogenesis and/or regulation of MS. CD8+ T cells have been found to be oligoclonally expanded in MS lesions, and this indicates that these CD8+ T cells recognized antigen in the lesion and proliferated at the site of pathology. Thus some genetic association between HLA Class I haplotypes and MS has been demonstrated. Moreover, analysis of brain MS lesions has shown a clear predominance of CD8+ T cells, compared to CD4+ T cells.

#### ROLE OF B CELLS & THEIR ANTIBODY PRODUCTS IN MS

B cells specifically proliferate to produce a particular antibody in response to an immunologic challenge. Antibodies have been suspected to play a role in the pathogenesis of MS since the early 1970's. It was demonstrated that, instead of a large population of very diverse antibodies, antibody proteins from the spinal fluid of MS patients were oligoclonal. This was detected as a smear of proteins on an isoelectric focusing gel that separates proteins by charge. The cerebrospinal fluid of MS patients had a limited sub-set of antibody proteins that were detected as distinct bands on an isoelectric focusing gel (IgG bands). This oligoclonal banding phenomenon was not limited to MS patients. It had also been observed in even more punctuated patterns in patients with infections of the CNS. This similarity, however, was one of the foundational observations to support the concept that MS may be caused by an immune reaction to a narrow list of candidate antigens.

B cells can also act as potent antigen presenting cells (APCs) to neuro-antigen reactive T cells, which is a B cell activity that is independent of antibody secretion. The role of B cells in MS remains focused on how to better manipulate the B cell population to either prevent neuro-antigen reactive T cells from becoming activated, or to induce tolerance in the neuro-antigen reactive T cell pool.

#### CONCLUDING REMARKS

In this chapter, there was a discussion of how specific immune cells may contribute to MS disease activity. Understanding the role of these cells in MS is not merely an academic exercise but has real consequences for patients. As mentioned above the EAE animal model of MS, and laboratory studies in humans, have often identified how lymphocytes contribute to disease activity, and how they assist in regulating aberrant immune responses and ultimately contribute to repair of injured tissue. These observations are important as they represent the basis from which to develop novel pharmacological and non-pharmacological interventions.

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# Neuroimaging & Multiple Sclerosis

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## CLINICAL PEARLS

- Lesions characteristic of MS are in the deep white matter and often either ovoid in shape or have a trajectory that is perpendicular to the long axis of the ventricles. On sagittal FLAIR imaging, these perpendicular lesions extend from the white matter to the ventricular zone. This type of lesion is referred to as a Dawson's finger
- In contrast to the relatively clinically silent lesions (non-eloquent) around the ventricles of the cerebrum, brainstem periventricular lesions are typically eloquent and commonly are associated with predictable clinical signs and symptoms of double vision, nystagmus, ocular misalignment and even vertigo.
- During an acute exacerbation of MS gadolinium penetrates into the brain and can be visualized as a bright, hyperintense, 'enhancing' signal. This is considered a gadolinium enhanced lesion.
- As many as 75% of patients with MS will have lesions within the spinal cord, more commonly in the cervical spinal cord versus the thoracic spinal cord.

## A HISTORICAL PERSPECTIVE

Magnetic resonance imaging (MRI) is an enormously powerful technique that has revolutionized the way we think about MS. This tool has changed how clinicians approach MS diagnostically and therapeutically. In the nineteenth century MS was known to be associated with hardening or sclerosis within the white matter, with focal lesions referred to

as ‘plaques’. Pathological specimens from that era contained a cardinal hallmark, perivenular collections of inflammatory cells, now known to be composed of mononuclear immunological cell infiltrates (B and T cells and macrophages).

Then, in the early 20th century, Dawson recognized from sagittal sections of the brains of MS patients that plaque-like abnormalities spanned from the ependymal lining of the cerebral ventricles into the overlying white matter in a finger-like projection profile. Today, the inflammation in the brain of MS patients is known to be a product of lymphocyte trafficking across post-capillary venules that express adhesion molecules to facilitate this redistribution of immune cells from the blood into the brain and spinal cord. Further the highest concentrations of these microvessels, (post-capillary venules) occur around the cerebrospinal fluid containing ventricles; hence the high predilection for the so-called periventricular plaques. MS lesions are now widely recognized to occur anywhere within the white matter, notwithstanding the predominance of MS lesions to occur around the ventricles. The imaging power of MRI has made this recognition possible.

Increased MRI sensitivity continues to reveal details that challenge one’s views. MS plaques have been recently appreciated as lesions within the cerebral cortical layers and deep gray matter structures like the thalamus and the hypothalamus. While such profiles were recognized pathologically as far back as the late 19th century, older MRI methods were less sensitive to these gray matter plaques.

#### FUNDAMENTALS OF MS DIAGNOSIS

The diagnosis of MS has fundamentally been predicated on the multiple phases of the clinical course. Patients with MS exhibit multiple attacks of neurological dysfunction that occur at different epochs of life and afflict different CNS track systems. One can think of this as multiple events in ‘time and space’. This rubric has been the framework for the confirmation of clinically definite MS.

MRI creates the ability to confirm that patients may have multiple lesions in the CNS even at the time of their first clinical event (referred to as the clinically isolated syndrome; CIS). This obviously indicates the existence of spatially disseminated older lesions that existed before symptoms arose (the age of which cannot currently be determined). This observation indicates that the majority of patients with MS have had some period of occult disease prior to their first clinical exacerbation. Currently the term radiologically isolated syndrome (RIS) is a newer designation of MS that accounts for patients who are serendipitously identified when they undergo MRI of the brain for other purposes (ruling out a brain tumor in the headache patient; participation in a clinical trial that involves imaging, etc), and at which time, classic MS lesions are identified.

Recent small longitudinal studies have demonstrated that most patients with RIS proceed to develop more lesions and then experience a true clinical exacerbation. The principle of the clinico-radiologic paradox exists where subclinical radiographically documented disease activity is on average 5–10 times more frequent than clinical attacks. This partly relates to the principle of eloquence and non-eloquence. In particular, lesions that commonly develop in certain anatomic locations are not always associated with clinically consistent symptoms (so called concomitants). These lesions are referred to as non-eloquent lesions. Likewise, there are other abnormalities that occur in pathways that often, if not almost always, result in the development of a characteristic inflammatory demyelinating syndrome. These lesions are termed eloquent lesions as they are associated with predictable neurological symptoms and syndromes *[Table 3:1]*.

TABLE 3:1: ELOQUENT MS SYNDROMES

<i>Eloquent Syndrome</i>	<i>Localization</i>	<i>Clinical Manifestations</i>
Optic neuritis	Optic nerve	Visual acuity loss Visual field suppression Color desaturation Pain Relative afferent pupillary defect
Internuclear ophthalmoparesis (INO)	Medial longitudinal fasciculus (MLF)	Slowing of adducting eye movements Diplopia Oscillopsia
Skew deviation	Otolith pathways	Vertical or oblique diplopia Subjective deviation of visual vertical
Cranial nerve palsies	Brainstem	Facial weakness Facial numbness (CNV) or pain Diplopia (CN III, IV, VI) Vestibulopathy (CN VIII or nucleus)
Rubral Tremor	Superior cerebellar peduncle	Tremor
Ataxia	Cerebellum	Instability and reduced postural control
Trigeminal neuralgia	Trigeminal system	Paroxysmal facial pain
Myelitis	Spinal cord	Sensory disturbances Spasticity Bowel/Bladder/Sex Weakness

IMAGING MULTIPLE SCLEROSIS

Clinicians will request an MRI of the brain and/or spinal cord to make the diagnosis of MS or to document any interval changes in disease activity that might influence treatment decisions. A battery of different MRI sequences is performed in order to display different histopathological features of the MS plaque. At a fundamental level, these sequences are ‘weighted’ to emphasize water or fat. T2 and proton density weighted

MRI scans are particularly good at demonstrating lesions with high water content. These images are partially confounded by the bright signal of the water content of the cerebrospinal fluid (CSF).

A modification of a water-biased T2 sequence is the fluid-attenuated inversion recovery (FLAIR) imaging, where the water signal of the CSF is suppressed in order to enhance the image of water-biased hyperintense lesions within the cerebral white matter. The presence of lesions on these sequences signifies water, but there is great histopathological heterogeneity in that two lesions may appear similar on MRI, and yet be distinctly different compositionally. Specifically, hyperintensity on FLAIR, T2, or proton density weighted images can be on the basis of an increase in extracellular water content, astrocyte proliferation (known as astrogliosis) with increased intracellular water, demyelination, or even remyelination.

There are a number of lesions (by shape and location) that are highly representative of the disease process in MS while not absolutely specific for MS [Table 3:2].

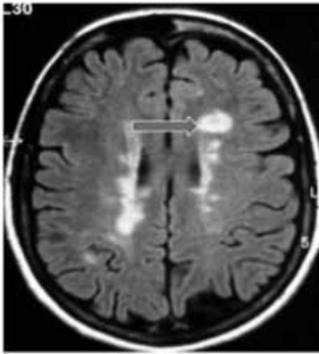
TABLE 3 : 2 : MS LESIONAL PROFILES

<i>Brain</i>	<i>Spinal Cord</i>
Ovoid Lesions in the Corona Radiata and Centrum semiovale	Cervical > Thoracic
Corpus callosum lesions	Skip lesions (spanning 1–2 vertebral segments)
Lesions perpendicular to the long axis of the ventricles	Dorsal column
Cerebellar peduncle (middle > superior > inferior)	Hemicord
Brainstem tegmentum (adjacent to the IVth ventricle and cerebral aqueduct)	Patchy
Juxtacortical and cortical lesions	Dorsal root entry zone

Lesions characteristic of MS are in the deep white matter and often either ovoid in shape or have a trajectory that is perpendicular to the long axis of the ventricles [Figure 3:1].

FIGURE 3:1

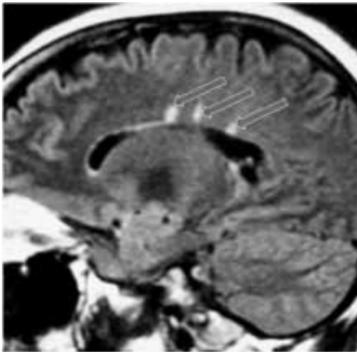
An axial T2 weighted MRI of the brain demonstrating a number of hyperintensities, including an ovoid MS plaque (Arrow).



On sagittal FLAIR imaging, these perpendicular lesions extend from the white matter to the ventricular zone. This type of lesion is referred to as a Dawson's finger

FIGURE 3:2

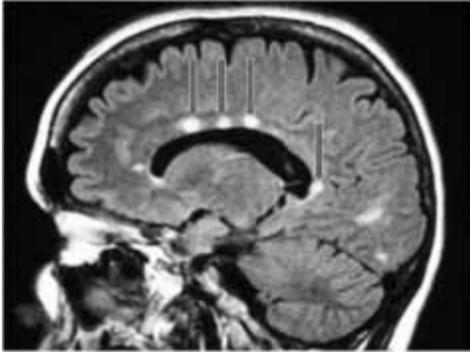
A sagittal FLAIR MRI of the brain shows lesions perpendicular to the long axis of the ventricles extending from the ventricular surface into the overlying white matter consistent with Dawson's Fingers (Arrows).



Lesions within the corpus callosum are highly suggestive of MS and the sagittal FLAIR images are superior to other sequences in revealing these [Figure 3:3].

FIGURE 3:3

A sagittal FLAIR MRI of the brain with highly conspicuous plaques within the corpus callosum (Arrows).



There are a number of other zones that have a high predilection for inflammatory demyelination lesions and some are near the ventricular system. These include the white matter of the cerebellar hemisphere and the middle cerebellar peduncle that are found in the roof and lateral wall of the fourth ventricle. In the brainstem lesions can be seen ventral to the fourth ventricle of the medulla, pons, or in association to the cerebral aqueduct within the midbrain [Figures 3:4–3:8].

FIGURE 3:4

An axial T2 weighted MRI of the brain shows a right cerebellar hemispheric hyperintensity (Arrow). This patient exhibited right hemiataxia.



FIGURE 3:5

An axial weighted T2 MRI of the brain shows a left middle cerebellar peduncle lesion (Arrow). This patient complained of left arm tremor, slurred speech, and jerky eye movements.

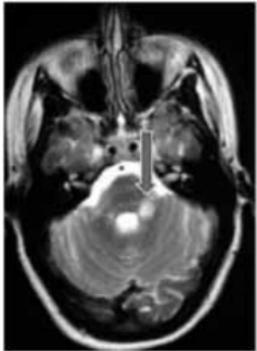


FIGURE 3:6

An axial T2 weighted MRI of the brain shows a medullary plaque (Arrow) in an MS patient with vertigo, double vision, gait ataxia (falling to the right), a right Horner's syndrome (small right pupil and right ptosis with right forehead anhidrosis), right palatal weakness, and a hoarse voice.

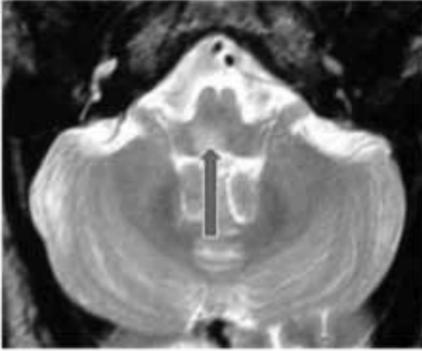


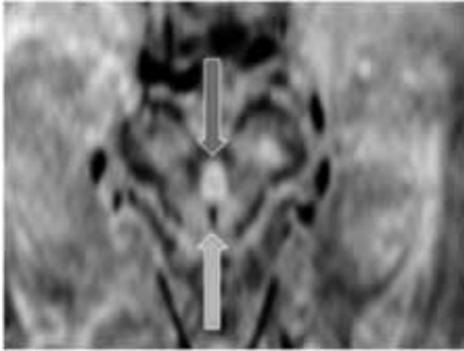
FIGURE 3:7

An axial proton density weighted MRI of the brain shows a hyperintensity in the pontine tegmentum (Arrow). This patient had evidence of bilateral internuclear ophthalmoparesis (INO).



FIGURE 3:8

This axial proton density weighted MRI of the brain shows a bright plaque lesion just ventral to the cerebral aqueduct (Arrow). This patient was wall-eyed (bilateral exotropia) and had bilateral INO; the so-called WEBINO syndrome.



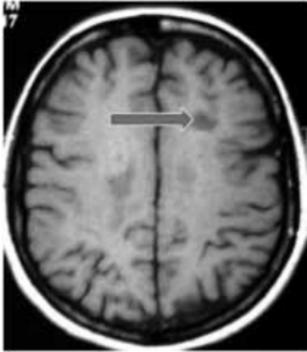
In contrast to the relatively clinically silent lesions (non-eloquent) around the ventricles of the cerebrum, brainstem periventricular lesions are typically eloquent and commonly are associated with predictable clinical signs and symptoms of double vision, nystagmus, ocular misalignment and even vertigo.

There is a high degree of variability in the composition of different MS plaques. The application of MRI techniques is useful diagnostically but not necessarily with respect to predicting the type and extent of tissue damage. The imaged tissue damage does not necessarily correspond to the severity of the neurological dysfunction. When considering the MRI modality and where a lesion may be found, different areas are optimally visualized with different imaging methods. For investigations of the cerebral hemispheres, that is the area above the tentorium cerebelli or the supratentorial compartment, FLAIR sequences have been validated to provide the best overall resolution to identify hyperintense MS plaque lesions. For lesions in the brainstem, or cerebellum, below the tentorium, T2 and proton density weighted images are more sensitive and specific for plaque lesions. FLAIR scans in this territory are often associated with a variety of artifacts, including those contributed by blood flow.

T1 weighted images are useful for the assessment of lesions that are tissue hypointensive and appear as gray or black. This is in contrast to water-biased imaging sequences such as FLAIR or T2. Gray to black lesions reflect either excessive tissue water, or a loss of brain tissue architecture and may reflect loss of myelin, axons, or both [Figure 3:9].

FIGURE 3:9

An axial T1 weighted MRI of the brain shows a hypointensity or black hole (Arrow) consistent with loss of tissue architecture.



Bright signals on T1 imaging are associated with high fat content, whereas dark or gray signals on T1 reflect tissue water. This is the opposite of characteristics when compared to T2 sequences. Brain atrophy is best revealed with T1 weighted images and is characterized by enlargement of the ventricles (lateral, 3rd, cerebral aqueduct, and 4th), thinning of the cortical grey matter and/or thinning of the corpus callosum [Figure 3:10, 3:11].

FIGURE 3:10

A sagittal T1 weighted MRI of the brain shows a normally sized corpus callosum (Arrow) and no evidence of brain atrophy.

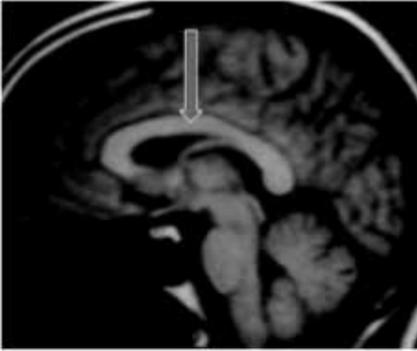
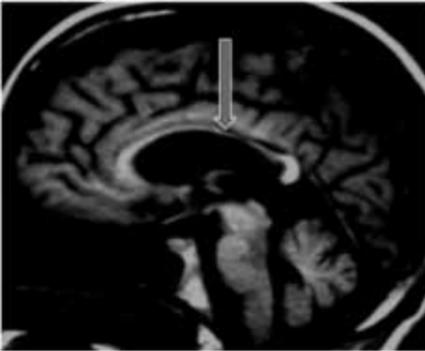


FIGURE 3:11

A sagittal T1 weighted MRI of the brain shows marked thinning of the corpus callosum (Arrow) along with cerebral atrophy. The patient complained of significant cognitive slowing and chronic fatigue.

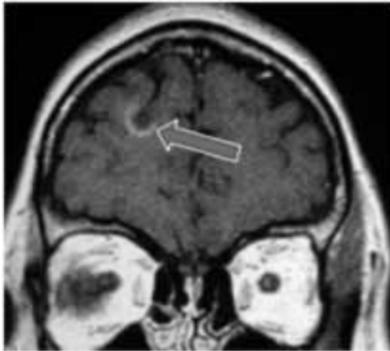


T1 black or gray holes and brain atrophy also constitute the CNS changes that best correlate with intellectual and physical disabilities.

In the acute phase, MS lesions involve a breach in the integrity of the tight junctions between the cerebral vascular endothelial cells, the so called blood-brain-barrier. Gadolinium is a very large, polar, and electrically charged molecule that is excluded from the CNS under normal conditions by vascular endothelial cells that create the blood-brain-barrier. During an acute exacerbation of MS however, gadolinium penetrates into the brain and can be visualized as a bright, hyperintense, 'enhancing' signal, which can be homogeneous, ring, or open ring in configuration [Figure 3:12]. This is considered a gadolinium enhanced lesion.

FIGURE 3:12

A coronal T1 weighted MRI of the brain with gadolinium infusion demonstrates an area of focal enhancement taking on an open ring configuration (Arrow).



The gadolinium enhancement generally persists for only weeks to months and then disappears as the blood-brain barrier integrity reconstitutes. Therefore, the enhancement of MS lesions that appears with the onset of symptoms reflects newly active lesions. This temporary nature of gadolinium enhanced MS lesions is so characteristic that if enhancement persists for longer periods of time, alternative diagnoses should be considered (e.g. tumor, sarcoidosis, infection, etc).

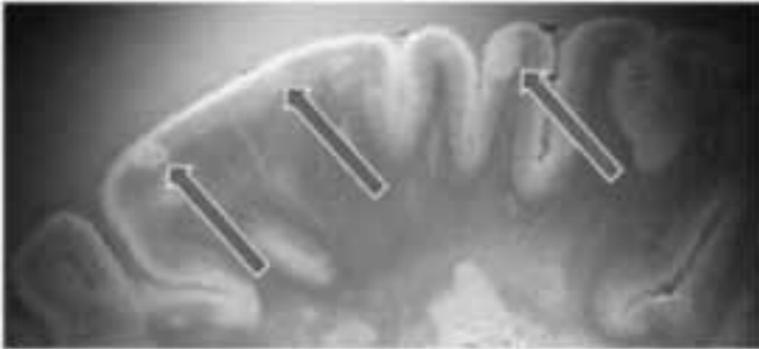
Obviously T1 weighted images have value in following the progression of gadolinium enhanced MS lesions associated with acute exacerbations. T2, proton density, and FLAIR imaging sequences cannot be used to accurately determine the acuity or age of an MS lesion.

#### GRAY MATTER PLAQUES

Conventional MRI methods are not as sensitive for showing lesions within nuclear aggregates of the gray matter or the cortical ribbon. Newer analyses of MRI data and techniques have allowed better visualization of cortical lesions. The development of double inversion recovery (DIR), MPRAGE, and high Tesla field imaging have all been used to augment cortical lesion conspicuity [Figure 3:13, 3:14].

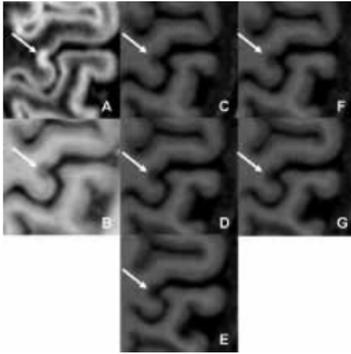
#### FIGURE 3:13

This axial MRI of the brain was performed at 8 Tesla field strength and reveals a number of definite intracortical MS plaque lesions (Arrows). (Courtesy of Dr. K. Rammohan).



#### FIGURE 3:14

A new technique for demonstrating cortical type lesions in MPRAGE (Arrows). (Courtesy of Dr. Flavia Nelson).



Because of the enhanced imaging capacity with these newer modalities a contemporary nomenclature for cortical lesions has been developed. Type I lesions are those that occur at the white and gray matter interface, the juxtacortical zone. Type II lesions are those that are wholly within the cortical gray matter layers (intracortical). Type III lesions are subpial areas of demyelination, usually not extending beyond layers 3 and 4 of the cortex. These latter profiles are of great interest in that they appear to be potentially related to pial and perivascular structures that are reminiscent of B cell follicles or germinal centers. These structures may be active in contributing to immune mechanisms of injury targeting neurons within the cerebral cortex.

#### SPINAL CORD IMAGING

MS lesions in the spinal cord usually result in identifiable symptoms; spinal lesions are highly eloquent of the MS disease process. New spinal MS lesions are associated with new clinical manifestations. One of the most common early clinical syndromes in MS is inflammatory myelitis. The majority of spinal cord lesions are localized to the dorsal columns. As many as 75% of patients with MS will have lesions within the spinal cord, more commonly, in the cervical spinal cord versus the thoracic spinal cord. Spinal MS lesions often are ovoid or cigar shape. Lesions may span one or two vertebral segments, and are described as 'skip lesions'. [Figure 3:15].

FIGURE 3:15

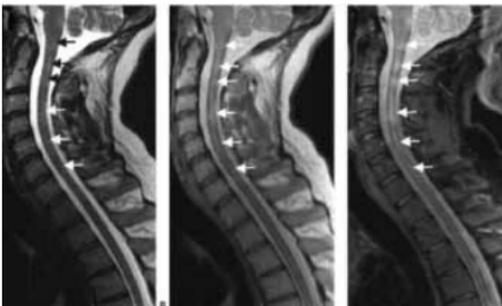
A sagittal T1 MRI of the cervical spinal cord shows multiple MS 'skip lesions' that display gadolinium enhancement (Arrows).



New spinal lesions are associated with T1 gadolinium enhancement lasting weeks to a few months. Further, in the sagittal plane, T2, proton density, and short tau inversion recovery (STIR) images reveal MS plaque lesions. Sagittal STIR images are generally sensitive and reveal lesions better than other sequences [Figure 3:16].

FIGURE 3:16

In this figure we show the differences in lesional conspicuity for sagittal T2 (left), proton density (center), and short tau inversion recovery (STIR) (right) MRI imaging of the spinal cord. In this example, STIR imaging appears to best identify the spinal cord lesions. (From Fox, RJ. Picturing multiple sclerosis: conventional and diffusion tensor imaging. *Sem Neurol* 2008;28:453–466.)



In the axial plane, T2 weighted imaging best demonstrates MS plaques and localizes the lesions to particular tracts (e.g. dorsal columns, corticospinal, spinothalamic, etc) [Figure 3:17].

FIGURE 3:17

An axial T2 weighted MRI of the spinal cord demonstrates the distribution of an MS plaque (Arrow) in a patient with acute sensory-motor myelitis.



In some circumstances patients will complain of symptoms suggestive of radiculopathy. Typically such symptoms occur when degenerative disc material extends into a spinal root and provokes pain in a discrete distribution. Alternately, when on the basis of demyelination, the MS lesion can extend from the spinal cord root entry zone into the extra-axial segment of the nerve root and produce symptoms indistinguishable from those derived from degenerative spine disease.

Acute enhancing lesions of the spinal cord are visualized on T1 weighted imaging sequences with gadolinium infusion in both the sagittal and axial images [Figure 3:18].

FIGURE 3:18

A sagittal T1 weighted MRI of the thoracic spinal cord with gadolinium infusion shows an area of ring enhancement (Arrow). This image is from the same patient as in *Figure 3:17*.



A variety of other conditions can be associated with spinal lesions resembling the demyelination seen in MS [*Table 3:3*].

TABLE 3:3: DIFFERENTIAL DIAGNOSIS OF SPINAL CORD LESIONS

Multiple sclerosis
Neuromyelitis optica (NMO)
Sarcoidosis
Sjogren's syndrome
Lupus
HTLV-1/2
HIV
Neurosyphilis
Herpes family virus infections
Nutritional deficiency (B-12, folate, copper)
Hyperzincemia
Neoplasms
Vascular malformations (dural A-V fistula, venous ectasias)
Stroke (rarely)

For instance, when the extent of the lesion spans beyond a few vertebral segments in an acute attack or myelitis, the provider should give serious consideration to neuromyelitis optica (NMO). NMO requires long-term immunosuppression to reduce the risk of future lesions within the spinal cord, optic nerve, and on occasion in the brainstem tegmentum [Figure 3:19].

FIGURE 3:19

A sagittal T2 weighted MRI of the spinal cord illustrates a long confluent region of hyperintensity (Arrows) from a patient with neuromyelitis optica (NMO).



#### DIAGNOSTIC CRITERIA

The development of MRI criteria for the confirmation of the MS diagnosis has been of great utility in the context of randomized controlled trials. These criteria are based on the ‘golden rule’ of MS diagnosis; dissemination of disease activity in ‘time and space’. The most recognized and utilized MS diagnostic schema is the McDonald Criteria which were updated in 2010 [Table 3:4]. While the application of these criteria are highly specific for MS, (once mimicking conditions have been excluded [Table 3:5]) the clinical acumen and diagnostic judgment of the provider to this day remains tantamount.

TABLE 3:4: MCDONALD MS DIAGNOSTIC CRITERIA

*Requirements for the Diagnosis of MS / \*\*Diagnosis of exclusion in right clinical setting*

<i>Attack / Time</i>	<i>Clinical Lesion / Space</i>	
2 or more	Objective clinical evidence of 2 or more lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	** None
2 or more	1 lesion	Dissemination in space, demonstrated by: >1T2 lesion in at least two MS typical CNS regions (periventricular, juxtacortical, infratentorial, spinal cord); OR Await further clinical attack implicating a different CNS site
1 attack	2 lesions	Dissemination in time, demonstrated by: Simultaneous asymptomatic contrast-enhancing and non-enhancing lesions at any time; OR A new T2 and/or contrast-enhancing lesions(s) on follow-up MRI, irrespective of its timing; OR Await a second clinical attack
1 attack	1 lesion	Dissemination in space, demonstrated by > 1T2 lesion in at least two MS typical CNS regions (periventricular, juxtacortical, infratentorial, spinal cord); OR Await further clinical attack implicating a different CNS site AND Dissemination in time, demonstrated by Simultaneous asymptomatic contrast-enhancing and non-enhancing lesions at any time; OR new T2 and/or contrast-enhancing lesions(s) on follow-up MRI, irrespective of its timing; OR Await a second clinical attack

<p>0 attack, but neurologic progression suggestive of MS</p>		<p>One year of disease progression (retrospective or prospective)  AND at least 2 out of 3 criteria:  Dissemination in space in the brain based on &gt;1 T2 lesion in periventricular, juxtacortical or infratentorial regions;  Dissemination in space in the spinal cord based on &gt;2 T2 lesions; OR  Positive CSF</p>
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**TABLE 3:5: DIFFERENTIAL DIAGNOSIS OF DEMYELINATING LESIONS**

Age-related white matter changes
Acute disseminated encephalomyelitis
Behcet disease
Bacterial infections (syphilis, Lyme disease)
Cerebral autosomal dominant arteriopathy, subcortical infarcts, and leukoencephalopathy (CADASIL)
Cervical spondylosis or stenosis
HIV infection
Human T-lymphotrophic virus I/II
Ischemic optic neuropathy (arteritic and nonarteritic)
Leukodystrophies (e.g., adrenoleukodystrophy, metachromatic leukodystrophy)
Neoplasms (e.g., lymphoma, glioma, meningioma)
Migraine
Sarcoid
Sjogren syndrome
Stroke and ischemic cerebrovascular disease
Systemic lupus erythematosus, antiphospholipid antibody syndromes, and related collagen vascular disorders
Unidentified bright objects

Vascular malformations
Vasculitis (primary CNS or other)
Vitamin B12 deficiency

## CONCLUDING REMARKS

The application of MRI technology has contributed to the remarkable progress that has been achieved in our ability to expedite the confirmation of a diagnosis of MS. Following the initiation of treatment, the MRI has been increasingly utilized for surveillance purposes in order to document evidence of stability in radiographic measures of MS disease activity. Sophisticated non-conventional imaging methods are evolving that will further refine our ability to objectively monitor evidence of tissue injury, neuroprotection, and, perhaps, even neurorestoration. Research techniques such as magnetization transfer imaging, diffusion tensor imaging, and MR spectroscopic imaging are contributing to our understanding of the biological underpinnings of MS and the relationship between changes in CNS tissue architecture and the consequent alteration of neurological functioning. Insights derived from these novel capabilities are likely to influence the discovery of more effective treatments for our deserving patients.

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# Diagnostic Approach to Multiple Sclerosis

*Benjamin M. Greenberg, MD, MHS, Paula Hardeman, PA-C*

## CLINICAL PEARLS

- Optic Neuritis is usually associated with pain. Painless loss of vision should raise suspicion for alternate explanations
- Not everything that causes episodic multifocal demyelination is multiple sclerosis
- Longitudinally extensive transverse myelitis should prompt evaluations for other conditions such as Neuromyelitis Optica (NMO), Sjogren's syndrome, lupus, and sarcoid

## CASE VIGNETTE

A 26 year old woman with no significant past medical history presents to her primary care physician with a 3 day history of blurred vision. She reports being in her usual state of health until 3 days prior to the visit when she awoke with a perceived “film” over her vision in her right eye. This was associated with a dull temporal headache. Over the next two days, the visual changes intensified to the point where she could not read signs or work on her computer. Other than pain with eye movement there were no other symptoms. Her internist did a complete ophthalmologic and neurologic exam at which time the right eye visual acuity was 20/400, and an afferent papillary defect (APD) was detected on that side (pupil not dilating appropriately to the level of light reaching it). The patient was referred to ophthalmology for consultation where a dilated fundoscopic exam showed a normal retina and optic disc.

The patient was treated with 5 days of intravenous solumedrol at one gram per day followed by an oral prednisone taper. Brain MRI revealed 3 hyperintense white matter lesions on fluid attenuated inversion recovery (FLAIR) sequences in the periventricular cerebral white matter. One of these had an ovoid configuration and was observed to be perpendicular to the long axis of the ventricles on sagittal FLAIR imaging. Later, the consulting neurologist obtained a history of an episode of acute bilateral sensory loss that occurred nine months ago and involved a distribution from the abdomen to the feet. This event lasted for 2–3 weeks and resolved without treatment intervention. In fact the event, albeit highly conspicuous to the patient, was so mild in magnitude that she canceled her clinic appointment with her internist when the sensory disturbance began to abate approximately three days after its inception.

#### SUMMARY

This is a 26 year-old woman with clinical evidence of optic neuritis (decreased acuity, APD, pain with eye movement) and an antecedent history of a clinical event that suggested a partial sensory transverse myelitis (acute bilateral sensory loss and involved a distribution from the abdomen to the feet). Brain MRI demonstrated multiple lesions characteristic (by shape and location) for inflammatory demyelinating disease.

#### CLINICAL APPROACH & MANAGEMENT

The diagnosis of relapsing remitting multiple sclerosis (RRMS) remains a clinical exercise supported by ancillary clinical tests that can enhance accuracy and precision of identifying surrogate markers of demyelinating events. In order to confirm a diagnosis of RRMS patients must essentially fulfill three criteria based on a scheme proposed in 2001 by a consensus panel and was termed the McDonald Criteria:

1. Display evidence of demyelination affecting more than one CNS white matter tract system (separation in anatomical space);

2. Demonstrate evidence of demyelination occurring at two separate points in time (separation in time), signifying the multiphasic nature of the disorder;
3. Exclusion (or at least take into consideration) of a myriad of conditions that can mimic RRMS;

The McDonald criteria were revised in 2005 and then again in 2010 to codify the MS diagnostic process and outline how clinical investigations like MRI and cerebrospinal fluid analysis could be used with clinical presentation to help in the diagnosis of MS. In past versions of the McDonald Criteria, guidelines were presented for using MRI to demonstrate dissemination of disease in time and space, based on comparison of earlier baseline studies with a reference study performed at least 30 days after the clinical event. For the 2010 Revised Criteria dissemination in time can be demonstrated by a new T2 or gadolinium-enhancing lesion on a follow-up MRI, with reference to a baseline scan, regardless of when the baseline MRI was obtained (a 30 day interval between reference scan and baseline scan is no longer required). Dissemination in space can now be demonstrated with at least one T2 lesion in at least two out of four areas of the central nervous system: periventricular, juxtacortical, infratentorial, or spinal cord. None of these lesions have to be gadolinium enhancing.

Providers can make the diagnosis of RRMS even before two distinct clinical events have occurred as long as other diagnostic characteristics are found. MRI images that show characteristics of MS plaques can be combined with the finding of antibodies in the cerebrospinal fluid (CSF) that are oligoclonal bands. Antibodies derived from CNS epitopes are said to be compartment driven. A CSF analysis that identifies an elevated IgG index or oligoclonal bands would be of value, because it would suggest an immune mediated cause.

These can be utilized to substitute for multiple clinical attacks of demyelination separated in time or space. MS is not a condition that can be diagnosed with a single test (in contrast to HIV). It requires a set of criteria that can obviate the need to subject patients to the invasive brain biopsy. Biopsy has been considered a gold standard diagnostic test in that it can directly reveal the cardinal features of MS as a disease that results in demyelination, glial scarring or astrogliosis, inflammation, and axonal transection.

A systematic and extensive history should always accompany a careful and detailed physical and neurological examination as the cornerstones for making any neurologic diagnosis. However, MRI is very helpful in making the diagnosis of MS. There are several conventional MRI sequences that best display a number of cardinal radiologic features that are strongly correlated with the pathology of demyelinating disease. For example, T2 or FLAIR hyperintense ovoid lesions, particularly those that are geometrically oriented in a perpendicular trajectory to the long axis of the lateral ventricles (the so called Dawson's Fingers, and best appreciated on sagittal cuts) are nearly pathognomonic for MS. Despite the highly specific nature of these brain plaque profiles, not all patients with MS exhibit Dawson's Fingers.

While CSF is not necessary for diagnostic confirmation of MS, there are some patients in whom the analysis can be quite helpful. CSF can be practically useful in two ways. CSF analysis can identify evidence of intrathecal synthesis of antibodies (e.g. oligoclonal bands, IgG Index elevation and increased IgG synthesis rate). In those patients with clinically definite MS about 90% will have some evidence of compartment specific (the central nervous system) synthesis of antibodies. Despite this very high sensitivity in MS, a similar pattern of antibody synthesis in the CSF can be identified in patients afflicted with a broad diversity of infectious, inflammatory, collagen vascular, neoplastic or paraneoplastic conditions. Alternately, CSF analysis can sometimes exclude other conditions that might mimic MS such as infections and lymphoma.

The CSF profile itself may be indicative of an alternative diagnostic consideration. For example, either a pleocytosis in excess of 50 WBCs or a CSF protein concentration higher than 100mg/dL that is not explained by some other coincident disorders should trigger a consideration of a different diagnosis than MS. As with any diagnostic investigation, laboratory findings, like CSF analysis, must be interpreted in the context of the clinical situation. Consequently, not all patients with oligoclonal bands have MS. Of course, not all MS patients will necessarily have abnormal CSF testing. Some of the conditions that have been associated with oligoclonal bands include sarcoidosis, lymphoma and neuromyelitis optica; all are less likely associated with such changes when compared with MS.

#### CONDITIONS THAT MIMIC MS

The diagnosis process of confirming MS mandates exclusion of conditions that mimic MS and that can confuse the clinical picture. Any conditions that can cause intermittent neurologic dysfunction can potentially mimic MS. As in any differential diagnosis, there are vascular, metabolic, infectious, nutritional, autoimmune and physiologic processes that have symptoms reminiscent of MS. Focal decreases in blood flow can lead to hypoperfusion and is seen in transient ischemic events or vascular malformations. These can cause intermittent changes in strength, vision, sensation and balance. While the time course may help with differentiation, these events can easily be mistaken for demyelinating events. Metabolic vitamin deficiencies and endocrine derangements can mimic some of the features of MS (including fatigue). Some of the most common of these include vitamin B12, folate, vitamin D, iron (best assessed with serum ferritin), thyroid and copper deficiency and/or hyperzincemia. Although these conditions can cause symptoms and MRI changes, they would not generally cause CSF changes or the same types of enhancing lesions on MRI.

Immune mediated mimics include neuromyelitis optica (NMO), acute disseminated encephalomyelitis (ADEM), sarcoidosis, paraneoplastic syndromes and antibody mediated channelopathies. These disorders deserve the most attention as they are the most difficult to exclude from a patient's differential diagnosis. These are among the numerous diseases that can cause symptoms and corresponding white matter lesions on MRI. They frequently result in an evaluation to exclude MS. *Table 4:1* lists several of the conditions that cause white matter lesions on MRI, and some features that may differentiate them from the typical findings in an MS patient. Although this list provides general features that can differentiate other pathologies from MS, the features outlined are not absolute. There is considerable overlap between these conditions and MS-related MRI findings even as there is considerable variability from patient to patient within each of these conditions.

**TABLE 4:1: EXAMPLES OF RADIOGRAPHIC MIMICS OF MULTIPLE SCLEROSIS**

<i>Condition</i>	<i>Commonalities in MS</i>	<i>Features Different from MS</i>
Migraine	Scattered discrete white matter abnormalities	Tend to be smaller ( $\leq 3$ mm), non-enhancing
Stroke	Can be ovoid, discrete and scattered. Similar to acute demyelinating lesions, there can be restricted DWI.	Association of gray and white matter relative to vascular distribution. Small vessel ischemic changes tend to exclude commissural pathways such as the corpus callosum in favor of deep white matter.
Vascular Malformations	Discrete lesions	Evidence of draining veins, association with flow voids.
Sarcoidosis	Discrete white matter lesions, can be enhancing (which can be recalcitrant despite steroid treatment), can involve the corpus callosum.	Sometimes associated meningeal inflammation. Spinal cord lesions tend to be longitudinally extensive and may exhibit chronic enhancement.

ADEM- Acute Disseminated Encephomyelitis	Multifocal white matter lesions, enhancing and non-enhancing lesions, similar size and shape to MS.	Number of enhancing lesions, prominent gray matter involvement on conventional MRI.
Neuromyelitis Optica (NMO)	Multifocal white matter lesions, some with enhancement.	Spinal cord lesions tend to be longitudinally extensive, relative sparing of brain relative to optic nerve and spinal cord. Can produce diffuse brain lesions on occasion.
Systemic Lupus Erythematous	Multifocal white matter lesions, possible presence of post contrast enhancement.	Spinal cord lesions can be longitudinally extensive
Sjogren's	Multifocal white matter lesions, possible presence of post contrast enhancement	Spinal cord lesions can be longitudinally extensive
HIV	Diffuse white matter changes	In the absence of opportunistic infections, lack of enhancing lesions.
Progressive Multifocal Leukoencephalopathy (PML)	White matter lesion, can have enhancing characteristics	Usually monofocal
Leukodystrophy	White matter changes, periventricular location	Confluent changes, lack of enhancement
Perinatal Events	Multifocal T2 hyperintense white matter lesions	Static number, non-enhancing
B12 Deficiency	Can have spinal cord lesions with T2 changes. Can have multifocal white matter lesions.	Lack of enhancing lesions
Copper Deficiency and/or Hyperzincemia	Can have spinal cord lesions with T2 and post contrast changes	Relative lack of brain pathology
CNS Lymphoma	White matter lesions, ring enhancing post contrast	Callosal involvement follows different pattern
Gliomas	White matter lesion, can be enhancing	Tends to be monofocal, associated vasogenic edematous changes

The typical workup for suspected demyelinating disease includes a variety of tests. The exact battery may vary based on the presentation. Patients with vision loss may require evaluation for certain conditions that a patient with a myelopathy does not require. Certain infections will look like MS and should be tested for if the patient comes from specific regions or has had an exposure to these diseases. For example tick exposure in a locale of endemic *Borrelia burgdorferi* should lead to an investigation for Lyme Disease. Another infectious cause of demyelination and myelopathy is the retrovirus, human T-lymphotropic virus (HTLV-I/II), prominently seen in tropical settings and sexually transmitted. *Table 4:2* summarizes a standard workup that most patients should have, but is not comprehensive for all circumstances.

**TABLE 4:2: BASIC WORKUP FOR PATIENTS WITH SUSPECTED DEMYELINATING DISEASE**

<i>Test</i>	<i>Reason</i>
Brain MRI	Multifocal brain lesions suggest MS
NMO IgG	Neuromyelitis Optica (NMO)
SSA/SSB	Sjogren's Associated transverse myelitis
ANA	Lupus Associated transverse myelitis
Anticardiolipin Antibody	Antiphospholipid Syndrome Associated Transverse myelitis
Copper and Zinc	Copper Deficiency (and/or Zinc excess) Associated Myelopathy
Vitamin B12	Subacute Combined Degeneration
RPR	Tabes Dorsales
Chest CT Scan (consider gallium or indium scan); Angiotensin converting enzyme (ACE)	Sarcoidosis
CSF Oligoclonal Bands/IgG Index/IgG rate	Associated with MS

Neuromyelitis optica (NMO) deserves special attention among all the potential mimics of multiple sclerosis. Patients that have NMO are often misdiagnosed with MS because of the conspicuous clinical and radiographic similarities. Unfortunately, patients with NMO do not respond to conventional MS disease modifying therapies and the outcomes can be disastrous. Thus, identifying the features of NMO early, and differentiating them from MS, is critical.

In general, NMO patients suffer from a demyelination called transverse myelitis that extends over at least 3 vertebral segments so that it is described as *longitudinally extensive*. In patients with MS, the spinal lesions are smaller so are called *skip lesions*. Generally patients with NMO have less severe involvement above the spinal cord than MS patients. Even so, the MRI in patients with NMO can demonstrate some white matter lesions, and some can be bizarre, extensive, and affect the midline structures such as the hypothalamus and the brainstem tegmentum. In general, patients with NMO have no oligoclonal bands in their CSF, and have a positive serum anti-Aquaporin-4 antibody test (NMO-IgG or AQ4-Ab) and patients with MS have abnormal CSF antibodies and a negative serum NMO-IgG antibody test.

These differences are summarized in [Table 4:3](#) and can be used as a guide to evaluate patients when considering these two diagnoses. This table is merely a guide, as no feature is absolute. For example, there are many NMO patients with brain MRIs that look exactly like that derived from a typical MS patient. However, one must collect and consider the available data about a patient to render the most appropriate ‘working diagnosis’. The experienced clinician knows that the diagnosis in all patients must be periodically reconsidered and reserve the right to change their minds about a diagnosis when new data or test results become available. Likewise, a change in symptoms or clinical circumstances can mandate reconsideration of the most likely ‘working diagnosis’. From the diagnostic standpoint, to be ‘right’ is less important than to work tirelessly to ‘get it right’ on behalf of patients.

TABLE 4:3: DIFFERENTIATING MS FROM NMO

<i>Feature</i>	<i>Multiple Sclerosis</i>	<i>Neuromyelitis Optica</i>
Optic Neuritis	Tends to be mild and unilateral	Tends to be severe and/or bilateral
Transverse Myelitis	Small partial myelitis with skip lesions (generally spanning up to 2 or at most 3 vertebral levels)	Tends to be longitudinally extensive (more than 3 segments), but not always
Brain MRI	Abnormal	Normal or mild involvement
Oligoclonal Bands	Tend to be present	Tend to be absent
Anti-Aquaporin 4 IgG (NMO IgG)	Absent	50–70% Positive

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# Disorders Related to Multiple Sclerosis

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## CLINICAL PEARLS

- Acute disseminated encephalomyelitis (ADEM) is usually associated with changes in mental status
- Chest x-rays and serum angiotensin converting enzyme (ACE) levels are poor screening tests for sarcoid
- The anti-aquaporin 4 IgG is highly specific for Neuromyelitis Optica (NMO)

## CASE VIGNETTE

A 32 year old previously healthy patient presented 4 months ago with a longitudinally extensive transverse myelitis and on exam exhibited spastic upper extremities and spastic paraplegia, and a C2/C3 sensory level. Spinal Cord imaging identified extensive inflammatory lesions from C2 to L4 with no lesions identified on brain MRI. She has now presented in clinic again with another transverse myelitis attack and optic neuritis. She also tested positive for serum NMO-IgG.

## SUMMARY

This patient fulfils criteria for neuromyelitis optica (NMO). Neuromyelitis optica (NMO) is an idiopathic, severe, inflammatory demyelinating disease of the central nervous system that causes severe optic neuritis and myelitis attacks. Early discrimination between multiple sclerosis (MS) and NMO is important, as optimum treatment for both diseases may differ considerably.

*Transverse Myelitis*

A fairly common presentation of MS occurs in patients who develop demyelination of the spinal cord, so called transverse myelitis. These individuals can present with numbness, weakness, walking difficulties, and/or bladder and bowel dysfunction. When inflammation of the spinal cord is identified patients must be aggressively treated to limit the scope of damage. Subsequently patients must be carefully and systematically evaluated in an attempt to understand the underlying cause of the myelitis so that an appropriate treatment and prevention plan can be formulated. One possibility is that the myelitis is a first attack of MS but lacks sufficient complimentary evidence to confirm the diagnosis of MS. This is sometimes referred to as a *forme fruste*, French for the partial presentation of a disease. Yet at the time of the myelitis there is clinical evidence of only one lesion and only one event in time. Remember the basic tenet of MS diagnosis is that the disease is characterized by multiple events in space and time. In this case the patient has only the one event.

A screening MRI is important at the time of the first clinically significant neurologic syndrome to assess whether this event may be a first attack of MS. The individual has an 80% risk of the transverse myelitis being a first clinical attack of MS if two or more lesions in the brain are seen on the screening MRI, and the lesions are found in the white matter consistent with demyelinating disease. If the MRI is normal, then the risk is only 20% over 14 years, and the patient most likely has idiopathic transverse myelitis, especially if the remainder of the workup is negative. The diagnosis of MS would be confirmed if the patient had a subsequent episode of demyelination, or exhibited a new lesion on MRI that was consistent with demyelination.

*Acute Disseminated Encephalomyelitis (ADEM)*

Idiopathic transverse myelitis is a demyelinating disease that generally targets a single location once. Acute disseminated encephalomyelitis (ADEM) strikes multiple locations only once. ADEM is more common

in children than adults and causes multifocal demyelination, often associated with changes in consciousness or mental status. The CSF profile can be indistinguishable from that observed in MS. ADEM can be quite difficult to differentiate from a first attack of MS in many cases. Monophasic ADEM may be a disorder that results from an infectious or post-infectious process (although an infection is rarely identified).

### *Sarcoidosis and neuromyelitis optica (NMO)*

There are two more conditions that can closely mimic MS and should be considered in any patient being evaluated for MS. Sarcoidosis and neuromyelitis optica (NMO) are rare conditions. If identified early it can make a significant difference because the clinical treatments are so different. Both of these conditions can cause attacks and corresponding symptoms that are separated in time and space. Sarcoid, while more common in African American women, can also occur in Caucasians and men. Five percent of patients with sarcoidosis present with neurologic symptoms, but without the pulmonary symptoms typical of sarcoidosis. Serum angiotensin converting enzyme (ACE) levels have been used for years to diagnose and monitor sarcoidosis. However, ACE levels are elevated in only about half of those with neurosarcoidosis, and that limits the effectiveness of this test. More valuable tests for sarcoid would include a chest CT, gallium scan, indium scan, or a PET scan to look for evidence of metabolically active lymph nodes. Activated lymph nodes could be targeted for biopsy in order to look for evidence of granulomatous (non-caseating) inflammation that is diagnostic of sarcoidosis.

NMO has been thought of as a variant of MS until recently. These patients present with severe and recurrent loss of vision from optic neuritis and change in sensations of the body from spinal cord inflammation and demyelination (transverse myelitis). Historically, NMO patients were described as having normal brain MRIs; but this is inaccurate. These patients can have brain lesions in addition to the well known spinal and optic abnormalities.

Autoimmune targeting of a transport protein, aquaporin, of cells in the brain seems to underlie the pathogenesis of NMO and the identification of the anti-aquaporin-4 IgG has broadened the spectrum of disease associated with NMO. Patients can present with a variety of brain lesions, similar to ADEM events. Brainstem tegmentum events can be associated with vomiting, vestibular or ocular motor abnormalities, and the more classic syndromes of optic neuritis or transverse myelitis. The differentiation of NMO from other inflammatory CNS conditions cannot be overemphasized. Typical MS disease modifying treatments do not work for these patients with NMO. Instead patients with NMO respond best to immunosuppression with steroids, mycophenolate mofetil, azathioprine or Rituximab.

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# Disease Modifying Interventions

*Elliot M Frohman, MD, PhD*

## CLINICAL PEARLS

- The two principle classes of MS treatments are the  $\beta$ -interferons and *glatiramer acetate*.
- Natalizumab can be used in patients not benefitting sufficiently from interferons or glatiramer acetate, or who can not tolerate injection therapy.
- Natalizumab may be considered for first line treatment in patients with very active disease or in those individuals who present with features that portend a more ominous disease trajectory (e.g. African Americans and those with MS targeting the brainstem, cerebellum, and spinal cord motor tracks).
- Mitoxantrone is a powerful anti-inflammatory treatment. There is demonstrated benefit for patients with different forms of MS including relapsing-remitting, secondary progressive and progressive-relapsing subtypes. This agent is associated with an increased risk of leukemia and cardiotoxicity
- Fingolimod (FTY-720) was recently approved by the FDA as the first oral agent indicated for relapsing forms of MS. Its mechanism of action involves modulation of the sphingosine-1-phosphate receptor. This drug promotes the redistribution of lymphocytes from the circulation to the lymphoid organs and inhibits the egress of lymphocytes back into circulation.

## CASE VIGNETTE

A twenty-three year old woman felt well with no past neurological history until four years ago when she noted a peculiar sensory disturbance localized to her right foot first thing in the morning. She described the sensation as 'tingling', like 'pins and needles' (i.e. paresthesias). When touching her skin she noted reduced sensation (numbness). Over the course of the morning, these sensations moved up to her chest on the right side in conjunction with a squeezing sensation around her mid thorax. She denied any weakness, alteration in gait, or change in bowel or bladder function.

She was seen briefly in the local emergency room and a neurologist was consulted. She was not able to relate a prior history of neurological dysfunction. She had no antecedent fever, infection, trauma, or known exposures to explain the symptoms. On neurological exam, she had reduced sensation to soft touch in a circumferential distribution with a sensory level at approximately T5. In addition, she had evidence of mild optic disc pallor in the left eye that was suggestive of a subclinical optic neuropathy. The patient denied having an episode of visual disturbance that would correlate with optic neuritis.

In this patient, the MRI investigations revealed a gadolinium enhanced plaque in the spinal cord dorsal column on the right from about T3-T4. In the brain, the MRI showed a few bright lesions in the deep white matter on FLAIR and T2 images. She also had lesions in the corpus callosum. One of the white matter lesions was ovoid in shape, and another was oriented perpendicularly to the long axis of the ventricles. Cerebrospinal fluid showed ten lymphocytes, normal protein and glucose, two oligoclonal bands and an elevated IgG index of 1.60 (normal range <0.7). All other laboratory tests were normal including a diagnostic search for mimics.

The neurologist diagnosed inflammatory thoracic myelitis. The patient was treated with intravenous methylprednisolone at 1gm daily for three days without a taper. Her neurologic symptoms improved to the patient's baseline within about two weeks. Following the various investigations and treatment of myelitis, the patient had a follow-up clinic appointment with the neurologist to discuss the implications of having had an episode of myelitis in the context of her brain MRI and spinal fluid findings.

Although this patient had only a single clinical inflammatory event documented, also known as a clinical isolated syndrome (CIS), there was clear evidence of disseminated brain lesions that likely predated the episode of myelitis (they were not enhancing). This patient also had evidence of optic disc pallor. Optic disc pallor is a manifestation of both inflammatory optic neuritis and subclinical optic neuropathy. Optic disc pallor signifies the presence astrogliosis, a cardinal feature of the histopathological signature of MS. The diagnosis of MS was confirmed by the MRI findings and the antibodies in the CSF. Now, the discussion would turn to the topic of disease modifying therapy. In essence, what could be offered to this patient to reduce the risk of future clinical events of the disease process? We want to reduce clinical attacks and disease progression, as well as MRI lesions, even if these lesions are ineloquent or clinically silent.

#### S U M M A R Y

This case takes us through the history of a patient who first presented with signs and symptoms of thoracic myelitis and was diagnosed with clinically isolated syndrome (CIS) and treated with steroids. She subsequently was found to have optic neuropathy, oligoclonal bands in the CSF and brain lesions consistent with multiple sclerosis. She was diagnosed with Multiple Sclerosis at that time.

In such a patient, we have effective and safe treatments that can be self-administered by patients either by subcutaneous or intramuscular parenteral injection. The two principle classes of MS treatments are the  $\beta$ -interferons and *glatiramer acetate*.

### $\beta$ Interferon

Interferons are naturally occurring immune modulating agents that are synthesized within the immune system and serve to regulate the development of immune responses, influence trafficking of immune cells across the blood brain barrier, and influence the kinds of cytokines and chemokines that are produced by T and B Lymphocytes and macrophages (e.g. immune mononuclear cells).  $\beta$ -interferon also has antiviral activity. The use of  $\beta$ -interferon has been shown to reduce the risk and severity of clinical exacerbations of MS by about 30% and to reduce the risk of disease progression. This also means a reduction in the corresponding compromise or loss of functional capabilities including physical, emotional, and intellectual capacities. Further,  $\beta$ -interferon markedly reduces the risk of developing new MRI lesions by about 70–90%, depending upon the imaging metric being evaluated.

Three of the interferons (Betaseron<sup>®</sup>, Rebif<sup>®</sup>, and Extavia<sup>®</sup>) are administered by subcutaneous injection and taken either every other day (Betaseron and Extavia) or three times weekly (Rebif). These medications are available in prefilled syringes that can be used with an autoinjector device. This makes the process of taking treatment substantially convenient and highly practical. A once weekly formulation of interferon (Avonex<sup>®</sup>) is available and administered through intramuscular injection. The side effects of interferons are well recognized and include flu-like symptoms, headache, and arthralgias. In most patients, pre-treatment with a nonsteroidal anti-inflammatory agent is sufficient to abolish these side effects. A long-acting formulation like naproxyn (Naprelan<sup>®</sup>) can be a well tolerated and cost effective pre-treatment for interferon treated MS patients.

Despite pre-treatment patients may continue to have stereotyped interferon side effects. In such circumstances, the Interferon dosage can be re-titrated. Alternatively, a low dose of 10–30mg of prednisone can be implemented before the injections for a few weeks. Headache may become an issue and if not adequately suppressed with NSAIDS, patients can be treated with migraine abortive triptans. Triptans prevent headache in almost all patients. A combined preparation called Treximet® includes naproxyn (500mg) and sumitriptan (85mg).

Injection site reactions are more common with subcutaneous interferon treatment when compared to weekly intramuscular interferon. Careful counseling and attention to injection technique and site rotation typically limits the impact of this frustrating side effect. Patients with MS who are treated with interferon should have surveillance laboratory studies to ensure that the treatment has not produced untoward side effects of liver dysfunction, anemia, leukopenia or thyroid dysfunction. These studies are performed at baseline, then again at three months after the initiation of treatment and every six months afterward.

### *Glatiramer Acetate*

Another first-line therapy for relapsing forms of MS is glatiramer acetate (Copaxone®). This therapy consists of a random polymer of the four principle amino acids contained in myelin basic protein. This polymer is administered by subcutaneous injection daily and appears to have potent immunomodulatory properties including the ability to increase the number of immune regulatory cells. These cells modulate by decreasing the immune responses and thereby reduce excessive inflammation. Glatiramer acetate, as with the interferons, has been demonstrated to reduce the risk and severity of MS attacks and to reduce MRI lesions over time.

Recent clinical trials compared interferon beta-1b (Betaseron or Rebif) to glatiramer (Copaxone) and reveal that these two different classes of agents have a similar efficacy on the magnitude of the MS disease process. Unlike the interferons, glatiramer acetate has fewer adverse side effects with the exception of site reactions.

Careful attention to injection technique and site rotation can help to mitigate post-injection site reactions (which can produce lumps under the skin, eschar, and, rarely, infection). Over time, and with repetitive injection, lipoatrophy can develop in patients treated with glatiramer acetate.

#### OTHER FDA APPROVED TREATMENTS

Another FDA approved treatment for MS is mitoxantrone (Novantrone®), a powerful anti-inflammatory treatment that can effectively and rapidly reduce inflammation and promote accelerated resolution of large magnitude exacerbations in the brain and spinal cord. Mitoxantrone is given parenterally at 5–12mg/m<sup>2</sup> monthly to every three months. There is demonstrated benefit for patients with different forms of MS including relapsing-remitting, secondary progressive and progressive-relapsing subtypes. This agent is associated with an increased risk of leukemia and cardiotoxicity. Therefore, mitoxantrone has principally been utilized in patients with very active and aggressive variants of MS as a temporizing therapy to induce remission.

Once remission is achieved, the use of mitoxantrone is discontinued and a safer agent is utilized indefinitely for disease modification. A heightened risk of a vacuolar cardiomyopathy is associated with doses of mitoxantrone greater than 140mg/m<sup>2</sup>. This agent can compromise cardiac contractility that can be confirmed by a reduction in ejection fraction measured through a quantitative nuclear study of cardiac ejection such as multiple gated acquisition (MUGA) scanning. Ejection fraction studies should be determined before each dose of mitoxantrone, and then yearly, following cessation of therapy. This agent is not continued or used if a patient has an estimated ejection fraction below 50%, or if there is an interval reduction of the ejection fraction by 10–15%.

Natalizumab (Tysabri®) is a monoclonal antibody that binds to a well described antigen, VLA-4. This antigen is a cell-surface integrin receptor that is expressed on the surface of T lymphocytes, B lymphocytes and macrophages. Integrins are transmembrane glycoproteins that mediate cellular adhesion to substrates. The migration of lymphocytes and macro-

phages is necessary for immune surveillance as they move from the blood into the brain. This transmigration is markedly augmented in patients with MS. VLA-4 associates with an adhesion factor expressed by endothelial cells (vascular cell adhesion molecule or VCAM) as a crucial step in the trafficking of inflammatory cells into the brain and spinal cord. Natalizumab blocks this interaction and results in a profound decrease of CNS mononuclear cell trafficking that reduces MS exacerbations by almost 70% and disease progression by about 50%. Even more impressive, natalizumab will reduce new gadolinium enhancing lesions by over 90%. Many clinicians use natalizumab for patients who have not benefitted sufficiently from interferons or glatiramer acetate, or who cannot tolerate injection therapy. Natalizumab may be considered for first line treatment in patients with very active disease or in those individuals who present with features that portend a more ominous disease trajectory (e.g. African Americans and those with MS targeting the brainstem, cerebellum, and spinal cord motor tracks).

There are several issues associated with the use of natalizumab. Infusion related hypersensitivity occurs in about 1% of patients treated with natalizumab. This reaction is generally at the time of the second dose in natalizumab naïve patients and is associated with the development of a natalizumab neutralizing antibody. If the neutralizing antibodies are persistent, this can impact the bioavailability of the drug and even render the drug useless. The profound efficacy of this novel and highly targeted immunotherapeutic is counterbalanced by the associated risk of developing progressive multifocal leukoencephalopathy (PML). This disorder is caused by JC virus, a member of the human polyomavirus (formerly known as papovavirus), that infects oligodendrocytes and results in a rapid demyelination that can be life threatening. The disorder is most commonly associated with profound immunosuppression, and has been documented in patients treated with a variety of immunosuppressive agents for a diversity of autoimmune disorders (e.g. Crohn's disease, lupus, rheumatoid arthritis, psoriasis, etc).

Recent experience with natalizumab related PML has suggested that survival can be improved if the diagnosis is confirmed immediately (usually by testing the CSF for JC virus; occasionally via brain biopsy), and plasma exchange is instituted to remove the monoclonal antibody. A major risk of stopping immune suppressive agents in the context of PML is that the return of functional immune surveillance can result in massive inflammation and damage to the brain, and is referred to as the immune reconstitution inflammatory syndrome (IRIS). Recent experience in treating PML secondary to natalizumab therapy by our group suggests that plasma exchange effectively removes circulating monoclonal antibody, and weekly steroids can quell emerging IRIS. Further intravenous immune globulin (IVIg) has been used by our group to reduce inflammation, and promote viral clearance (since many blood donors have circulating JCV IgG). Frequent MRIs are useful to monitor for IRIS and to correspondingly adjust anti-inflammatory therapy. The addition of newly emerging antiviral agents, may represent a complex but effective regimen for optimizing the chances of survival and maintaining functional capabilities in those afflicted by IRIS.

Fingolimod (FTY-720) was recently approved by the FDA, as the first oral agent indicated for relapsing forms of MS. The mechanism of action involves modulation of the sphingosine-1-phosphate receptor. This drug promotes the redistribution of lymphocytes from the circulation to the lymphoid organs and inhibits the egress of lymphocytes back into circulation. Randomized controlled trials have shown significant efficacy of this agent and significant reduction of both clinical and radiographic MS disease activity. Adverse events observed in clinical trials have included first-dose bradycardia, cardiac rhythm changes, reactive airway events, macular edema, skin cancers, and risk of infections.

In the near future, a number of novel agents will emerge for the treatment of MS. Another intriguing oral agent under development is cladribine. This agent is a deoxyadenosine analog that prevents DNA replication and repair in lymphocytes, leading to potent anti-inflammatory actions that have been shown to mitigate MS attacks and MRI activity. Given its ability to irreversibly and profoundly suppress immune cell function and affect DNA, this agent if eventually approved will likely be restricted to carefully selected patients and totally avoided in women of child-bearing age. Vigilance for infection, organ toxicity, and cancer risk will be part of the risk map for the application of this agent in MS.

Laquinimod is an oral immunomodulatory agent under development for MS, and appears to not result in significant immune suppression but rather may promote skewing of the immune system toward a more anti-inflammatory bias. Teriflunamide is an oral agent that inhibits the synthesis of DNA pyrimidine bases in rapidly dividing cells such as T and B cells and macrophages, and may thereby reduce inflammation (and likely produce immune suppression).

Another novel oral therapy under development is dimethylfumaric acid (BG-12), which is related to fumaric acid, an agent used for many years in psoriasis. Fumarates appear to modulate a number of oxidative pathways and thereby may influence the mechanisms by which autoimmune mechanisms provoke downstream pathways of tissue damage. This agent will be administered three times daily and is associated with a number of side effects including flushing, headache, loose stools, and GI distress.

Two intravenous administered monoclonal antibodies under development exert highly active immune suppressive effects, with great promise for the treatment of MS. Ocrelizumab, the humanized version of rituximab (Rituxan<sup>®</sup>), is an antibody that targets CD20, a cell surface epitope on developing B cells. Upon binding to its target, these agents provoke rapid destruction of circulating B cells via two principal mechanisms, antibody-dependent cellular cytotoxicity, and complement-dependent

cellular cytotoxicity. A phase II controlled trial has shown that this therapeutic strategy had significant efficacy on reducing MS attacks and MRI metrics of disease activity. The effect of CD20 targeting has ramifications for both B and T cell immune function, and as such, these treatments can be associated with risk of infection (including PML), and organ toxicity. Alutuzimab (CAMPATH®) is a monoclonal antibody that binds to CD52, an epitope common to most cells within the immune system. Treatment with this agent essentially results in an antibody-mediated ablation of the circulating immune system. The consequence is that this agent appears to rapidly and profoundly establish both clinical and radiographic remission of MS. Correspondingly, alutuzimab has been associated with the risk of developing new autoimmune disorders including thyroiditis (in up to 30% of cases), idiopathic thrombocytopenic purpura (ITP) (in about 3%), and potentially others (e.g. Goodpasture's syndrome, infections, increased cancer risk, organ toxicity, and hypersensitivity reactions with potentially resultant neutralizing antibodies).

#### CLINICAL VIGNETTE: OUTCOME

Diagnosed with MS four years ago, the patient was initially treated with interferon beta and was highly adherent and experienced excellent tolerability with the use of Naprelan pretreatment. However, she developed an episode of left optic neuritis with significant residual visual loss after thirteen months of therapy. Her blood was tested for interferon neutralizing antibodies and it was negative. Hence the treatment was continued and a monthly steroids (one day) pulse was added to reduce the risk of attacks. After three months she developed horizontal binocular diplopia resulting from a left VI nerve palsy that was interpreted as another MS exacerbation. MRI showed a left pontine tegmentum lesion and four additional ineloquent lesions in the cerebral white matter, two of which were enhancing with gadolinium.

In all patients with exacerbations the clinician should assure adherence to the therapeutic protocol. This patient had done all that was prescribed. Monthly corticosteroids were continued (but increased from one to three days) and then treatment was transitioned to daily glatiramer acetate. Treatment intensification with the use of natalizumab was discussed especially in light of the pontine (infratentorial distribution) attack as this is a harbinger for a more ominous and disabling course of MS. However, her deep-seated concern about PML precluded a serious discussion about changing treatment to natalizumab.

The patient began glatiramer acetate and did very well with daily (and adherent) subcutaneous injections and monthly (3 days) steroids until about 14 months ago when she came to clinic for an urgent visit.

On examination she was ataxic, vomiting, and complaining of vertigo, vertical oblique diplopia, and profound fatigue. Examination revealed a dehydrated patient unable to walk, listing markedly to the right. Her eyes had a primary position downbeat nystagmus. She had pupillary anisocoria where the right pupil was constricted in conjunction with ptosis. The difference in the anisocoria was greatest when the small right pupil failed to dilate in darkness and this confirmed a sympathetic defect consistent with a right Horner's syndrome. The soft palate elevated/deviated to the left and was indicative of a right palatal weakness. Her voice was hoarse.

MRI revealed an enhancing plaque in the right medullary tegmentum with extension into the ipsilateral inferior cerebellar peduncle. Repeat diagnostic studies and a workup for stroke failed to reveal another explanation for the patient's new syndrome (including a NMO-IgG assay, MRA, and conventional angiogram to carefully exclude a posterior circulation dissection).

Over the course of four days the patient markedly stabilized. She was able to stand but was still ataxic with vertigo and nystagmus. However she now exhibited right tongue deviation as if the right side muscles of the tongue were weak as would be seen with right hypoglossal nerve/nuclear lesion, a lower motor neuron lesion of cranial nerve XII. Further, the right side of the face had hypesthesia to pin prick with reduced sensation in the left body. Attempted midline tongue protrusion was only mildly right deviating. A repeat MRI showed the persistent lesion, contrast enhanced, that now had some extension into the medial medullary zone, as was indicated by the eloquent symptoms.

This was a significant interval change with the emergence of novel neurological signs and symptoms that was consistent with more extensive enhancement of the medullary lesion. The patient was admitted to the hospital for aggressive therapy that was advanced to full volume plasma exchanges done five times over seven days.

The patient responded with remarkable and rapid improvement following the second consecutive daily exchange. Two weeks later most signs and symptoms had resolved with the exception of the voice hoarseness, the Horner's syndrome, and the tongue weakness. The patient was transferred to the physical medicine and neurorehabilitation unit where she received comprehensive multidisciplinary care. During her time in rehabilitation there was a discussion about the ominous nature of the current infratentorial attack to the brainstem. In this patient a transition to monthly natalizumab therapy would be advisable.

Since the inception of natalizumab treatment the patient has been attack and lesion free. Her fatigue had resolved and, her neurological signs and symptoms completely resolved in the first six months of natalizumab treatment. A search for a natalizumab neutralizing antibody at 24 weeks was unremarkable. This case illustrates how complex patient management can lead to excellent outcomes for the patient. In this patient, she indicated she had not felt as good in four years.

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# Treatment of Acute Exacerbations

*Elliot M. Frohman, MD, PhD*

## CLINICAL PEARLS

- Currently there is no data to support the use of a specific steroid for exacerbations with the exception of a first event of optic neuritis. In this case, high dose IV methylprednisolone (1gm daily for 3 days) followed by a prednisone taper has been shown to hasten recovery of vision.
- Bonafide exacerbations are typically expected to last for at least twenty-four hours and often involve the evolution of novel symptoms not previously experienced by the patient.
- With regard to MS it has been established that high-dose, short-term intravenous corticosteroid therapy provides symptomatic relief, improves motor function, and shortens the recovery phase of acute disease-related attacks

## CASE VIGNETTE

A 24 year-old patient was admitted to the hospital with acute onset of weakness and numbness of the lower limbs and urinary incontinence. She had a history of relapsing and remitting MS for which she had been treated with injections of the disease modifying treatment interferon-beta1a (IFNβ1a). Her last treatment was three months ago due to poor adherence with the treatment regimen. Physical exam showed hypesthetic-paraparesis and a sensory level at T8. MRI showed a new enhancing lesion within the spinal cord at T6. A test for interferon neutralizing antibodies was negative. There was a nationwide shortage of methylprednisolone (Solumedrol).

Instead she was treated with IV dexamethasone at 160mg/day for 5 days without a taper. (Most MS experts today do not use tapers, except in select circumstances). Physical therapy was started. She improved significantly over the course of two to three weeks.

## SUMMARY

This case illustrates the inflammatory nature of MS as a demyelinating disorder characterized by a multiphasic course of neurological exacerbations, periods of clinical remission, and ultimately progressive deterioration of functional capabilities. The relapsing-remitting phase of the disease involves acute interruption in neurological functioning related to areas of inflammation in discrete tract systems of the brain and spinal cord. The treatment of MS exacerbations with anti-inflammatory agents such as corticosteroids and adrenocorticopin hormone (ACTH) represents an established practice throughout the neurology community that is based on scientific rationale. However the use of these medicines has not been the subject of many randomized control trials. Rather, the approach to using anti-inflammatory drugs in clinical practice is derived from expert opinion and anecdotal experience.

## CLINICAL APPROACH & MANAGEMENT

### *Defining an Exacerbation*

- Exacerbations of MS are defined by episodes of neurological dysfunction that occur spontaneously and are not on the basis of an alternative etiology.
- Bona fide exacerbations have the following characteristics:
  - typically expected to last at least twenty-four hours
  - often involve the evolution of novel symptoms not previously experienced by the patient
  - The exacerbation would not be explained on the basis of some other etiology such as infection, stress, or elevation of core body temperature (i.e. the Uhthoff phenomenon).
- An important disclaimer to this description is that infectious processes are now well known to trigger the inflammatory process through signaling pathways that can culminate in an infection-associated exacerbation of MS.

The treatment of MS-related exacerbations has traditionally involved the employment of anti-inflammatory medicines such as corticosteroids and ACTH in order to accelerate resolution of the neurologic deficits sustained from the new area of inflammatory demyelination, as well as to mitigate the severity of the attack and potentially reduce the risk of persistent residual deficits.

### *Characterizing the Actions of Corticosteroids*

Corticosteroids are potent effectors in the prevention and suppression of inflammation caused by chemical, immunological, infectious, and mechanical stressors. The effect of corticosteroids on the immune system is thought to be largely dose- and duration-dependent. In MS, shorter courses of high dose steroid regimens are typically used to treat acute MS exacerbations, whereas relatively low doses of corticosteroids have been shown to be effective and relatively safe for long-term therapy of other inflammatory diseases.

Corticosteroids and ACTH have the capability to restore the integrity of the blood brain barrier, reduce inflammation and modulate mononuclear trafficking mechanisms. In a similar fashion, these agents can serve to reduce the activity of matrix metalloproteinases (MMPs), and have potent anti-edema effects, which can help prevent neuronal membrane dysfunction. Recent evidence indicates that steroids augment motor evoked potentials elicited by transcranial magnetic stimulation and thus may enhance the fidelity of electrical transmission in demyelinated axonal segments.

### *Objectives of Acute Intervention for MS Exacerbations*

The application of anti-inflammatory treatment for MS related exacerbations serves to accelerate recovery from the attack of functional disability, and potentially mitigates the severity of the attack itself. With respect to the use of corticosteroids and ACTH for treating MS attacks, an evidence-based assessment of these agents was undertaken by the Therapeutics and Technology Assessment Committee of the American Academy of Neurology that considered disease modifying therapies for MS.

In terms of using corticosteroids and ACTH the Committee found that:

1. Treatment with corticosteroids serves to accelerate recovery from attacks of MS and it is appropriate to consider employing these agents.
2. Long-term benefits of corticosteroids and ACTH on the disease course has not been demonstrated.
3. Compelling evidence does not currently exist to favor the utilization of a particular type of agent, route of administration, or dosage (although most neurologists use high doses of these agents for the treatment of attacks).

### *Practical Considerations for Treating Exacerbations*

A point of great controversy has been whether an oral steroid taper is useful following the initial IV ‘pulse’ of steroid. There is no good data to answer this question. The optic neuritis treatment trial (ONTT) did show that IV Methylprednisilone (IV MP) followed by an oral prednisone taper was associated with superior efficacy in reducing the risk of a second event of inflammatory demyelination when compared to patients randomized to placebo or low dose oral prednisone alone (without an antecedent IV pulse). An optic neuritis study by Herishanus showed that high dose IV steroids without a subsequent taper was associated with a higher risk of recurrent attacks when compared to patients treated with placebo.

### *ACTH gel*

An alternative approach to IV MP that is evidence based with respect to accelerating recovery from MS attacks involves the use of ACTH gel. This can be used parenterally by the intramuscular or subcutaneous route of administration [Table 7:1]. Although it has some theoretical advantages, it is more expensive than steroids, has more side effects, and gives less consistent results. ACTH can be used when patients are unresponsive to corticosteroids, or in cases where its positive effects on bone via stimulation of DHEA and mineralocorticoids may be desirable.

### *Steroids with interferons, glatiramer acetate and natalizumab*

While treatment of exacerbations for those taking interferons or glatiramer acetate can involve both the initial pulse (corticosteroids or ACTH) with or without a taper, for patients utilizing natalizumab therapy it may be prudent to utilize only short courses of these agents (up to three days) without a taper. The premise here is an attempt to avoid intensified compromise of immune surveillance that could be the pretext for PML.

### *Low dose vs. High dose steroid regimens*

'Low dose' regimens of corticosteroids have been used for the treatment of 'milder' MS exacerbations and this most certainly will continue. The potential problem with this approach is the lack of information with respect to efficacy, and there is a lack of evidence that mild attacks benefit from any treatment. For example, the ONTT indicated that low-dose oral prednisone (1mg/kg) was associated with an approximate doubling of the recurrence rate of optic neuritis when compared to the high-dose (IV followed by an oral taper) steroid limb or the placebo group. Because there are data demonstrating efficacy and safety, high doses of corticosteroids and ACTH should generally be used to treat MS exacerbations. There will certainly be individual exceptions based on co-morbid conditions, patient characteristics or the features of the attack. With regard to MS, high-dose, short-term intravenous corticosteroid therapy provides symptomatic relief, improves motor function, and shortens the recovery phase of acute disease-related attacks.

### *Orally Administered Corticosteroids*

A number of small studies have demonstrated that high dose oral steroid regimens appear comparable to those administered parenterally with similar benefit and tolerability. The use of oral steroid regimens has obvious advantages for treating MS attacks including markedly reduced cost, ease of use, and obviating the need for intravenous, intramuscular (ACTH), or subcutaneous (ACTH) administrations. High dose oral steroid treatment has no significant impact on gastric permeability.

This emphasizes the concept that steroid-related gastritis is not due to direct effects on the gastric mucosa but rather is secondary to systemic mechanisms regardless of the route of administration. Also, there is similar bioavailability of corticosteroids regardless of whether these agents are taken orally or parenterally. For instance, methylprednisolone (1000 mg daily) in 45 patients with a multiple sclerosis relapse demonstrated similar efficacy for clinical or MRI outcomes regardless of oral versus intravenous administration in a randomized trial.

Some clinicians routinely utilize a formulation referred to as ‘smoothie-medrol’; the pharmacist dissolves 1gm of MP powder in 25 cc of D5W and provides three vials for a three day course. The patient then mixes the MP/D5W solution in an 8oz smoothie (e.g. strawberry-banana) or juice and drinks the concoction with breakfast or dinner. If a patients finds the smoothie-medrol ‘cocktail’ taste to be noxious, an alternative is 40–200 mg of dexamethasone (as a single dose or divided with breakfast and lunch) mixed in 25 cc of D5W by the pharmacist. The patient then adds to an 8oz smoothie or fruit juice. This latter formulation is very well tolerated and nearly tasteless.

Other clinicians routinely prescribe oral prednisone tablets which are well accepted by patients despite the large number of pills that must be swallowed. Still others prescribe oral dexamethasone tablets. Dexamethasone may have advantages over other formulations because it has limited mineralocorticoid effects. Dexamethasone has been associated with higher predilection for behavioral changes, but this has not been shown to be significant with short term pulse therapy. [*see Table 7:1*].

**TABLE 7:1: CORTICOSTEROID REGIMENS FOR ACUTE EXACERBATIONS**

*Corticosteroids*

Mechanism	Immunosuppressive Immunomodulatory Adhesion molecules/metalloproteinases
Evidence-based Medicine	Class I & II evidence for accelerating recovery from relapses Some Class II evidence for pulse steroid treatment controlling relapses and progression
Lab Assessments	Acute Monitoring: 1. Diabetes 2. Anticoagulation patients 3. Glaucoma patients (Intraocular pressure)
Treatment Regimens	1. IV Methylprednisolone a) 1gm/day for 3–7 days for relapses 2. ACTH (ACTHAR Gel®) a) 80–120 units daily IM/SQ for 2–3 weeks b) 80–120 units daily IM/SQ for 1 week (the lead author’s preference) 3. Oral prednisone a) 500–1250mg daily/divided for 3–7 days for relapses 4. ‘Smoothie Medrol’ a) 1gm methylprednisolone mixed in smoothie or juice taken orally with breakfast for 3-7 days for relapses 5. Dexamethasone a) 160–200mg po/IV daily/divided for 3–7 days for relapses 6. Various tapering regimens a) Prednisone–200mg x 4days; 100mg x 4 days b) Methylprednisolone dose pak c) Dexamethasone–20mg x 4 days; 16mg x 4 days

### *Plasma Exchange*

New guidelines from the American Academy of Neurology indicate that in people with relapsing forms of MS, plasma exchange may be effective as a secondary therapy for exacerbations that have not responded to treatment with corticosteroids. The guidelines also indicate that plasma exchange may be useful for severe, rapidly progressive MS and similar disorders; however the treatment was not found to be effective for secondary-progressive MS or primary-progressive MS.

### *Drug Interactions*

Corticosteroids have traditionally been considered to have relatively few clinically important drug–drug interactions; however there are some notable exceptions. Interactions with warfarin (Coumadin®) can cause either increased or decreased anticoagulation effects and interactions between enzyme-inducing anti-epileptic drugs, such as phenytoin (Dilantin®), phenobarbital, and carbamazepine (Tegretol®) have been noted. Similar to these agents, corticosteroids are metabolized by the CYP isoenzymes. This may result in reduced serum levels of one or both drugs (corticosteroid and/or antiepileptic) because of enzyme induction and may require increasing the dose of both drugs. The need for anti-convulsant level monitoring should be considered as dexamethasone has clearly been shown to significantly reduce phenytoin serum concentrations and lead to an increase in seizures in patients with epilepsy.

### *Adverse Effects of Corticosteroids & ACTH*

Some of the more commonly occurring problems associated with corticosteroids and ACTH use include insomnia, emotional lability, depression, irritability, euphoria, dyspepsia, headache, hypertension and, rarely, even psychosis. Despite the strong preoccupation with the conception that these drugs frequently produce gastric irritation, there has been little data that indicates this is a major concern in the context of pulse therapy for exacerbations of MS.

## CONCLUDING REMARKS

Corticosteroids and ACTH are effective and generally well tolerated when carefully and systematically utilized for treating MS exacerbations. While there is a broad diversity of potential treatment regimens, providers must gain experience with those that they feel comfortable prescribing. There is a continuing need for investigation of the various agents, doses, routes of administration, and their application in specific pulse and tapering regimens.

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# Bladder Dysfunction

Wanda Castro, MD, Teresa C. Frohman, PA-C

## CLINICAL PEARLS

- Patients with high post void residual urine volumes (>100cc) are at risk of recurrent infections, calculi, and in some cases hydronephrosis.
- MS patients *with failure to store disorders* often complain of urgency, frequency and nocturia and have small volume bladders with a spastic detrusor muscle pattern on urodynamic testing. They are often treated with anti-muscarinics, anti-cholinergics, mixed agents (e.g. oxybutynin) and the tricyclic antidepressant imipramine (the latter to prevent incontinence episodes).
- Those patients whose primary problem is *failure to empty* commonly have an outlet disorder (e.g. overactive sphincter) or a hypo- or areflexic bladder. These patients may complain of frequency, slow initiation of stream (hesitation), slow stream, prolonged voiding time, double voiding, and dribbling of urine. They are often best treated with alpha antagonists.

## CASE VIGNETTE

A 24 year-old woman was diagnosed one year ago with relapsing remitting MS. She reported recent increased frequency of urination and had several episodes of urge incontinence. A bladder ultrasound was performed during the visit. The pre-void bladder volume was 254cc. She voided 215cc in 15 seconds with a residual of 39cc. She had small pre-void volume and a small post-void volume that indicates she has detrusor hyperreflexia. Thus, an anti-cholinergic agent was prescribed to block parasympathetic tone and promote bladder wall muscle relaxation.

## SUMMARY

Bladder dysfunction occurs in as many as 80% of newly diagnosed MS patients, and has an approximate prevalence of 96% after 10 years into the disease. Urinary incontinence may be the initial symptom for patients with MS. Common bladder disorders in patients with MS include neurogenic detrusor hyperreflexia due to an exaggerated parasympathetic tone to the bladder wall, the detrusor muscle. This disorder is essentially a “failure to store” disorder. There is poor compliance of the bladder wall and this exaggerates the bladder pressure even at low urine volumes.

There can be detrusor sphincter dyssynergia (DSD), which is a “failure to empty” disorder that is typically characterized by increased bladder sphincter tone in combination with either detrusor hyperreflexia or detrusor areflexia. In either of these patients there is a high post-void residual urine volume. The initial evaluation of a patient with MS who has bladder symptoms should include a history, physical exam, urinalysis (UA), and uroflowmetry (ultrasound) with a post-void residual (PVR).

## CLINICAL APPROACH & MANAGEMENT

Objective measurements of post-void residual volumes are not closely correlated with the patient’s subjective assessments of their bladder function. Thus, *all* patients with MS may benefit from urinary screening and evaluation. The PVR evaluation assesses the amount of urine in the bladder after attempted complete urination, including an attempt at double voiding. The PVR can be determined by catheterization or preferably by diagnostic ultrasonography. Patients with high PVRs (>100cc) are at risk of recurrent infections, calculi, and in some cases hydronephrosis. These patients should be referred to a neuro-urologist for further evaluation, which should include a thorough examination of the pelvic floor. Patients with MS who suffer from *failure to store disorders* often complain of urgency, frequency, nocturia and have small volume bladders with a spastic detrusor muscle pattern on urodynamic testing.

Those patients whose primary problem is *failure to empty* commonly have an outlet disorder (e.g. overactive sphincter) or a hypo- or areflexic bladder. These patients may complain of frequency, slow initiation of stream (hesitation), slow stream, prolonged voiding time, double voiding, and dribbling of urine.

Treatment of patients with MS who have *failure to store* problems should include use of anti-muscarinic, anti-cholinergic or a mixed agent like oxybutynin. In addition, the tricyclic antidepressant imipramine can be used to reduce incontinence episodes by increasing sphincter tone via activation of alpha-1 adrenergic receptors. Patients with nocturia or nocturnal enuresis should always empty their bladder prior to going to bed as well as decrease their fluid intake about 2–3 hours before going to bed. Some foods cause bladder irritation and may need to be avoided. Spicy foods, caffeinated products, alcoholic beverages and acidic foods can also result in bladder irritation and subsequent urinary frequency and should be avoided prior to bedtime. If behavioral strategies are not effective, nocturia can often be effectively managed with a form of anti-diuretic hormone, oral desmopressin (DDAVP). For patients with incontinence related to overactive bladder, sacral neuromodulation (InterStim®) has been found to be a very effective treatment alternative, though traditionally its use has been limited to patients with idiopathic overactive bladder disease.

Patients whose primary problem is *failure to empty* commonly have an outlet disorder. They are often managed with the alpha-antagonist class of medications (prazosin, terazosin, doxazosin, tamsulosin, and more recently the highly selective agent, silodosin). Some patients who experience difficulty with stream initiation, may benefit from gentle Valsalva or Crede's maneuver by placement of abdominal pressure in addition to pharmacologic management.

In some patients, clean intermittent catheterization (CIC) or permanent catheterization is required. If permanent catheterization is deemed necessary, a suprapubic catheter is preferred over the intraurethral (Foley) variety due to the higher risk of infection and urethral damage with the latter. Surgical options may need to be instituted for patients

with severely impaired emptying, or patients with recurrent infections resulting in MS exacerbations. Augmentation cystoplasty, ileovesicostomy, and ileal conduit urinary diversion are all complex surgical procedures that use segments of bowel to either augment or replace the function of the bladder. Each may have a role in some severely affected patients.

Urinary tract infections (UTIs) are common in patients with a long-standing history of MS, and the possibility of a UTI should always be considered when a patient presents with symptoms of an MS exacerbation. While most UTIs are uncomplicated, some patients will advance to sepsis and these are associated with the risk of further complications requiring management in the intensive care unit. Prophylactic antibiotic treatment (typically daily) with agents like nitrofurantoin or sulfamethoxazole/trimethoprim may be necessary in patients with recurrent UTI's.

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# Bowel Dysfunction

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## CLINICAL PEARLS

- Bowel dysfunction is characterized as disorders of storage or elimination with sympathetic innervation at levels of T5-L2 that are largely inhibitory through noradrenergic input.
- Parasympathetic input consists of input from the vagus and sacral nerves, and stimulation promotes peristalsis, blood flow to the gut and intestinal secretion.
- The external sphincter receives innervation from the pudendal nerve (S2-S4). These same spinal levels are responsible for perineal sensation.
- Constipation can be caused by a variety of factors.
  - Iatrogenic secondary to decreased fluid intake because of bladder dysfunction or dysphagia
  - Iatrogenic secondary to medications used to treat bladder urgency, pain and spasticity
  - Secondary to decreased physical activity and mobility due to physical impairment
  - A compromise in the parasympathetic nervous system resulting in inhibition in peristalsis and gut motility
- Fecal incontinence affects up to 24% of MS patients with mild disease and up to 66% of those with severe disease.

## CASE VIGNETTE

A 32-year-old patient with a 10-year history of relapsing remitting MS presented in clinic for routine follow-up. Since her last visit she had experienced several episodes of diarrhea with bowel incontinence. On further questioning, she admitted that the episodes of bowel incontinence were preceded by prolonged periods of constipation lasting 5 to 6 days.

She had not adhered to a regular bowel regimen and reported that she had not been able to exercise for the last 4 weeks. She indicated that she typically only drinks about 3 glasses of water a day.

#### SUMMARY

This 32 yr-old female patient was experiencing bowel dysfunction, a very common manifestation of MS. This is seen as a primary result of the MS pathophysiology or due to secondary etiologies.

#### CLINICAL APPROACH & MANAGEMENT

Bowel dysfunction is characterized as disorders of storage or elimination. Sympathetic innervation of the gut is largely inhibitory through noradrenergic input and derives from spinal levels T5-L2. However, this same sympathetic nervous system provides adrenergic innervation of the internal anal sphincters which are smooth muscles under autonomic control. Parasympathetic modulation of the GI tract consists of input from the medulla through the vagus nerve for the esophagus all the way through half of the large intestine. The remaining colon, rectum and anal canal have parasympathetic modulation from the sacral spinal cord, sacral nerves, and plexus. Stimulation of the parasympathetic nervous system promotes peristalsis, mass movements of stool in the large intestine, increased blood flow to the gut, and increased intestinal secretions. The external sphincter is composed of skeletal muscle and is under voluntary somatic control through innervations from the pudendal nerve (from sacral spinal segments 2–4). These are the same spinal levels that are responsible for perineal sensation.

#### CONSTIPATION

When patients say “I am constipated” they are frequently referring to straining, hard stools, or the inability to have a bowel movement (BM). Clinically, constipation is defined as less than three BMs a week. Constipation can be caused by several factors. A review of diet and fluid intake is recommended as a first line evaluation for patients complaining of constipation. Patients may have limited fluid intake due to bladder dysfunction or dysphagia. The causes may be iatrogenic and secondary to drugs used to treat spasticity, paresthesias, pain, or bladder

dysfunction. Decreased physical activity and mobility can also greatly impact BM frequency. Secondary medical causes that may or may not be related to MS require screening. Non-pharmacological techniques for prevention and/or management of mild to moderate constipation include increasing physical activity, drinking more fluids, increasing dietary fiber for stool bulking, and in some cases biofeedback therapy.

*Bulking agents*, when titrated up, are effective and reliable for preventing constipation. Common forms include psyllium (from the ispaghula husk), bran, and calcium polycabophil. Poorly absorbed sugars like lactulose or sorbitol are effective in managing constipation, but can produce fecal incontinence and should be used cautiously. Lactulose, polyethylene glycol (PEG) and sorbitol are effective in patients with more chronic constipation. PEG is now available over the counter (MiraLax®) and is approved for use in children. The most common adverse effect with PEG is abdominal cramping.

*Osmotic agents* commonly contain magnesium and are available as magnesium oxide and magnesium sulfate. Magnesium oxide is primarily used in mild to moderately severe constipation. Magnesium sulfate is dosed similarly to magnesium oxide but can cause a more explosive and liquid-like consistency BM. Magnesium sulfate should be avoided in the elderly.

*Prokinetic Agents* such as lubiprostone act to increase intestinal fluid secretion. This is a chloride channel activator that acts locally on the apical membrane of the gastrointestinal tract. Lubiprostone has been used off-label for the treatment of constipation in patients with MS.

*Enemas or suppository agents* include tap, saline and soapsud enemas that generally work quickly and effectively to soften stool and assist in expelling the contents of the rectum. Saline enemas are reported to be safest of the three. Health care providers are encouraged to monitor what type of enema a patient is using and with what frequency in order to prevent electrolyte imbalance. A unique device combines liquefied glycerine and docusate into a small, convenient and effective mini-dose enema (Enemeez®). For those with rectal pain, a similar formulation can

be utilized that also includes the local anesthetic benzocaine (Enemeez Plus®). Rectal pain can also be effectively treated by the use of belladonna and opium (B&O) suppositories. These small suppository-like devices are highly effective rectal analgesic agents. Bisacodyl and glycerin suppositories stimulate the rectal wall through stretch mechanisms. They are safe and effective in patients suffering from symptoms of dysphagia, nausea or vomiting.

*Stimulant agents* increase intestinal motility and secretions. Common agents include senna, cascara and castor oil. They generally work rapidly and can occasionally lose efficacy if abused. Senna is generally preferred over the other stimulant agents due to increased tolerability.

*Stool Softeners* such as docusate sodium is dosed at two 100mg tablets daily. Docusate sodium in combination with a stimulant (senna) quite effectively treats mild to moderate constipation in many patients with MS.

*Surgery* may be indicated in refractory cases to ease caregiver burden of management for severely debilitated patients. Often quality of life does improve in those with colostomies, as constipation can cause pain, discomfort and embarrassment to patients.

#### FECAL INCONTINENCE

Fecal incontinence correlates with duration of disease and disability status ranging from 24% in mildly disabled patients, to 66% of those with severe disease. Fecal incontinence is defined as an involuntary loss of stool from the rectum usually caused by reduced anal squeeze pressures. A diet and fluid history should be evaluated in the incontinent patient. Treatment will be targeted to the underlying cause. Drug therapy with loperamide can be used in patients with chronic diarrhea with or without fecal incontinence. This agent is not however recommended for use in patients with symptoms of diarrhea and concomitant constipation.

Biofeedback training has been effectively utilized to improve pelvic floor muscles and to thereby improve rectal sensory perception. Alternately, surgical repair is indicated for medically refractory or trauma cases. There are several techniques available including pelvic floor muscle repair, forming a new external anal sphincter via muscle transposition, and even the development of a 'false' anal sphincter using hydraulic rings. Fecal diversion with colostomy is used when the above options have failed or are not feasible. Opiate derivatives such as loperamide and diphenoxylate with atropine may decrease stool volume and frequency, and can also increase the sphincter tone. This treatment is usually effective when symptoms are mild, and not due to impaction with overflow. Decrease of fiber intake and/or biofeedback techniques may also be beneficial.

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# Depression & Cognitive Changes

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## CLINICAL PEARLS

- Patients will commonly deny feeling of depression, but when carefully questioned they will acknowledge that they suffer with some of the symptoms of a mood disturbance such as insomnia, early morning awakening, loss of appetite, not enjoying things that once brought them happiness, loss of concentration, difficulties with short term memory, cognitive difficulties and fatigue.
- For cognitive dysfunction neuropsychological testing can potentially aid in identifying other factors that could produce or exacerbate cognitive deficits (e.g. depression and fatigue). If a patient suffers from depression or fatigue, treatment of these conditions can often produce reversal of cognitive dysfunction.

## CASE

A 26 year-old woman has been diagnosed with relapsing remitting multiple sclerosis (RRMS). During a routine visit she reported that for the past 6 weeks she had experienced multiple crying spells, sadness, lack of motivation, insomnia and an inability to concentrate. Recently others had expressed concern that she was having difficulties with memory and information processing. Her grandmother had also recently passed away and she was having a hard time adjusting to her death.

In the weeks following the funeral, she was extremely sad, had become more reclusive and lacked motivation to be active — she was abulic. She also described a marked reduction in her usual appetite for food and interest in cooking. Further, she began to describe difficulty sleeping.

She had a hard time falling asleep and woke often. Consequently, she had corresponding daytime fatigue. In response to this depressed mood, her neurologist recommended treatment initiation with the selective serotonin reuptake inhibitor, fluoxetine.

#### SUMMARY

The 26-year-old patient presented over time with various symptoms of depression and mild cognitive abnormalities. Depression is more common in the MS population than in other chronic conditions and can cause problems with intellectual functioning. Mood and cognitive changes are major factors for patients living with MS. The fatigue and changes in cognition represent the most common reasons why patients with MS pursue disability benefits and cease gainful employment. The impact on the quality of the patient's life cannot be overstated. It is important for providers to understand these critical issues and proactively address them with their patients.

#### CLINICAL APPROACH & MANAGEMENT

The incidence of intellectual impairments in patients with MS ranges from 40–70%, and steadily increases with disease duration. The nature and degree of deficits leads to significant disability, affects employment, and impairs quality of life. The most common cognitive deficits for patients with MS include alterations in attention, compromised executive functioning, slowed information processing, and reduced memory retrieval. The ability of patients with MS to consolidate new memories typically remains intact. Therefore, although mild to moderate cognitive dysfunction is common in patients with MS, the incidence of dementia is distinctly uncommon.

Intellectual deficits in patients with MS can be quite subtle. Validated neuropsychological batteries, with sensitive measures reflecting changes in cognition, are often required to underscore these impairments. If baseline neuropsychological investigations are performed at the time of initial diagnosis, subsequent testing can reveal important changes.

Timely measurements and interventions can help to maintain gainful employment or support a patient's application for disability if needed. Without objective measurement the opportunity to be proactive is missed.

Neuropsychological testing can help identify other factors that can produce or exacerbate cognitive deficits such as depression and fatigue. If a patient suffers from depression or fatigue, treatment of these conditions can often reverse cognitive dysfunctions. Cognitive behavioral therapy (CBT), psychotherapy, and counseling can aid in compensating for the deficits, even if elimination of the dysfunction is not possible because of the underlying pathophysiology of the disorder.

Pharmacological strategies in treating cognitive symptoms have yielded some success in patients with MS. Donepezil is commonly used in dementia and may have modest efficacy in patients with MS. Other studies have shown that amphetamines have been associated with improved cognitive performance. This may be related to lessened fatigue and/or mood changes rather than strictly acting on cognition.

#### PSYCHIATRIC - MOOD DISORDERS

Depression is one of the most common symptoms of MS but patients with MS can be dealing with a wide range of other psychiatric issues as well. Mood disturbances should be explored with patients as part of their overall diagnostic workup and included in their treatment plan. Agitation, reduced initiative, sadness, demoralization, loss of self worth, decreased self-esteem, too much or too little sleep and eating derangements can all markedly impact quality of life. They can compromise relationships and reduce adherence to treatment and rehabilitation strategies. Adverse consequences of mood disorders can have significant impact on the disease. Patients often deny feelings of depression, but when carefully questioned or assessed the symptoms of a mood disturbance can be revealed. These include insomnia, early morning awakening, loss of appetite, the loss of enjoyment for things that once brought them happiness, and of course the loss of concentration, difficulties with short term memory, cognitive difficulties and fatigue that were discussed above.

Depression needs to be discussed with patients and their families carefully and systematically. When identified, the range of both pharmacologic and counseling options should be discussed. Patients should be reassured that depression is among the most treatable co-morbidities for patients with MS.

One of the most commonly used tools for diagnosing and evaluating depression is the Beck Depression Inventory (BDI-II). This is a questionnaire that measures the severity of depression and consists of 21 multiple-choice questions that allows self-reporting of a multitude of depressive symptoms. A rapid variation of the Beck's screen has been validated and consists of only 7 questions, making its application in clinical practice of great utility.

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), if five or more of the following symptoms are present for at least a two-week period, the diagnosis of a major depressive disorder (major depression) can be applied/considered:

- A depressed mood for most of the day; nearly every day
- Loss of interest or pleasure in all, or almost all, activities for most of the day
- Significant change in weight or appetite
- Insomnia or excessive sleepiness
- Observable agitation or lethargy
- Fatigue and loss of energy; nearly every day
- Feelings of worthlessness, low self-esteem, or excessive guilt
- Difficulty concentrating or indecisiveness
- Recurrent thoughts of death or suicide

Often the most effective approach to depression is a combination of a mood stabilizer agent in conjunction with a period of psychological counseling. Selective serotonin reuptake inhibitors (SSRIs) are a mainstay for treatment of depression in MS [Table 10:1].

TABLE 10:1

*SSRIs (Selective Serotonin Reuptake Inhibitors)*

The SSRI drug class has become the treatment of first choice for people suffering from depression and anxiety disorders. Compared to earlier generations of antidepressants, SSRIs are no more effective in treating depression, but are very well tolerated.

<i>Generic</i>	<i>Brand Name</i>
Citalopram	Celexa
Escitalopram	Lexapro, Cipralex
Fluoxetine	Prozac, Sarafem
Fluvoxamine	Luvox
Paroxetine	Paxil, Paxil CR
Sertraline	Zoloft

*Tricyclics (TCA)*

Currently, TCAs are used as a second or third-line treatment choice.

<i>Generic</i>	<i>Brand Name</i>
Amitriptyline	Elavil, Endep, Levate
Amoxapine	Asendin
Clomipramine	Anafranil
Desipramine	Norpramin, Pertofrane
Doxepin	Adapin, Sinequan
Imipramine	Tofranil
Maprotiline	Deprilept, Ludiomil, Psymion
Mianserin	Bolvidon, Norval, Tolvan
Nortriptyline	Pamelor
Protriptyline	Vivactil
Trimipramine	Surmontil

### *SNRIs (Serotonin & Noradrenaline Reuptake Inhibitors)*

SNRIs represent the newest class of antidepressants.

<i>Generic</i>	<i>Brand Name</i>
Desvenlafaxine	Pristiq
Duloxetine	Cymbalta
Milnacipran	Savella
Venlafaxine	Effexor, Effexor XR

### *NDRIs (Norepinephrine & Dopamine Reuptake Inhibitors)*

<i>Generic</i>	<i>Brand Name</i>
Bupropion	Wellbutrin, Wellbutrin SR, Wellbutrin XL, Zyban

If the patient's complaints are more related to insomnia, anxiety or emotional lability, often paroxetine, trazodone, or one of the tricyclic antidepressants are preferred. Venlafaxine or bupropion may be an appropriate first-line agent for mood stabilization if the patient suffers more from lack of energy (a very common problem in patients with MS) or concentration problems.

Sexual dysfunction is a common side effect of treatment of depression even though pharmacotherapy can effectively improve depressed mood. For these patients bupropion is given due to the lower incidence of this side effect. Many patients actually experience improvements in libido and sexual responsiveness with bupropion treatment, even when used in conjunction with an SSRI. Anxiety is managed, as with the general population, with anxiolytics such as lorazepam, alprazolam, and clonazepam. These agents are also often used for phasic spasticity or vertigo that are sometimes symptoms for patients with MS. Buspirone is also used for anxiety and is particularly effective for panic attacks.

The provider practicing in neurology can play a pivotal and productive role in encouraging patients with MS to remain positive, hopeful, and committed to their care plan. The suicide rate in patients with MS is higher than that of the general population and other chronic disease populations. As such, the issue of suicide should be addressed with any patient who suffers with mood problems. Immediate referral for psychiatric evaluation is important if there is any doubt as to whether suicidal thoughts or ideation has been contemplated by the patient.

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# Heat Sensitivity — Uhthoff's Phenomenon

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## CLINICAL PEARLS

- Exposure to heat, infection, or psychological stress, the perimenstrual period, or prolonged exercise may cause unmasking or worsening of neurologic symptoms (Uhthoff's phenomenon).
- Clinical symptoms caused by increases in temperature are reversible by removing heat stressors and allowing subsequent cooling.
- Cooling methods, including ingestion of ice cold liquids, cool water showering, application of a cold towel to the skin surface (e.g. neck or shoulders), cooling suits and pre-cooling, have been used to combat heat-induced worsening of symptoms in MS patients.

## CASE VIGNETTE

A 43-year-old female patient with relapsing remitting MS returned for a follow up visit and reported that she experienced increased fatigue and visual disturbances while attending her child's soccer tournament over the weekend. The symptoms were quite minimal, albeit noticeable in the morning, while her vision blurred and markedly worsened throughout the course of the day. During the soccer tournament the temperature outside was over 100°F and the humidity was very high. Conspicuously, all of these symptoms were transient, reversible, and were stereotypically mitigated or totally resolved following rest and cooling down after a cool shower that evening.

## SUMMARY

This patient is experiencing symptoms that are provoked by exposure to increased ambient temperature but are totally reversible and effectively resolved with rest and cooling. Collectively these represent the cardinal features of Uhthoff's phenomenon. In essence, neurologic symptoms are reflective of dynamic temperature-induced changes in the fidelity of axonal conduction mechanisms along demyelinated axonal pathways (the optic nerve in this patient). Patients must understand that these events do not signify inflammatory demyelination as would be seen in an exacerbation. As such, the administration of anti-inflammatory treatment interventions (as with corticosteroids) is not indicated.

## CLINICAL APPROACH & MANAGEMENT

The majority of patients with MS (60% to 80% of the MS population) are subject to reversible and often stereotypic symptoms provoked by increases in ambient or core body temperature. Wilhelm Uhthoff originally described increases in the frequency or severity of clinical signs and symptoms as a result of elevated body temperature in 1889. He reported transient visual loss precipitated by exercise or a hot bath in patients with MS who had a history of optic neuritis; this was consequently named Uhthoff's phenomenon. The temporary worsening of physical activities such as walking, running, or driving, cognitive memory retrieval, processing speed, or ability to multi-task due to heat exposure can greatly impact patient safety. Individuals with MS can have significant impairment in performing even routine activities of daily living when the temperature is elevated. Even in mildly affected individuals these transient symptoms may become worrisome. Typically deficits caused by increases in temperature are reversible by removing heat, stopping the exercise and avoiding the psychosocial stressors while promoting subsequent cooling.

There can be multiple events that contribute to the heat exposure effects. Exposure to high ambient heat, prolonged exercise, infection, perimenstrual elevated temperature, and even psychological stress that may occur with the activation of autonomic pathways can result in increased core body temperature. Anything that results in sweating may

cause worsening of neurologic symptoms attributable to the Uhthoff's phenomenon. It is important to remember however that sweating may become a defective function later in patients with MS, so patients may be suffering from temperature effects even when they are not actively sweating. Core temperature rises even faster if a patient does not sweat normally.

Common manifestations of Uhthoff's phenomenon include fatigue, increased or unmasked weakness, worsening of sensory symptoms including pain, altered gait mechanics and reduced balance mechanisms, falling, worsening of eye movement abnormalities, spatial disorientation, and derangements in cognition and visual processing. These types of transient worsening of symptoms due to heat exposure or exercise need to be distinguished from symptoms that represent a true exacerbation that might require anti-inflammatory treatments.

Heat related symptoms are transient in that they usually last less than 24 hours and often resolve in minutes to hours. In addition, these symptoms fluctuate during the day. The resolution of symptoms will be further resolved once the heat or exercise are removed. In some circumstances these transient symptoms can be difficult to differentiate from the beginning of an exacerbation. The development of clinical judgment will help in deciding whether to watchfully wait or to pursue further investigation or treatment.

Several treatment strategies have been employed to reduce the potentially detrimental effects of heat sensitivity in MS. At onset of heat-induced symptom worsening individuals with MS should find an environment with a cooler ambient temperature or stop exercising and ingest ice-cold liquids. Simple behavioral strategies can be used to minimize heat exposure such as performing activities or exercise outside during the early morning or late evening when temperatures are cooler. Cooling methods have been used to combat heat-induced worsening of symptoms. Mild to moderate benefits can be achieved by using simple cooling strategies such as cold showers, ice packs, and regional cooling devices. Sometimes an ice-cold towel or cold beverages will suffice.

Water immersion pre-cooling in a bathtub prior to heat exposure or exercise presents a viable option for minimizing heat stress in some patients with MS. Commercially available cooling garments may show some benefits in thermally sensitive patients. The beneficial effects of these methods of cooling can last for several hours, depending on the intensity of the activities performed.

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# Optic Neuritis & Eye Movement Abnormalities

*Amy Conger, COA, Darrell Conger, CRA, Teresa C. Frohman, PA-C*

## CLINICAL PEARLS

- Visual acuity loss, visual field defects, impaired color vision (particularly red and green), and reduced intensity of light perception are characteristic features of acute optic neuritis (AON).
- Patients complaining of transient, reversible, and stereotypic vision blurring during or immediately following a heat stress, exercise, around the time of the menstrual period, at times of psychological stress, or during a febrile illness likely have Uhthoff's phenomenon rather than a true MS exacerbation (be careful, there are always exceptions).
- Internuclear ophthalmoparesis (INO) represents the most common eye movement abnormality in MS patients and is characterized by adduction slowing and abduction nystagmus during horizontal eye movements (particularly saccades).

## CASE VIGNETTE

A 30-year-old woman with relapsing-remitting MS presents with new complaints of blurred vision and pain upon movement of the left eye. About two months prior to these symptoms she had double vision when reading or while turning her head to prepare to change lanes while driving.

On ophthalmoscopic examination there was temporal optic disc pallor in the left eye. On the swinging flashlight test the left pupil did not constrict but the left and right pupil reacted normally when the right eye was tested. This indicates she has a left relative afferent pupillary defect (RAPD). Further, as she moved her eyes quickly to the right (horizontal saccades) the left eye moved slower toward the nose when compared to the velocity of the right eye movement away from the nose. This abnormal finding signifies a left internuclear ophthalmoparesis (INO). This would likely involve a tegmental lesion in the pons or midbrain. These changes in vision and eye movements would be treated as an MS exacerbation and the patient would be scheduled for a three-day course of intravenous methylprednisolone or an oral steroid regimen of similar dose magnitude.

An MRI of the brain was requested to include coronal fat-suppressed views of the orbits to visualize optic nerve inflammation and gadolinium enhancement and 3mm axial cuts through the brainstem. T2 and proton density weighted images showed a lesion in the left medial longitudinal fasciculus (MLF) that would explain her left INO. Also, left optic nerve enhancement was observed on T1 coronal fat-suppressed views with gadolinium infusion. *[Figure 12:1].*

#### S U M M A R Y

This 30-year-old female had an acute optic neuritis with classic manifestations of painful visual loss and a left RAPD. The presence of optic disc pallor suggested a concomitant chronic process of optic neuropathy. The interstitial cells of the optic nerve are similar to those of the central nervous system and the optic disc pallor signifies astrogliosis which requires weeks to months following an episode of acute optic neuritis to become manifest *[Figure 12:2].*

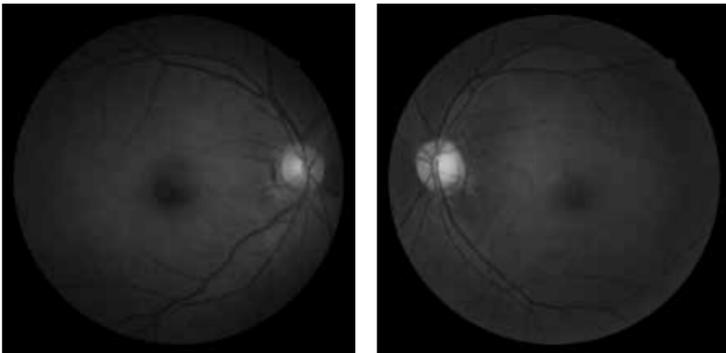
FIGURE 12:1



A coronal, fat-suppressed T1-weighted MRI demonstrates enhancement of the left optic nerve (arrow), signifying acute optic neuritis.

FIGURE 12:2

MRI revealed evidence of an enhancing lesion of the left optic nerve, consistent with inflammation [Figure 12:1]. In this case, in addition to the left optic neuritis, the MRI showed there was a periventricular lesion affecting the left MLF, ventral to the fourth ventricle that would explain a left INO.



Fundus photography reveals left optic disc pallor consistent with old optic neuropathy.

*Acute Optic Neuritis*

The presentation of an optic neuritis is the first sign of MS for up to 30 percent of patients with MS. These patients will describe acute or sub-acute onset of visual symptoms that evolve over several days. This typically prompts urgent medical evaluation. If symptoms continue to progress beyond 1 to 2 weeks, this should raise suspicion for an alternative etiology for the optic neuropathy. Visual acuity loss, visual field defects, impaired color vision (particularly red and green), and reduced intensity of light perception are characteristic features of acute optic neuritis (AON). Patients often describe their vision as “blurred” as though the patient is looking through a “frosted shower door,” or that ambient illumination is reduced on the side of involvement compared to the opposite eye. If there is a bilateral AON the patient senses a diffuse loss of brightness.

Some patients with MS will present with complaints of transient vision loss when over-heated during/following exercise, after a hot bath or sauna, or when exposed to hot weather. This is referred to as Uhthoff's Phenomenon. This is further discussed in the chapter on Heat Sensitivity. Transient vision loss related to being over heated (Uhthoff's phenomenon) typically recovers when the patient rests, is cooled, or is removed from a warm ambient environment. This could be confused with optic neuritis that may require treatment intervention with corticosteroid agents. One should keep this phenomenon in mind when evaluating a patient with transient visual disturbance.

*Eye Movement Abnormalities*

Eye movement coordination travels through brainstem pathways that localize to the brainstem tegmentum of the pons or midbrain, ventral to the fourth ventricle or cerebral aqueduct, respectively. These pathways coordinate all eye movements including saccades (fast eye movements), smooth pursuits, and the vestibular ocular reflexes (VOR). VOR is the movement of the eyes as the head moves in the opposite direction in order to maintain straight ahead fixation upon objects of visual interest.

The most common disturbance of eye movements in MS is internuclear ophthalmoparesis (INO). This syndrome is best appreciated during horizontal saccades where the adducting eye is slowed and this is referred to as adduction ‘lag’. [Figure 12:3]

FIGURE 12:3

An MS patient with a right INO attempts to saccade to the left. The left eye normally abducts (note the pupil has deviated far away from the midposition vertical black line marker) whereas the right eye lags behind (note that the pupil is still in registration with the midposition vertical black line marker).



This syndrome results from a lesion within MLF in the dorsomedial brainstem tegmentum of either the pons or midbrain. This type of lesion is eloquent and the slow adduction is on the side of the lesion. In essence, a right medial longitudinal fasciculus lesion gives rise to slow adduction of the right eye. INO produces de-synchronization/dysconjugation of horizontal eye movements and can result in double vision and/or the illusion of environmental movement (oscillopsia). Patients may report being dizzy or feeling funny when they move their eyes but this is due to the brief loss of binocularity during dysconjugate eye movements.

There are a number of other eye movement abnormalities that can be frequently observed during the bedside exam in MS. These include cranial nerve palsies of any of the nerves involved with the extraocular eye muscles such as CN III, IV, and VI. A vertical misalignment of the eyes not on the basis of eye muscle weakness is called a skew deviation and results from damage to specialized CNS structure referred to as the otolith pathways.

All forms of nystagmus (jerky eye movements) can be the result of MS pathology involving the pons or midbrain tracts or nuclei.

As the brain works to maintain fixation of an object on the macula, the image on the weakened side moves off the macula (so-called ‘retinal slip.’) Normally, overlapping visual fields are crucial for visual processing.

In MS the primary strategy for treatment of acute-onset oculomotor syndromes is high dose corticosteroids. Rapid intervention with this anti-inflammatory treatment has commonly aborted syndrome progression. Thus steroid treatments decrease progression and will reduce residual deficits more than ‘watchful waiting’ for spontaneous recovery. If the syndrome has not begun to improve within two to four weeks of starting corticosteroids, we generally advance therapy to plasma exchange; and if necessary, we employ chemotherapy with an agent such as cyclophosphamide, or more rarely mitoxantrone.

Pendular nystagmus is a constant ‘to and fro’ movement of the eyes in a number of possible planes. The movements can be horizontal, vertical, rotary, or elliptical. This represents one of the most disabling eye movement abnormalities in patients with MS. Nystagmus is among the most challenging of symptoms to treat in MS. Many patients develop compensatory mechanisms that can either dampen the amplitude of the abnormal eye movements, or they may identify a head position that minimizes symptoms (a null zone). The perceived bouncing of a visual image due to abnormal eye movements is called oscillopsia. One effective therapy for pendular nystagmus has been the use 10–20mg of memantine two to three times daily or 100–2,000mg of gabapentin (three times daily). In some patients we have achieved efficacy when employing a combination of these agents.

The bedside neuro-ophthalmologic examination [*see Table 12:1 and Table 12:2*] is highly useful in identifying abnormalities within the visual and ocular motor systems, and should be carefully and skillfully performed.

**TABLE I 2:1: BEDSIDE EXAMINATION  
OF THE AFFERENT VISUAL SYSTEM**

Visual acuity	Spectacle correction Pinhole correction Near card or distance
Visual Fields (by confrontation)	Monocular testing Static versus dynamic
Color	Color plates Red Green desaturation
Pupils	Anisocoria Shape and position Reactivity Relative afferent papillary defect (RAPD during swinging flashlight test)
Fundoscopy Exam	Optic disc pallor Nerve fiber loss Disc edema/hemorrhage Occult nystagmus Perivenular phlebitis (peripheral retina)

**TABLE I 2:2: BEDSIDE OCULOMOTOR EXAMINATION**

Ocular alignment	Tropia Crosscover for phorias Is there a hyperdeviation Skew deviation Ptosis Head tilt
Ocular Motility	Ductions (monocular motility) Versions (binocular motility) Diplopia CN VI>III>IV in MS
Nystagmus	Visual inspection Primary position and with eccentric gaze Funduscopy exam (occult nystagmus)

Saccades	Latency Velocity Accuracy internuclear ophthalmoplegia (INO) Disconjugate nystagmus Gaze palsies
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The examination should include maximally corrected visual acuity using pinhole correction, the patient's own glasses, or both. Color perception should be tested one eye at a time and can be performed with the Ishihara Color Test. Although visual field defects are most effectively documented with the use of the automated perimetry testing, confrontational visual fields can be of value at the bedside. Confrontation fields initially should be performed using static images. Oculomotor testing will provide information about individual eye muscles and conjugate eye movements such as nystagmus, ocular misalignments, cranial nerve III, IV, and VI palsies, INO, and other abnormalities. Examine the pupils for light response with the patient first looking at a distance and then have the patient converge to look for the near response. Look for a relative afferent papillary defect (RAPD) with the swinging flashlight test. Carefully evaluate the fundus for optic disc pallor or edema in addition to abnormal vascular markings.

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# Sexual Dysfunction

*Wanda Castro, MD, Teresa C. Frohman, PA-C*

## CLINICAL PEARLS

- The only United States Federal Drug Administration (FDA) approved therapy for female sexual dysfunction is EROS-CTD.
- For male primary sexual dysfunction, specifically erectile dysfunction, the use of prostaglandin-5 inhibitors is frequently beneficial (e.g. sildenafil, vardenafil, tadalafil) when neural circuitry is intact.

## CASE VIGNETTE

Louise is a 28 year-old woman who was diagnosed with relapsing remitting MS 8 years ago. She presents for transfer of care. She indicates that she is doing well and is compliant with her disease-modifying agent (DMA). She also reports that she is taking a selective serotonin reuptake inhibitor (SSRI) prescribed by her primary care physician. During the visit, Louise reported that since starting the SSRI she has had adequate treatment of her depression but is experiencing sexual issues such as decreased lubrication, virtually absent libido and some anorgasmia.

## SUMMARY

The prevalence of sexual dysfunction (SD) among patients with MS is twice that reported in individuals with other chronic diseases, and up to 5 times higher when compared to the general population.

Sexual dysfunction is commonly seen in MS but not as commonly treated. Obviously sexual dysfunction can severely impact a patient's self esteem, integrity of relationships, and quality of life. There are three basic designations for sexual dysfunction as it relates to MS: primary, secondary or tertiary. Each subtype requires a different therapeutic approach. Primary sexual dysfunction is a direct consequence of the demyelinating process where the affected areas in the brain and spinal cord have direct action during sexual functions. In secondary sexual dysfunction, symptoms are a consequence of MS and/or result from the side effects of medications used to treat MS. Tertiary sexual dysfunction is related to psychological, emotional and cultural influences that may interfere with sexual activity.

Reduced libido is one of the most commonly reported manifestations of primary sexual dysfunction for women with MS (31.4 to 80.5%). Of men with MS that are still ambulatory erectile dysfunction (ED) is likely to affect about 60%; ejaculatory dysfunction, orgasmic dysfunction or both affects about 50%; and reduced libido afflicts 40%.

Both women and men with primary SD can benefit from body mapping, a technique in which the patient systematically explores all of her/his body parts using touch in order to identify body areas capable of erogenous stimulation. As the sensation (soft touch, pain and temperature, pressure, etc) of body regions change in the person with MS there are potentially corresponding changes in erogenous zones. In fact, body regions that when previously stimulated produced pleasurable sensations may now instead be associated with disturbing, distorted, excessive, and even painful experiences. The technique of body mapping can be utilized in order to potentially modulate these sensations by employing stimuli that purposely vary the rate, rhythm and pressure of repetitive stimuli.

For male primary sexual dysfunction, specifically ED, the use of prostaglandin-5 inhibitors is frequently beneficial (e.g. sildenafil, vardenafil, tadalafil) when neural circuitry is intact. Other alternatives for ED include the vacuum erection device, penile prostheses (rigid, semirigid, and dual-chamber inflatable penile prosthesis), MUSE (meatal urethral alprostadil suppository; prostaglandin E-1), testosterone supplementation, and intracavernosal injections of alprostadil (Caverject®).

The only United States Federal Drug Administration (FDA) approved therapy for female SD is EROS-Clitoral Therapy Device (EROS-CTD). By causing clitoral engorgement EROS-CTD has been clinically demonstrated to significantly improve vaginal/clitoral sensations, lubrication, ability to achieve orgasm, and overall sexual satisfaction in women with SD. While this device has not been specifically tested in patients with MS the range of symptoms that are improved are in fact indistinguishable from those that characterize SD in females with MS.

The utility of phosphodiesterase-5 inhibitors for female SD has not been sufficiently studied, and where evidence is available the findings across studies are not consistent. For women who describe diminished arousal, sensation, and difficulty achieving orgasm, the use of high intensity, high frequency wall-power vibrator devices has been reported as beneficial. For those with vaginal dryness and poor arousal-related lubrication, over the counter water-soluble agents can have benefit. When these over the counter agents are not effective, consultation with gynecological colleagues is in order to explore the use of vaginal estrogens or testosterone.

#### DEPRESSION & SEXUAL DYSFUNCTION

A common dilemma for practitioners is how to adequately control depression in MS patients without adversely affecting sexual function. If an SSRI antidepressant is required for satisfactory mood stabilization, but is associated with SD, adding a dose of a norepinephrine-dopamine reuptake inhibitor (bupropion XL at 150-300mg) might be helpful. Albeit anecdotal, this intervention has been reported highly effective in reversing symptoms of SD in SSRI-treated patients. Experience in our center corroborates this observation.

The cornerstone of management for tertiary SD is counseling or psychotherapy, either as monotherapy or as adjunctive treatment in conjunction with other strategies. The individual patient may benefit from cognitive and behavioral therapy, knowledge of sexual stimulation techniques, and interpersonal communication training.

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# Sleep Disorders

*Jeffrey L. Ortstadt, M.D.*

## CLINICAL PEARLS

- When the chief complaint is difficulty falling asleep, contributing causes to be considered include anxiety, stress, depression, restless legs, circadian rhythm sleep disorder (delayed or advanced sleep phase), and medication effects.
- When the chief complaint is difficulty staying asleep, consider the possibility of sleep disorders such as periodic limb movement disorder (PLMD), obstructive sleep apnea (OSA), and central sleep apnea. Nocturia, a common phenomenon in MS, may accompany PLMD and OSA without the patient realizing their awakenings are caused by limb movements or respiratory events
- Severe excessive sleepiness and a habit of taking multiple short naps during the day is suggestive of narcolepsy, especially when appearing fairly abruptly in a young person, or when accompanied by episodes of cataplexy, sleep paralysis or hypnagogic hallucinations

## CASE VIGNETTE

### *Case 1*

A 36 year-old woman with relapsing-remitting MS and spastic paraparesis complained of frequent awakenings at night despite use of baclofen at 20 mg and zolpidem 10 mg each evening before retiring. She occasionally had difficulty falling asleep accompanied by “pinching and pulling” sensations in her lower extremities. These sensations began when lying down and were relieved by walking or vigorously moving her legs, only to return when she tried to relax. Her partner had started sleeping in another bed because of the patient’s restlessness and kicking at night, which disturbed his sleep. She was referred to a local sleep center where polysomnography revealed low sleep efficiency with frequent periodic limb movements, accompanied by arousals and awakenings.

Her serum ferritin level was 30 mcg/ml. Restless legs syndrome (RLS) with periodic limb movement disorder (PLMD) was diagnosed, and oral iron replacement was started in addition to ropinirole 0.5 mg each evening, taken an hour before bedtime. Within two months she was sleeping more soundly with resolution of her restless legs symptoms, fewer awakenings, and more satisfying sleep. Her ferritin level had risen to 60 and she had been able to eliminate zolpidem at night.

### *Case 2*

A 43 year-old woman with relapsing-remitting MS had to retire from work on disability and had become dysphoric with a loss of her sense of purpose and self-esteem. Bupropion 150 mg bid was prescribed. She complained of difficulty initiating and maintaining sleep, and found sleep un-refreshing. She frequently missed morning appointments. A two-week sleep diary revealed erratic bedtime and rising times each day with multiple nightly awakenings, and variable total sleep times of 4 to 9 hours. She commonly went to bed after 1 AM and rarely got up before 10 AM. Her schedule of meals and daytime activities was irregular, and she often spent most of the day lounging in bed watching television. She disliked the darkness and quiet of her bedroom at night, and described intrusive and repetitive thoughts (so-called ruminative thoughts) after going to bed, which prevented her from sleeping. She reported that she slept better when she visited her sister overnight in another city. A diagnosis of delayed sleep phase type of circadian rhythm sleep disorder was made, with components of psychophysiological insomnia and poor sleep hygiene, complicated by depression. She was switched to extended release bupropion once daily in the morning and was prescribed melatonin 5 mg each night, which she took at 10 PM. She created a daily schedule for herself and began going to bed at 1 AM and arising each day at 8AM, and using a 10,000 lux therapy light device for 30 minutes after awakening each morning. She was encouraged to practice sleep hygiene and stimulus control measures. Within 3 months she was maintaining regular sleep and daytime activity schedules and reported markedly improved mood and outlook.

### Case 3

A 54 year-old man with secondary progressive MS had long complained of fatigue and worsening nocturia. He was under treatment with glatiramer acetate and was taking fluoxetine for depression. He found modafinil to be more effective to improve daytime alertness and energy than amantadine, acetyl-L-carnitine or 4-aminopyridine (4-AP). His wife reported that he snored heavily and exhibited pauses in his breathing during sleep. He had a large tongue with scalloped edges, a long, edematous uvula, and a neck circumference of 18 inches, with a body mass index of 33. He was referred to the sleep center for polysomnography due to suspected sleep apnea. He was found to have an apnea-hypopnea index of 35 and was treated with continuous positive airway pressure (CPAP). Within a month his excessive daytime sleepiness and snoring had resolved, nocturia had improved, and he was able to discontinue modafinil and maintain satisfactory control of fatigue with 4-AP alone.

### SUMMARY

A majority of patients with MS experience unsatisfactory sleep. The presence of sleep complaints is directly associated with lower quality of life scores and an increased likelihood of depression. Insomnia, defined as difficulty initiating or maintaining sleep, comprises the largest category of sleep complaints, affecting up to 40% of patients with MS. Contributing factors include tonic muscle spasticity and phasic spasms, nocturia, depression, anxiety, and medication side effects. Among the sleep disorders associated with insomnia, restless legs syndrome (RLS) and periodic limb movement disorder (PLMD) are more common among patients with MS when compared to control populations. Obstructive sleep apnea, central sleep apnea, and circadian rhythm disturbances have not been found to occur more frequently in patients with MS than in the general population. Notwithstanding these observations, these are common and potentially disabling, even dangerous, sleep derangements (e.g. apnea is associated with hypertension, heart attack, stroke, and cor pulmonale) and must be considered for further investigation in the appropriate setting.

There is no apparent correlation established between sleep complaints and disease severity in MS. Only a few studies have reported a relationship between sleep disturbances and MS lesion localization. MS subjects with sleep complaints had a significantly higher frequency of lesions in the frontal and insular areas of either cerebral hemisphere. Further, a correlation has been reported between restless legs complaints and the presence of cervical spinal cord lesions. Periodic limb movements identified on polysomnography in MS subjects has correlated positively with lesions in the cerebellar hemispheres. Narcolepsy with low hypocretin levels in CSF has been diagnosed in patients with MS with plaques involving the hypothalamus. REM sleep behavior disorder (RBD) has been reported in association with demyelinating disease in the brainstem.

Evaluation of sleep complaints in patients with MS should be careful and systematic. A practical approach is to first categorize the complaint as primarily one of difficulty falling asleep, difficulty staying asleep, disturbing phenomena during sleep, or excessive sleepiness when awake. Any patient may of course experience two or more of these symptoms, but one of them is usually the predominant concern. Standardized and validated clinical questionnaires can be very helpful, such as the Pittsburgh Sleep Quality Inventory (PSQI) and the Epworth Sleepiness Scale (ESS). The PSQI focuses on the patient's sleep experience for the past month and the ESS assesses the severity of any sleepiness experienced during usual wake time activities. These are completed by the patient prior to the provider interview and can be used during the visit to help clarify the patient's current sleep status. Interviewing the patient's bed partner is usually helpful to establish the pattern and character of sleep phenomena such as snoring, apnea, limb movements, confusion upon arousals and complex motor behaviors. Current medications and dosing times should be carefully reviewed since a number of medications prescribed for MS patient symptoms may contribute to insomnia, disturbed sleep and/or daytime sleepiness.

Difficulty falling asleep is commonly caused by anxiety, stress, depression, restless legs, circadian rhythm sleep disorder (delayed or advanced sleep phase), and medication effects. The patient should be asked about their habits around sleep. Rules of good sleep hygiene and stimulus control measures should be encouraged (*see Tables 14:1 and 14:2*).

**TABLE 14:1: SLEEP HYGIENE RULES TO IMPROVE SLEEP**

Go to bed when you are sleepy.
Get up when you awaken in the morning.
Establish a regular time for arising each morning.
Avoid napping after 3 PM, or more than one hour a day.
Avoid large meals within 2 hours of bedtime.
Avoid bright light in the evening.
Avoid caffeine and alcohol within 4 hours of bedtime.

**TABLE 14:2: STIMULUS CONTROL MEASURES TO IMPROVE SLEEP**

Reserve your bedroom for sleep and intimacy; don't work, conduct family discussions or do other stressful activity in your bedroom, or close to bedtime.
Use the hour before bed for relaxing activity, such as reading, taking a warm bath, or playing a game with your family.
Don't watch TV in your bedroom, especially before sleep.
Minimize noise and light intrusion in your bedroom.
Make your bedroom a comfortable sanctuary where you feel safe and relaxed.
If you cannot sleep after going to bed, get up and go to another room and do a quiet activity under low light, such as reading, until you feel sleepy, then return to bed.

Typical symptoms of restless legs should be asked about (*Table 14:3*).

TABLE 14:3: RESTLESS LEG SYMPTOMS (URGE)

U: An irresistible urge to move the legs (or arms), often accompanied by Unpleasant sensations in the limbs, usually below the knees, like bugs crawling or wires pulling under the skin.
R: Symptoms occur while at Rest, not when active or moving.
G: Getting up and walking or vigorously moving the legs (or arms) relieves the symptoms.
E: Symptoms typically occur in the Evening or at the end of the day.

Current medications should be reviewed and any that may contribute to insomnia adjusted or discontinued. An attempt should be made to understand the patient’s ideal sleep schedule, i.e., the schedule they would keep if they did not have to comply with any other schedule demands, such as a bed partner’s preferred sleep times, or the expectation to be at work by a certain time, etc.

Patients with delayed sleep phase may not realize that if they allow themselves to stay up until they are sleepy, and sleep until they naturally awaken, they could maintain a more satisfying sleep routine. Having the patient complete a two week sleep diary can be helpful to understand their sleep habits and to establish when best sleep can be obtained.

When the chief complaint is difficulty staying asleep, consider the possibility of sleep disorders such as periodic limb movement disorder (PLMD), obstructive sleep apnea (OSA), and central sleep apnea. Nocturia, a common complaint for patients with MS, may accompany PLMD and OSA without the patient realizing their awakenings are caused by limb movements or respiratory events. Patients with frequent awakenings should be referred for polysomnography at a sleep center to identify specific treatable causes.

A complaint of disturbing phenomena during sleep requires that the nature and characteristics of the disturbances be explored. A bed partner’s complaint of loud snoring should prompt the clinician to consider OSA, particularly if the patient complains of fatigue or daytime sleepiness. Witnessed excessive movement during sleep suggests PLMD. Episodes of kicking the legs and waving the arms, especially if associated with

dreaming or resulting in injury to the patient or bed partner, may be indicative of REM sleep behavior disorder. Suspicion of any of these conditions is sufficient to warrant referral for polysomnography. Excessive sleepiness during the day despite regular sleep during the night is characteristic of OSA, and may also accompany PLMD and circadian rhythm sleep disorders. Severe excessive sleepiness and a habit of taking multiple short naps during the day is suggestive of narcolepsy, especially when appearing fairly abruptly in a young person, or when accompanied by episodes of cataplexy, sleep paralysis or hypnagogic hallucinations.

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# Spasticity & Gait Dysfunction in MS

*Anjali Shah, MD*

## CLINICAL PEARLS

- Spasticity can affect patients with MS, regardless of subtype.
- Persons with MS and spasticity should be screened for factors that could trigger or worsen spasticity. These include infection (urinary or systemic), constipation, pain, distended bladder or fever.
- All patients with MS should be advised to stretch daily in order to delay or prevent the development of abnormal tone. The muscles of emphasis are the two-jointed muscles (gastrocnemius, lumbricals, hamstrings, etc.) as they are most prone to spasticity
- Balancing between the benefits of adequately treating spasticity and causing fatigue or cognitive changes is vital.
- Patients frequently benefit from treating spasticity with a combination of maintenance and restorative therapies, medications and assist devices.

## CASE VIGNETTE:

A 36 year old male with a history of relapsing-remitting MS was referred to neurology for evaluation of right foot drag and difficulty ambulating. He was diagnosed with MS in 2001 following an episode of visual loss in conjunction with disseminated brain lesions identified on MRI. CSF analysis had revealed five oligoclonal bands and an elevated IgG Index. He began disease-modifying therapy in the winter of 2002 and has been highly adherent to the treatment regimen. Since the initial episode, he has had two additional episodes of optic neuritis that required treatment intensification with oral dexamethasone at 160mg for one day each month.

He has experienced some tonic stiffness in his legs, particularly across the ankle and knee. In addition he noticed an increased frequency of jerks and spasms, so called phasic spasticity, in the evenings and it was most prominent while lying down in bed. He had noticed a heavy sensation in his right leg a few times, once after mowing the lawn for about fifteen minutes, and again after 15 minutes of simply walking. Further, he was bothered by the dragging of his right foot. To compensate he had to start circumducting the leg during the swing phase of walking in order to avoid catching his toe and tripping.

Examination revealed pelvic obliquity that corresponded to recent complaints of hip pain and hyperextension of the knee, genu recurvatum. These altered gait mechanics resulted in multiple trips and falls. This increased his energy utilization with resultant fatigue and he recently started to use a single prong straight cane for stability. He did report a modest improvement in his symptoms after his monthly oral pulse of steroids. The oral baclofen regimen was increased from 15mg three times daily to 20mg three times daily with some improvement in his tonic stiffness. A limited physical therapy program showed no obvious benefit. He had not regularly stretched nor engaged in any regular conditioning program.

He was independent and had good Activities of Daily Living (ADLs) but occasionally needed help with getting dressed due to his right leg spasticity and weakness in hip flexion. His impairments had begun to interfere with his duties as a pastry chef in a French restaurant as he had marked difficulty completing the complex tasks involved in preparing sophisticated menu items. Furthermore, his work was impacted by his chronic fatigue, slowed ambulation around the kitchen, and his need to sit down frequently to rest. The ambient temperature in the restaurant's kitchen provokes worsening in his mobility and fatigue.

#### S U M M A R Y

Spasticity is a disorder of increased resistance of a muscle, or group of muscles, to an externally imposed stretch across a musculotendonous unit. As the velocity of the stretching increases, the spasticity increases.

Greater than 80% of patients with MS report some spasticity, with one-third of these having symptoms so significant that they modify or eliminate daily activities as a result of their spasticity. Obviously patients with spasticity perceive a compromised quality of life due to their impairments.

When involuntary movements occur, jerks and spasms are produced and this is classified as phasic spasticity. Phasic spasticity is frequently seen with tonic spasticity in patients with MS where there is significant upper motor neuron weakness. These more dynamic symptoms tend to be most frequent and severe in the evening when the patient is lying down in bed. Not surprisingly, both tonic and phasic spasticity can impair sleep hygiene and contribute to daytime fatigue, produce or exacerbate pain, exacerbate cognitive problems, increase the risk of motor vehicle accidents, and compromise work performance.

During the day spasticity is energy depleting. This increases the likelihood of worsening fatigue and increases the possibility of tripping and falling, making walking more troublesome. On the other hand, for patients with MS who experience significant limb weakness, a certain amount of spasticity can be advantageous to help with stability, postural control, transfers, standing, and even ambulating. This makes the goals of treatment difficult to balance; some spasticity can help but too much can create significant challenges. With these principles in mind the goals of treating spasticity must always take into account the tradeoffs between reduction in tone and spasms in order to optimize function, but not to the extent that safety and stability is compromised.

Gait dysfunction related to weakness and tonic spasticity, fatigability and heat sensitivity are often significant factors. These MS manifestations markedly impact a patient's quality of life, sense of wellbeing, and the ability to be adequately productive in one's work life. These are well illustrated in the case presented above.

## CLINICAL APPROACH & MANAGEMENT

The optimal management of spasticity requires a multidisciplinary framework that involves the patient and the care team, and is multi-modal including pharmacological and non-pharmacologic approaches. Appropriate management of spasticity begins with a thorough history and comprehensive neurologic examination. Specific focus needs to be directed at the musculotendonous units and the corresponding joints involved. While there are several scales available that classify spasticity, the most commonly used are the Ashworth and Modified Ashworth scales. [See Table 15:1]

TABLE 15:1: MODIFIED ASHWORTH SCALE

0	No increase in tone
1	Slight increase in tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of motion (ROM)
2	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

The practical value of these scales in the clinic relates primarily to the ability to be semi-quantitative and reproducible in the way the patient is evaluated and to gauge the response to therapy over time.

Through careful history and systematic physical examination the provider should determine the location, nature, and severity of the spasticity. Persons with MS and spasticity should be screened for factors that could trigger or worsen spasticity. These include visceral pain from internal organs seen in systemic or urinary infections, constipation, pain, distended bladder with urine retention or fever of some undetermined origin.

Clear objectives for the treatment of spasticity should be articulated early in any discussion. Patients should understand that the goals are to reduce pain, decrease unwanted spasms, reduce falls to increase safety, and improve sleep. The provider will also have to relate how treatments may impact other functions and impact the quality of life. All patients with MS, (whether they have spasticity or not) should be instructed on how to stretch daily. Exercise represents a cornerstone of management for all patients. It should include resistance training in order to maintain strength and function. The range of exercise routines should be reviewed with each patient so that they are safe and feasible. Methods of stretching should be illustrated so that they can be employed upon awakening from sleep, during the day, and as a priority before going to bed at night.

In more complex cases with long established spasticity, patients should be referred to physical therapists with experience in working with MS patients. They will help design individualized routines that can mitigate symptoms while optimizing function and safety at home and in the workplace. The muscles of emphasis are typically the two-jointed muscles (gastrocnemius, lumbricals, hamstrings, etc.) as they are most prone to spasticity. For the patient who has already developed severe spasticity, other modalities can be considered besides the oral medicines discussed below. Some patients may need chemical denervation therapy to decrease the tension in chronically spastic muscles. In some patients there can be surgical interventions to decrease the impact of spastic muscles and these can be considered for patients with particularly difficult symptoms.

Often stretching alone is not sufficient to effectively manage muscle tone and spasms and oral anti-spasticity agents can be added to help with increased muscle tension associated with spasm. There are well recognized drawbacks associated with the use of oral anti-spasticity drugs. All of these agents have the potential to produce sedative effects and slowing of cognition. This is particularly vexing because many patients with MS are already dealing with increased fatigue and slowed information processing.

Notwithstanding these limitations an acceptable balance between risks and benefits can be achieved in most.

Oral medications commonly used to treat spasticity include baclofen, tizanidine, benzodiazepines (diazepam and clonazepam) and, rarely, dantrolene sodium. Single medication therapy with agents like baclofen should be initiated with slowly increasing titration to avert any potential fatiguing effects. The agent of first choice often tends to be baclofen, starting at 5mg three times daily and then escalating the dose (at 5–7 day intervals) until the desired effect is achieved. Some patients respond quite robustly to even an initial small dose of baclofen, whereas others require substantial doses (even as high as 30–40mg three times daily) to adequately control spasticity. If not tolerated, or if the medication unmasks marked weakness, smaller doses can be used in combination with other agents, or the patient can be transitioned to a different drug entirely.

Baclofen produces only modest effects on phasic jerks and spasms, particularly when they are severe, even though it is highly effective in reducing tonic spasticity. In patients with phasic jerks and spasms benzodiazepines, like clonazepam or diazepam, are highly effective in reducing these dynamic symptoms. The benzodiazepines are more sedating than baclofen and must be used with great caution and slower increases in titration schedules. Given that phasic spasticity tends to be most prominent at night, consider using these agents mostly/solely at bedtime where they can facilitate sleep, reduce spasms, decrease nocturnal bladder urgency and nocturia. This drug treatment regimen can relieve several bothersome issues related to sleep alteration.

Oral tizanidine is highly effective in reducing tone and phasic jerks and spasms. Generally this treatment begins at 2mg three times daily and then the dose is escalated by 2mg/dose every 5–7 days. A typical dose ranges from 2mg to 12mg three times daily as needed, and sometimes dosing goes higher. Unfortunately many patients with MS do not tolerate tizanidine, principally because of excessive sedation and/or post-dose hypotension that occurs about 20–40minutes following ingestion. Even in such patients tizanidine can still be used but only at bedtime.

Other oral agents that have been utilized for treating spasticity include cyproheptadine, carisoprodol, and cannabis. Combination therapy can be implemented if needed. [Table 15:2]

Patients with focal spasticity or difficulty tolerating oral medications may benefit from chemical denervation with botulinum toxin (BT), phenol, or alcohol injections. BT temporarily blocks acetylcholine release at the neuromuscular junction (NMJ), which allows for muscle relaxation, and this effect lasts approximately 90 days. The effects of phenol are indefinite. Both can improve gait, reduce spasticity and improve hygiene and overall care of patients. BT does not have the fatigue or sedating effects that are common with the oral anti-spasmodics.

Often the most common application of BT is to weaken the posterior leg compartment muscles in patients with toe drag and circumduction due to weakness of dorsiflexion and heel-cord (Achilles tendon) tightness. The mismatch between the gastrocnemius and the tibialis anterior underlies the pathophysiological signature of progressive MS where posterior muscles are overactive and the tibialis anterior is weakened. Ultimately this leads to shortening of the Achilles tendon. The application of BT to the posterior compartment muscles then allows physical therapy to work at lengthening the tendon through aggressive stretching, foot mobilization, and even the use of assist devices. Either an ankle-foot orthosis (AFO) and/or a functional electrical stimulator (FES) can assist with foot elevation during the swing phase of walking and decrease the need for circumduction, pelvic obliquity, and genu recurvatum.

Surgical intervention is often required when profound spasticity or contracture(s) is present. An intrathecal baclofen pump (ITB) is ideal in patients with uni- or bilateral lower limb spasticity that affects the hip, knee and ankle flexors. The ITB allows for constant medication delivery with little waxing and waning. An ITB trial is highly recommended prior to implantation to allow the clinician and patient to assess the potential responsiveness and experience with intrathecal therapy.

TABLE 15:2: SPASTICITY MEDICATIONS

<i>Medication</i>	<i>Recommended Daily Dosage</i>	<i>Half-life</i>	<i>Metabolism</i>
Baclofen	10–80 mg	2–6 hours	Kidney, liver
Cannabis	5–20 mg (in 2 to 4 divided doses)	19–36 hours	Liver, renal
Clonazepam	0.125–3 mg (max 3 mg/day); often dosed at night only.	12 hours	Liver
Clonidine	0.1–0.4 mg oral/transdermal patch	5–19 hours	Liver, kidney
Cyproheptadine	4–16 mg (in one to two divided doses)	1–4 hours	Renal
Dantrolene	25–100 mg (in four divided doses)	4–15 hours (after oral dose)	Liver
Diazepam	2–40 mg (in two to four divided doses)	20–80 hours	Liver
Gabapentin	300–3600 mg (in 3–4 divided doses)	5–7 hours	Excreted unchanged in urine
Levetiracetam	25–3000 mg (one to three divided doses)	7 hours	Renal
Piracetam	12–24 gm (in one to three divided doses)	5–6 hours	Excreted unchanged in urine
Tizanadine (capsule and tablet form)	2–36 mg (in 1–3 divided doses) — slow titration recommended	2.5 hours	Liver

GABA = gamma aminobutyric acid

RLS = restless leg syndrome

<i>Site of action</i>	<i>Lab monitoring</i>	<i>Side effects</i>	<i>Notes</i>
CNS, GABA-B inhibition	LFT q6 months	Somnolence, fatigue, constipation, nausea, vomiting	Only generic form is available
unknown		Nausea, vomiting, somnolence, increased appetite	Not legal in all states
Benzodiazepine	LFT q 6 months	Drowsiness, sedation, ataxia	Preferred in phasic spasms, myoclonic movements or in RLS
Central alpha — 2 agonist		Bradycardia, depression, syncope, fatigue, hypotension	
Serotonergic antagonist		Increased appetite, weight gain	Also helpful for patients with myoclonic movements or RLS
PNS — inhibits Ca release at sarcoplasmic reticulum	LFT q3–6 months	Most hepatotoxic, postural instability, slurred speech, diarrhea	no blood brain barrier passage
CNS, facilitates GABA A agonist	Patient should not consume alcohol when using diazepam	Sedating, memory impairment	Used to treat oral and intrathecal baclofen withdrawal symptoms
GABA analogue		Somnolence, dizziness, ataxia, fatigue	Safe for those with hepatic dysfunction
Unknown; believed to work through GABA & glycine channels		Loss of appetite, mood disorder, fatigue, headache	
GABA derivative; nootropic agent	LFT q6 months	Nausea, flatulence	
Central alpha — 2 agonist, glycine facilitator	LFT q6 months	Orthostatic hypotension, drowsiness, dry mouth, dizziness, MS patient prone to muscle weakness	Recommend initiating at night

LFT = liver function testing

SCI = spinal cord injury

Finally, implantation requires due diligence on the part of the patient as regular follow up for refills and adjustments is necessary. Surgical procedures such as rhizotomy or tendon lengthening procedures are also useful in carefully selected patients with contractures.

As previously mentioned, physical activity and stretching are important for all patients, no matter what other interventions are implemented, and these should be regularly encouraged by every clinician. The intensity and duration must be highly individualized for each patient. Patients may need focused restorative therapy with a physical, occupational or recreational therapist. They may also benefit from core body strengthening programs in a private or group setting. Maintaining as high a level of activity as possible is critical for patients with MS as those who remain active can help delay the onset of physical disabilities that would set in with inactivity.

#### CASE OUTCOME

The following interventions for the patient presented in this chapter resulted in a marked improvement in his mechanics of walking where his pain was resolved, his pelvic obliquity improved and the genu recurvatum improved. He also experienced improvements in his fall safety, energy conservation, work performance, sleep hygiene, activities of daily living and sense of wellbeing. The main interventions were as follows:

1. Intensive stretching of the heel cords and hamstrings
2. A regular exercise program consisting of stationary cycling and swimming
3. Botulinum toxin injections to the posterior compartment muscles of the right leg followed by physical therapy and the application of a functional electrical stimulator device
4. Baclofen for tonic spasticity
5. Low dose clonazepam at bedtime for phasic jerks and spasms

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# Swallowing & Speech Disorders

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## CLINICAL PEARLS

- Aspiration pneumonia due to dysphagia is the leading cause of death in patients with MS
- Adequate evaluation of dysphagia involves a videofluoroscopic swallowing study (VFSS) with a modified barium swallow (MBS) and/or fiberoptic endoscopic evaluation (FEES).
- Several pharmacologic and rehabilitative therapies are available to treat the patient with Neurogenic Dysphagia.
- Both muscle weakness and incoordination can give rise to speech dysfunction and in MS it is often caused by lesions in the cerebellum, brainstem or connecting pathways.

## CASE VIGNETTE:

Our patient is a 67 year-old man with a long history of primary progressive multiple sclerosis that has culminated in his nearly constant use of an electric wheelchair for mobility. While he is unable to cut his food, he is able to feed himself using adapted utensils. During a recent continuity of care visit to the clinic his wife describes multiple episodes over the last four months where her husband has exhibited choking while eating. It appears that thin liquids (water, coffee, tea) are most problematic in precipitating dysphagia, although he is also having problems when attempting to eat crackers and rice. Due to this difficulty in swallowing our patient has begun to lose weight. His voice has a soft, wet, gurgly sound with hypophonia (low voice volume due to muscle incoordination and weakness).

## SUMMARY

Dysphagia refers to difficulty with swallowing and should be addressed at each office visit as it can lead to aspiration pneumonia, the leading cause of death in multiple sclerosis.

## CLINICAL APPROACH & MANAGEMENT

Aspiration pneumonia is reported to be a leading cause of death in patients with MS. Screening for solid and liquid dysphagia should be a part of each office visit with the patient with MS. An intact ability to swallow is vital in order to ensure adequate nutrition and hydration. The provider's ability to accurately characterize the mechanisms responsible for liquid and solid dysphagia is germane to formulating a treatment and aspiration prevention plan. It is contingent upon knowledge of oropharyngeal and central nervous system anatomy and the physiology of swallowing. Patients with advanced MS and associated dysphagia will typically have corresponding lesions in the lower brainstem affecting the most caudal cranial nerve nuclei or nerve fascicles (cranial nerves IX, X, XI, and XII).

A compromise in respiratory function has been reported to be the proximal cause of death in up to 46.5% of persons with MS. Symptoms of dysphagia can become evident in patients with an Expanded Disability Status Scales (EDSS) score as low as 2–3 (mild disability), with increasing prevalence as the EDSS score further increases. A study of 309 consecutive MS patients reported that 24% (73 patients) had symptoms of unrelentingly persistent dysphagia. Conspicuously the prevalence of dysphagia has been observed to be present in 65% of MS patients with an EDSS score of eight or higher.

Two regions of the forebrain appear to be most involved with swallowing, the anterior insula and the frontoparietal operculum. Descending projections from these cortical regions innervate the pontine and medullary nuclei responsible for swallowing and chewing (trigeminal, facial, glossopharyngeal, vagal, and hypoglossal nerves).

Individuals with liquid dysphagia may complain of coughing or choking while eating, whereas those with solid food dysphagia may complain of food ‘sticking’ in the throat or chest. Other features include dysphonia, “wet” voices/phonation, coughing, gastroesophageal reflux (GERD), oral malodor or an abnormal gag.

The physical exam of the dysphagia patient should involve inspection and palpation of the neck and throat for structural abnormalities or masses. The neurological examination should carefully interrogate the function of the lower cranial nerves as emphasized above. Careful monitoring of the patient’s weight is relevant to the impact of dysphagia upon nutritional status and general health.

Additional tools can be employed in order to screen and characterize swallowing function. A videofluoroscopic swallowing study (VFSS) can be done in the form of a Modified Barium Swallow (MBS). While the principal advantage of MBS is allowing direct visualization of swallowing, it requires that the patient to be able to sit upright. Repeated use of MBS is limited due to radiation exposure. This test should be conducted in conjunction with a Speech-Language Pathologist Therapist who can both delineate the areas of dysfunction and formulate the strategy for improved swallowing. Alternately a Fiberoptic Endoscopic Evaluation (FEES) can be performed by an otorhinolaryngology physician (ORL). FEES utilizes a flexible laryngoscope that is inserted transnasally into the pharynx. This test can provide an analysis of the dynamics of real-time oropharyngeal mechanisms of the swallowing function. This procedure is very helpful in identifying regional anatomy and vocal cord function. FEES is more portable and can be done at the bedside but does not allow for direct visualization of the swallowing process.

Treatment of dysphagia can involve pharmacologic, rehabilitative, and/or surgical interventions. Those patients with hypersalivation may benefit from medications with anti-cholinergic properties or side effects in order to produce a dry mouth. Transdermal scopolamine patches are also effective in reducing saliva production and thereby mitigates aspiration. Botulinum toxin injection for sialorrhea is can also be effective. Proton pump inhibitors (PPI) are commonly used to treat symptoms of GERD.

There are three methods to improve functional swallowing:

### *Restitution*

This technique focuses on restitution of disturbed functions by exercises and repetition of movements made by the tongue, cheek, and lips. No food is typically swallowed during the exercises or therapies.

### *Compensation*

This involves postural techniques and dietary modifications without changing actual swallowing physiology.

### *Adaptation*

Adaptation involves modification of the environment to improve nutrition. Examples include thickening liquids, pureeing food, as well as stimulating the sense of taste.

In some cases where nutritional needs cannot be met due to severe neurogenic dysphagia or hypersecretion, a nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tube may be temporarily or permanently required to maintain optimal nutritional and fluid intake, decrease the risk of choking, improve quality of life and increase survival. When the need for enteral feeding is necessary for the short term (<30days) NG tubes are usually appropriate. However, because these tubes can be associated with considerable discomfort as well as other complications such as epistaxis, direct enteral access is preferred when feeding needs require a long-term access strategy.

## SPEECH DYSFUNCTION

Dysarthria refers to speech problems that are caused by muscles involved with speaking or the nerves controlling them, and can occur in approximately 40% of all patients with MS. When speech and voice disturbances do occur, they usually present as a spastic-ataxic dysarthria with disorders of voice intensity, voice quality, articulation, and intonation. Both muscle weakness and incoordination can give rise to dysarthria and in MS it is often caused by lesions in the cerebellum, brainstem or connecting pathways.

Speech problems often become more pronounced during times of stress or fatigue. Reduced ability to communicate can have a serious impact on social interactions as the person with MS experiences communicating as a very tiring effort.

There are no pharmacological therapies for dysarthria but speech therapy can often be of great benefit. Speech language therapy can be effective in improving dysarthria, voice volume, and language. Speech language pathologists may be able to recommend assistive devices to aid communication such as voice amplifiers.

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# Vestibular Dysfunction

*Teresa C Frohman PA-C, Elliot M Frohman, MD, PhD*

## CLINICAL PEARLS

- Benign Paroxysmal Positional Vertigo (BPPV) is the most common cause of vertigo in the MS patient.
- BPPV can be elicited by the Dix Hallpike Maneuver and resolved by the Epley maneuver

## CASE VIGNETTE:

A 44-year-old patient with stable relapsing remitting MS woke up extremely dizzy, ‘like the room was spinning.’ The symptoms were worse every time she moved her head to get out of bed. This same symptom had occurred several years ago and her neurologist at the time performed what was probably a Dix Hallpike maneuver in the office and the vertigo immediately subsided. She had not been sick recently, had no known sick contacts and the ‘spinning’ would stop after about 30 seconds if she remained very still. On physical exam there was a noted nystagmus. Upon performance of the Dix Hallpike maneuver with the head in the left head-hanging position.

## SUMMARY

The patient who was in her normal state of health woke to experience vertigo that was exacerbated by movements of her head and subsided if she lay very still. This is obviously vertigo associated with positional changes. These symptoms can be very disabling to any patient and can create a more complex picture for patients with MS. There are a myriad of etiologies for vertiginous symptoms in patients with MS. The most common however is the same common condition seen in the general population, namely benign paroxysmal positional vertigo

(BPPV). This condition is associated with inner ear abnormalities. The second most common cause of vertigo in MS in an MS patient is when the demyelinating process targets vestibular CNS circuitries within the brainstem, and on occasion, the cerebellum. This latter etiology would appropriately trigger the administration of corticosteroids as with any MS exacerbation. Other, albeit much less common causes of vertigo in MS patients include vestibular migraine, vestibular neuritis, Meniere's disease, perilymphatic fistula, basilar meningitis (e.g. TB, Syphilis, Lyme, HIV, Carcinomatous, etc.) neurosarcooidosis, neoplasms and other mass lesions.

#### CLINICAL APPROACH & MANAGEMENT

Vestibular abnormalities and the jerky involuntary eye movements of nystagmus are typically associated with lesions of the brainstem vestibular apparatus, and occasionally the cerebellum. When this is seen in a patient with MS the disease process of inflammation, demyelination and sclerosis may be targeting the pons, cerebellar and vestibular pathways. Nystagmus comes in numerous types such as horizontal, vertical, pendular, etc. Nystagmus produces intrusions upon fixed, or steady gaze. Consequently, in primary or eccentric eye positions, images of interest can 'slip' off of the macula of the retina, secondary to unwanted eye movements that degrade vision and can produce the illusion of environmental movement, oscillopsia.

Patients with nystagmus commonly experience the visual illusion of self or environmental movement called oscillopsia. This is commonly referred to as true vertigo by neurologists and should and not be confused with complaints of disequilibrium or dizziness related to lightheadedness from low blood pressure, cardiac arrhythmia, hypoglycemia, feelings of faint (presyncope), or imbalance. A mismatch between vestibular signals that project centrally into the brainstem can result in a bias which produces a vestibular slow phase eye movement, usually toward the side of the lesion. The vestibular signals originate from the inner ear organs such as the semicircular canals, and the static labyrinth, the utricle and saccule. The slow phase bias movement is followed by a

fast snap back movement, or saccade, in order to reset the eyes on the visual object of interest. For example, these could represent slow and fast phases of most forms of nystagmus. Pendular nystagmus is different in that the phases are of equal amplitude, velocity and acceleration in all directions, horizontal, vertical and/or elliptical.

#### PATHOPHYSIOLOGY OF BBPV

The pathophysiology of BBPV is basically mechanical and involves the dislocation of small calcium carbonate particles (otoliths) from the utricular maculae, followed by their migration into the semicircular canals most commonly the posterior. Movement of the particles within one canal provokes unbalanced nerve activity that is transmitted to the brainstem eye movement control centers. This results in nystagmus of a highly characteristic type.

The symptoms of BPPV can be easily identified and ameliorated with simple bedside examination techniques. The Dix Hallpike maneuver is both diagnostic and leads to a therapeutic result. This maneuver involves reclining the supine patient into a head-hanging position off the end of an exam table. When this is done torsional and vertical vectors of the eyes movements can be observed and even measured with the proper instruments. While laying the patient down like this they will become vertiginous as their vestibular signals are mismatched and their eyes will reflect this with the characteristic abnormal movements.

The patient continues in the same position at which point the examiner employs additional maneuvers. This second-phase of the intervention is referred to as the Epley maneuver. At this point the head is rotated to reposition the particles out of the semicircular canal and back on to the macular membrane. The patient is quickly returned to a seated position to complete the repositioning. This will again make patients dizzy but when the symptoms resolve the patients will now feel an improvement of symptoms. The maneuver can be repeated to the opposite side to ascertain whether the process is potentially bilateral. With the resolution of symptoms providers can be assured that the patient was experiencing BPPV. If the symptoms do not resolve or improve, the patient may need further workup and treatment.

The second most common cause of vertigo in patients with MS is related to the development of demyelinating plaques in one of two anatomic localizations. The first is the medullary tegmentum below the floor of the fourth ventricle, in the vicinity of the vestibular nuclei. The second is at the entry zone for the root of the vestibulochoclear nerve, cranial nerve VIII, at the pontomedullary junction. In these patients the Dix Hallpike maneuver would have little or no effect in resolving symptoms. Also, if brainstem nuclei or the root of cranial nerve VIII is involved there may be some decrease in auditory acuity on that side. However, despite demyelination of the cranial nerve VIII nerve at the root entry zone, a perceived hearing loss is very uncommon in this particular scenario and for MS in general. This is likely due to the broad redundancy and bilateral representation of hearing pathways throughout the central nervous system.

In patients with MS who have vertigo that fails to improve while testing for BPPV, or who have additional complicating neurologic symptoms, a rapid application of high dose corticosteroids is appropriate to effectively mitigate symptoms. If the steroids do not improve symptoms within 2–4 weeks, the treatment may require advancement to plasma exchange or chemotherapeutic anti-inflammatory drugs, as has been described in the chapter focused on treating MS exacerbations.

#### REFERENCES

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# MS & the Family

*Katherine Treadaway, LCSW*

## CLINICAL PEARLS

- Communication is key in maintaining healthy relationships when a parent has MS. Patients with MS can continue to be excellent parents, role models, and productive members of the family and in society.
- There are many reasons to encourage our patients to talk to their children about MS. These include assurance that parents and/or healthcare providers are the source of news, validation of a problem that the child has already sensed (their imagination could lead them to think that the situation is significantly worse than it actually is), giving children a sense of control, allowing questions and concerns to be expressed, and building trust.

## CASE VIGNETTE:

The patient is a 36-year-old woman with a history of relapsing MS, currently on natalizumab for disease modifying therapy. She was well until 1996 at which time she developed an episode of left sided optic neuritis. She subsequently noted some involuntary movements of her eyes. A neuro-ophthalmologist recognized bilateral internuclear ophthalmoparesis (INO) in May 2001. An MRI of the brain was performed at that time and demonstrated disseminated lesions consistent with MS.

She was started on weekly intramuscular interferon beta1a and significantly improved. However she subsequently discontinued the medication in order to have a child in 2003. When she returned to therapy, she began to have intolerable side effects and was converted to daily glatiramer acetate in May 2005. She had further progressive deterioration in her cognitive capabilities in the next several years and was transitioned to natalizumab in January 2008. She has tolerated it without significant

reactions. She has taken disability leaves from work in the past but is now at home with plans for long term disability due to disabling fatigue, cognitive impairment, physical symptoms and eye movement problems that affect reading, writing, and her driving, particularly when changing lanes or making turns. She is working with the health-care team regarding her disability application. During her last clinic visit she commented that her 6 year-old son is having a real problem lately with “mom’s MS.” She reported that her son was verbalizing his belief that there was nothing wrong with her and she is just “faking”.

#### SUMMARY

This young mother has relapsing remitting MS associated with symptoms that include cognitive impairment and fatigue. There is the added stress of dealing with a growing family. She and her spouse are wondering what they should do to help their son better understand MS and how his mom is affected by it.

#### CLINICAL APPROACH & MANAGEMENT

Members of the family share significantly in the impact of MS. Some of the most prominent challenges associated with MS include the stresses placed on daily family life. Families have described MS as a separate entity like an “uninvited and unwanted” guest that intrudes on the family. We want to try and help families maintain open and honest communication about all facets of MS, even in the face of substantial physical, emotional, and intellectual difficulties. We want to help them anticipate and negotiate the possibility of a significant change in the role played by the patient in the family, in the marriage, and at work. A creative and collaborative working alliance is required on behalf of all the team players, including the families and healthcare team providers, in order to maintain healthy, energetic, and productive relationships.

Patients with MS and their families should be encouraged to continue to talk openly with the clinical team and to bring their young children or concerned family members to the next appointment to ask questions. Patients should also be encouraged to think about long-term and short-term plans that should be in place for “what-if” situations.

Having plans and goals replaces worries with resolve and “buy-in” for situations that may need to be addressed in the future. Providers should reassure their patients and family that people who have MS who are on disability (short or long-term) can continue to be excellent parents and network with others dealing with MS. Patients should consult with a financial planner to try and anticipate some of the challenges ahead.

A referral for family counseling/therapy might be helpful in some situations. There are educational programs and camps provided by the National Multiple Sclerosis Society (NMSS) and the Multiple Sclerosis Association of America (MSAA) that are for families and children/teens. Unfortunately parents often avoid educational or support programs for their children until there is a health crisis. A more productive strategy would anticipate these challenges early and avoid an understandable reactionary response to crisis.

There are many reasons to encourage patients to talk to their children about MS. Assurance that parents and/or healthcare providers are their sources of information validates a problem that the child has already sensed. Their imagination could lead them to think that things may actually be much worse than they actually are or that a problem does not exist when there is already a significant issue or stressor. This interaction can provide children with a sense of control. The opportunity for the child to ask questions and express concerns can build trust and confidence between the kids and their parents as well as the healthcare team.

Most children of a parent with MS adapt well over time. Patients and families are afraid of the reality that there is no cure for MS. Nevertheless, children need to know that MS is not contagious, that there is nothing that they said or did that caused the parent to get MS, and that there are effective treatments that often establish periods of remission. Children tend to find emotional/cognitive symptoms more difficult to comprehend and reconcile than physically evident ones and may ultimately misinterpret them. Healthcare providers can and should educate children on symptoms. The National MS Society is an enormous information resource for patients and families that are coping with MS and they even have literature just for kids and teenagers to help them understand MS.

From the point of view of the clinician/provider everyone should recognize and understand the impact that MS has on the patient's spouse and children. Providers should reach out to family members and encourage them to sustain outside activities, stay rested, and continue a healthy lifestyle. Clinicians should refer families for counseling to manage any feelings of anger or guilt.

Children should not be expected to be a primary caregiver for a parent but should continue with school and outside activities. While children should stay involved with the parent with MS they are not in an emotional position of maturity to deal completely with the challenges of taking complete care of that parent. That being said, children of patients with MS have a unique opportunity to learn vital life principles of service and responsibility and to see how their contributions are important and valued. These experiences can be important in accelerating maturity and building self-esteem. They can also lead to deeper more gratifying relationships. Children of parents who have MS often impress health care professionals with their sophistication, their empathetic caring, and their intelligence.

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# MS & Workplace Issues

*Katherine Treadaway, LCSW*

## CLINICAL PEARLS

- While many patients can continue with full and productive careers some may require the assistance and advocacy of the health care team with respect to identifying and submitting applications for specific and appropriate accommodations
- The clinical team plays a critical role in the preparation of documents justifying long and short-term disability with their corresponding medical benefits.

## CASE VIGNETTE:

A 40 year-old art director with MS and a history of bipolar disorder calls the clinic social worker for assistance with job accommodations. She was well neurologically until three years ago when she began to note a visual disturbance while looking at her computer monitor at work. This was characterized by a degree of microsomia (objects appearing smaller than their actual size) in addition to altered orientation of letters and numbers. She also noted pain in both of her eyes, reduced color perception, and blurred vision. An MS exacerbation (bilateral optic neuritis) was confirmed and she was treated with IV solumedrol (1gm/day for three days) and ultimately returned almost to baseline vision. She is currently using monthly IV natalizumab for disease modifying therapy and has been free of exacerbations or evidence of progression since starting this treatment.

Despite the remarkable stabilization of her disease course, persistent symptoms have had an adverse impact on her activities of daily living, work performance and quality of life. These have included chronic fatigue, urinary frequency, intermittent and transient visual problems, and complaints of cognitive dysfunction.

She requests assistance with getting zoom text on her computer which would enhance her visual performance and comfort, reduce eye strain-related headaches, and mitigate visual fatigue. She is also requesting a modified work schedule that would allow her to engage in mental health counseling, attend appointments with her psychiatrist, and participate in a yoga program.

#### SUMMARY

This 40 year-old patient is in need of workplace assistance to help her remain employed. While she carefully developed a proposal to improve her work performance, reduce MS related symptoms, and support her quality of life and job satisfaction, her supervisor appears to be reluctant to seriously consider her requests. Her requests for accommodations involve modest and appropriate workplace and scheduling changes that would fulfill the terms of employment as well as facilitate greater productivity by mitigating the physical and emotional manifestations of her MS. Ultimately she states that her supervisor is “all about working by the books.”

#### CLINICAL APPROACH & MANAGEMENT

The patient was recently seen in the clinic at which time cognitive problems were identified prompting a request for neuropsychological testing in order to characterize her deficits and establish a baseline of intellectual performance from which future evaluations can be compared. Also during the visit Family Medical Leave Act (FMLA) paperwork was completed. Given that the patient has exceeded the one-year threshold for employment at her current workplace, she is eligible for this benefit. While not all employers are required to grant FMLA leave time, employers with such coverage in force must grant an eligible employee up to a total of 12 work weeks of unpaid leave during any 12 month period. Patients with MS fall under an FMLA designation that grants medical leave when the employee is unable to work because of a serious health condition. Employees can work under the auspices of this program for either intermittent leave to attend appointments, infusions, imaging studies, as well as other appointments, or for a block of time during an MS exacerbation or progressive change in disability.

In the current set of circumstances the decision was made to request intermittent leave for her doctor appointments, as well as for her to be allowed to leave at a certain time at least 3 days a week to attend her counseling sessions and for yoga classes as a form of physical therapy. Patients with MS who are employed have an important protection from being fired during FMLA leave time.

A social worker can work collaboratively with the counselor at that agency to facilitate the requested accommodations given that the social worker had already referred this patient to the local state vocational rehabilitation program. As per the employer's requirements, a formal accommodations request letter was drafted that included the computer program for zoom text to be loaded on the patient's computer. In this particular case the employer was able to provide this computer program to help the patient with her vision at work. However, had it not been financially feasible for the employer to purchase this modification, an application for support to the state vocational program would have been the next strategy to provide this visual aid.

A useful resource for employees with MS who are in the process of becoming familiar with workplace accommodations is the Job Accommodation Network <http://askjan.org/>. This website also provides detailed information concerning the Americans with Disabilities Act (ADA). The most authoritative resource available for interrogating the intricacies of this law can be found at the ADA website [www.ada.gov](http://www.ada.gov).

Employers are required to provide reasonable accommodations to qualified individuals who have a disability, as long as it does not create a hardship upon the company. If an employee feels that their ADA rights have been violated, then he or she should contact the nearest office of the Equal Employment Opportunity Commission (EEOC) to explore whether filing a charge of discrimination should be pursued. Charges may be filed with the EEOC in person, by mail, or by telephone. To contact the EEOC look in the telephone directory under U.S. Government or call 1-800-669-4000 (voice) or 1-800-669-6820 (TTY), website [www.eeoc.gov](http://www.eeoc.gov). During the process of inquiry or filing a charge of discrimination, a person is not required to disclose their medical

diagnosis. Notwithstanding this protection against mandatory declaration of a diagnosis, there are circumstances where disclosure of a patient's diagnosis may be germane to successfully achieving the ultimate goal of workplace accommodation.

When accommodations are not sufficient to allow a person with MS to continue performing their job duties an application for disability benefits may need to be considered. Many employers offer short and long-term disability policies that will require documentation by the patient's physician. Characterization of a patient's symptoms and limitations within the medical record is especially important when applying for social security disability insurance (SSDI). This particular benefit is based on a person's work history and current disability status. Extensive information on the requirements and process for securing SSDI benefits can be found at [www.ssa.gov](http://www.ssa.gov). The National MS Society also has a publication on its website, [www.nationalMSSociety.org](http://www.nationalMSSociety.org), entitled *Social Security Disability Benefits for People Living with Multiple Sclerosis: A Guide for Professionals*. Once approved for SSDI, Medicare coverage will subsequently commence 24 months from the determined onset date of disability. If a person becomes disabled and has no or limited household income, they can instead apply for Supplemental Security Income (SSI). This disability benefit is not based on work history. In contrast to Medicare coverage following 24 months after approval of SSDI, Medicaid coverage is extended to individuals who are approved for SSI.

#### REFERENCES

The Job Accommodation Network <http://askjan.org/>. This website also provides detailed information concerning the American Disabilities Act (ADA).

With respect to the ADA, the most authoritative resource available for interrogating the intricacies of this law can be found at the ADA website [www.ada.gov](http://www.ada.gov).

Extensive information on the requirements and process for securing SSDI benefits can be found at [www.ssa.gov](http://www.ssa.gov).

# Hope & Spirituality

*Katherine Treadaway, LCSW*

## CLINICAL PEARLS

- All healthcare providers should remain aware that the spiritual and religious beliefs of their patients may impact how they manage and cope with living with MS.
- A brief spiritual history can be taken with patients to help healthcare providers become more aware of the individual needs of the patient

## CASE VIGNETTE

A 49-year-old female with secondary progressive MS presented to clinic. She was an architect until approximately age 28 when she developed an acute attack of diplopia. She had intermittent changes in her visual acuity, but ultimately had significant deterioration in her interocular tracking movements. Subsequent events have involved left-sided trigeminal neuralgia for which she was treated with Gamma Knife. While talking with the social worker about a medication resource the patient ends the call with a spiritual request, asking if the social worker will “please pray for me”.

## BEYOND JUST THE CLINICAL APPROACH & MANAGEMENT

Multiple sclerosis can be particularly difficult because it is most commonly diagnosed in the prime of life between the ages of 20–50. This is the time when most people are in the midst of establishing their careers and building their families. Some patients in turn question their religious or spiritual beliefs. Religious and spiritual beliefs can impact how patients manage their illness in both positive and negative ways.

Some of the positive effects of spirituality are believed to be associated with perceived improvements in coping skills, greater sense of self control and well-being, reduced anxiety and depression, increased community support, enhanced recovery, and longer survival rate. Religious and spiritual beliefs can also be harmful, such as when a patient uses religion as a replacement for necessary medical care.

A brief spiritual history can be taken with any patient to bring the healthcare provider more awareness about the individual needs of the patient. There are several examples of instruments for healthcare providers in the suggested reading “Spirituality in Patient Care”. In the book Harold Koenig, MD, states that “The information gathered has nothing whatsoever to do with the healthcare provider’s beliefs. The purpose is to understand the patient’s beliefs and what role they play in health and illness without judgment or attempt to modify those beliefs or lack of belief.” Our awareness of these beliefs may lead to a greater understanding of how to best serve the patient.

This particular patient made a specific request. The healthcare provider may feel comfortable granting this request and a referral to pastoral care or to the hospital chaplain would certainly be appropriate. Members of the healthcare team must know that such services are available, who to contact, and under what circumstances.

Healthcare team members can also help patients by encouraging hope, activity, creativity, and wellness. There are activities that may foster this such as exercise, guided imagery, and spiritual practices — essentially whatever works for the patient! Providers should encourage anything as long as it is directed at obtaining greater health and functionality and is not harmful. Patients should stay involved in their communities through volunteer work, pursuing passions and advocacy. These facets of care are especially important for patients who are no longer working due to disability so that they can continue to maintain a strong sense of self-worth, value to society and their families, and a sense of life’s purpose.

Care team members should not forget to explore their own spiritual needs, and those of their co-workers. In some treatment centers a special gathering occurs annually to honor and remember patients who have died during the year. Bringing together staff and family members can be an uplifting, healing, and spiritual activity. It provides a time to remember those who have been lost and to support each other in moving forward to serve and care for others. The quality of this disease that causes frustration and turmoil for the patients and family will have emotional and spiritual impact on the truly empathetic provider. Connecting and sharing with others on the team, and with the surviving families can provide needed support and feedback to the busy and stressed provider.

#### SUGGESTED READINGS

Spirituality in Patient Care: Why, How, When, and What By Harold G. Koenig 2nd ed, 272 pp Templeton Foundation Press

The Courage to Give : *Inspiring stories of people who triumphed over tragedy to make a difference in the world.* by Jackie Waldman Coronari Press; 2000

# Social Work & Case Management

*Katherine Treadaway, LCSW, Caroline Williamson, LCSW*

## CLINICAL PEARLS

- Social workers and other team members should work together to assure that patients maximize their use of national/community resources and receive appropriate and coordinated health/rehabilitation services.
- Advocacy on behalf of patients and their families is important.

## CASE VIGNETTE

A 70 year-old female with severe MS and a history of transverse myelitis called the social worker for assistance. She had been treated in the past with cyclophosphamide, mitoxantrone, interferons, and glatiramer acetate. She was now on quarterly rituximab with great stabilization and no further attacks. She is married and they have one adult daughter. She lives in a rural area about three hours from the clinic. Her most significant challenges include symptoms of neuropathic pain, severe spasticity, constipation, bladder dysfunction, gait impairment, heat sensitivity and limited vision.

She called the clinic to speak to the social worker about several issues. She required financial help for her medications, physical therapy that could take place in the home, and more personal assistance due to health issues of her spouse. She needed an MRI but she had a limited ability to pay the cost of her deductible. In addition to her MS this patient had numerous other medical issues and this made coming into the neurologist difficult.

## SUMMARY

This 70-year-old patient with MS needs numerous services. She has experienced severe disease that is physically limiting, and yet she wants desperately to continue living independently with family in her own home.

## CLINICAL APPROACH & MANAGEMENT OF SOCIAL WORK ISSUES

The social worker/case manager will do a psychosocial assessment to determine the needs and corresponding available resource options for this patient. Generally social workers and case managers assist with coordination of care including arranging home health services, ordering durable medical equipment (e.g. bedside commode, shower chair, hospital bed and mattress, etc), orchestrating physical and occupational therapy, referring to medication assistance programs, and identifying local and national resources. Nurses and/or physician assistants often assist with these services should a social worker not be available.

The local chapters of the National MS Society ([www.nationalMSSociety.org](http://www.nationalMSSociety.org)) often have social workers on staff or may offer case management services, particularly for complicated and seriously debilitated patients. Most Society chapters provide direct financial assistance to patients. Some host wellness classes and offers self help groups. Society chapters offer other networking opportunities by hosting family events and by providing educational programs and other resources for patients, families, and healthcare providers.

For the patient described above, a medication assistance program was identified through a pharmaceutical company and arrangements were made for physical and occupational therapy in the home under her Medicare insurance. A life alert system was instituted and she received help in submitting an application for state aide services. Every state has special services available for the aging and disabled. The Multiple Sclerosis Foundation is an organization that often provides for short term help

through its Home Care Program for people awaiting services and dealing with MS. The Multiple Sclerosis Foundation was contacted in this case to provide assistance while waiting for the state wide services to be activated.

The patient received help with securing grab bars and a ramp through a local home modification organization and was enrolled in Meals on Wheels. An overall evaluation was initiated to see whether there were any new equipment needs, services or diagnostic studies that should be addressed such as a power chair, bedside commode for more independence (through insurance), talking book program (local divisions for blind services are resources) or cooling vest from one of the MS organizations (all of them have a program to provide cooling devices). The patient's physician requested an MRI for disease surveillance. A social worker assisted the patient with an application to the Multiple Sclerosis Association of America (MSAA) for assistance. Infusions and follow-up clinic appointments were coordinated so that both services could occur on the same day. This was important because of her distance from home to the clinic.

The MSAA ([www.MSAA.com](http://www.MSAA.com)) has a program called the MRI Institute to help with MRI coverage. In addition MSAA can provide an equipment loan distribution program, cooling vests, and numerous other services. Some patients may have financial resources to pay privately for help at home. Local hospitals should have a list of agencies that would be resources. Most pharmaceutical companies provide assistance for medications either through providing the medication free or connecting patients with an organization for financial help. All the companies that produce MS disease-modifying therapies have assistance programs available. Please, refer to the resource table for contact information.  
*[Table 21:1]*

TABLE 2 I : I : MS RESOURCE TABLE

<i>Resource</i>	<i>Education</i>	<i>Referrals</i>	<i>Research</i>	<i>Assistance, devices &amp; evaluation</i>
National Multiple Sclerosis Society 800-344-4867 <a href="http://www.nationalMSSociety.org">www.nationalMSSociety.org</a>	✓	✓	✓	✓
Multiple Sclerosis Association of America 800-532-7667 <a href="http://www.msassociation.org">www.msassociation.org</a>	✓	✓		✓
Multiple Sclerosis Foundation 888-673-6287 <a href="http://www.msfacts.org">www.msfacts.org</a>	✓	✓		✓
Rocky Mountain MS Center website on complementary and alternative medicine for people with MS <a href="http://www.ms-cam.org">www.ms-cam.org</a>	✓		✓	
National Institute of Health Clinical Trial listing <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a>			✓	
ASSISTIVE TECHNOLOGY Abledata <a href="http://www.abledata.com">www.abledata.com</a> Vehicle modification National Highway Traffic Safety Administration <a href="http://www.nhtsa.dot.gov">www.nhtsa.dot.gov</a> National Mobility Equipment Dealer's Association <a href="http://www.nmeda.org">www.nmeda.org</a> Comprehensive driving exam Association for Driver Rehabilitation Specialists <a href="http://www.driver-ed.org">www.driver-ed.org</a>		✓		✓
CAREGIVERS National Family Caregiver's Association <a href="http://www.nfcacares.org">www.nfcacares.org</a> National Caregiver's Library <a href="http://www.caregiverslibrary.org">www.caregiverslibrary.org</a>	✓			

<p>DISABILITY</p> <p>Social Security 1-800-772-1213 <a href="http://www.ssa.org">www.ssa.org</a></p> <p>Provided by federal government: <a href="http://www.disabilityinfo.gov">www.disabilityinfo.gov</a></p> <p>National Organization of Social Security Claimant's Representatives 1-800-431-2804 <a href="http://www.nosscr.org">www.nosscr.org</a></p>	✓	✓		✓
<p>ADVOCACY</p> <p>Equal Employment Opportunity Commission <a href="http://www.eeoc.gov">www.eeoc.gov</a></p> <p>MS Workplace <a href="http://www.msworkplace.com">www.msworkplace.com</a></p> <p>Job Accommodation Network (JAN) (Office of Disability Employment Policy of the US Department of Labor) 1-800-526-7234 <a href="http://www.jan.wvu.edu">www.jan.wvu.edu</a></p>	✓	✓		✓
<p>MEDICATION ASSISTANCE PROGRAMS FOR DISEASE MODIFYING AGENTS</p> <p>MS Active Source (Avonex &amp; Tysabri) 1-800-456-2255</p> <p>Shared Solutions (Copaxone) 1-800-887-8100</p> <p>MS Lifelines (Rebif) 1-877-447-3243</p> <p>Beta Plus (Betaseron) 1-800-788-1467</p> <p>Novartis (Gilenya) 1-800-277.2254</p> <p>All other medications contact the manufacturing company or go to: <a href="http://www.rxhope.com">www.rxhope.com</a> <a href="http://www.rxassist.org">www.rxassist.org</a> <a href="http://www.needymeds.com">www.needymeds.com</a></p> <p>Partnership for Prescription Assistance 1-888-477-2669 <a href="http://www.pparx.org">www.pparx.org</a></p> <p>The National Organization for Rare Disorders 1-800-999-6673 <a href="http://www.raredisease.org">www.raredisease.org</a></p>	✓	✓		✓

The patient was in great need of finding a primary care physician close to her home willing to work collaboratively with her neurologist. A local physician was identified and the clinic's physician assistant and nursing staff worked with that physician in the management of this patient's myriad of symptoms.

Some patients may require consideration of an assisted living or long-term care facility if there is insufficient support at home and/or ineligibility for community services. Families and patients can research such facilities via the website <http://www.newlifestyles.com>. Patients and families are strongly encouraged to tour several facilities when possible in order to appreciate the differences and nuances of care that are offered in different settings.

Patients should be encouraged to write a list of what is most important to them and the family when looking at assisted or long-term care settings. In the majority of circumstances patients and families will be responsible for the full cost of an independent/assisted living or a skilled nursing facility. The family may be able to have some financial help for living situation if the patient with MS qualifies for long term care Medicaid or has long term care insurance. Patients should be reminded and encouraged to consult with an attorney and/or financial planner as additional resources.

# Informed Consent & Clinical Trials

*Gina Remington, RN*

## CLINICAL PEARLS

- Remain sensitive to the myriad influences and motivating factors that contribute to a patient's non-adherence to therapy.
- Providers should be aware of the ethical concerns related to placebo-controlled clinical trials in MS.
- Informed consent is a process and requires multiple discussions with the patient to reinforce expectations, explain risks and benefits, and discuss alternative treatment options.

## CASE VIGNETTE

Jack was diagnosed with MS five years ago and was started on a disease modifying treatment. In the past two years he had not experienced any clinical relapses or radiographic changes on MRI, but continued to have fatigue and injection related side effects. He then presented in clinic with questions about his current treatment plan and a clinical trial he recently read about on the internet. Upon reviewing the information he printed from the website you learn that the clinical trial is placebo-controlled and requires a three-month wash-out period of the current disease-modifying therapy prior to randomization. When queried Jack states that he went ahead and stopped taking his injection two weeks ago, scheduled an appointment in three months with the research site for screening, and would like to discuss your thoughts on his participation.

## SUMMARY

This patient was diagnosed with relapsing remitting MS five years ago. He has been on interferon for approximately one year. Because he continues to have injection-related side effects, he would like to explore other treatment options and is now considering participation in a clinical trial. The provider learns that the proposed trial is placebo-controlled and would require the patient to discontinue current therapy in order to be considered for randomization.

## CLINICAL APPROACH & MANAGEMENT

This case vignette addresses three primary concerns: maintenance of current treatment adherence, consideration of aggressive treatment options, and potential participation in a clinical trial. Patients on an FDA-approved therapy for relapsing remitting MS can often have persistent injection site reactions and other side effects, despite attempts to mitigate symptoms. Over time these effects dramatically increase the risk for non-adherence and consequently impact the frequency and severity of future exacerbations. One option — replacing an injectable therapy with another — might result in an abeyance of both side effects and injection site reactions. Physicians may also recommend discontinuing current injectable treatments and switching to intravenous (such as natalizimab or mitoxantrone) or an oral therapy (fingolimod). However, the risks involved in switching to more aggressive therapies, with potentially life-threatening side effects, may not outweigh the benefits for all patients. The option suggested by the patient (discontinuing current therapy, participating in a clinical trial) requires further consideration of ethical questions.

In 1964, the World Medical Association (WMA) convened in Helsinki, Finland, to standardize universal ethical principles for physicians conducting clinical research. The WMA's meeting resulted in the Declaration of Helsinki, which provides guidance for medical research according to a foundational, central theme: "The health of my patient will be my first consideration."<sup>1</sup> The Declaration requires research investigators to ensure that participants are not exposed to excessive risk for the sake of science, and, by officially recognizing that participation in clinical research was voluntary.

Investigators were also required to obtain documented informed consent and offer explanation of current alternatives to participation in research. Often, experts in MS disagree about the interpretation of clinical equipoise in the context of placebo-controlled trials. Clinical equipoise refers to uncertainty about whether an experimental treatment in a clinical trial is equal or superior to standard treatment. Thus, the aim in clinical research is to design protocols whereby various treatment arms are perceived to be equitable with each other and also with the current standard of care available for the diagnosis being studied.<sup>2</sup> The most recent revision of the Declaration of Helsinki (2000) suggests that placebo-controlled trials are unethical in a disease such as MS that has efficacious treatment to minimize functional disability and reduce the risk of irreversible harm. The revision states that “the benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods.”<sup>1</sup> Despite the patient’s proactive approach in contributing to MS research, these ethical concerns must inform any discussion regarding proper placement into a clinical trial.

#### REFERENCES

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