

Review Article

MULTIPLE SCLEROSIS AND THE UROLOGIST

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ABSTRACT

Purpose: We provide an updated reference detailing the neurological and urological state of the art approach to multiple sclerosis (MS) with special emphasis on the pathology and physiology, effects on the genitourinary tract, diagnostic evaluation, and treatment of neurological and urological manifestations.

Materials and Methods: A MEDLINE computerized reference search and manual bibliography review were performed to find pertinent peer reviewed articles on the neurological and urological manifestations and treatment of MS. A meta-analysis was performed on the urodynamic findings of 22 studies involving 1,882 patients from well-defined MS populations.

Results: The majority of patients with MS have genitourinary symptoms ranging from urgency, urge incontinence and frequency to urinary retention. Symptoms do not accurately reflect the underlying urological pathology but parallel pyramidal tract dysfunction. Urodynamic evaluation has an important role in determining proper bladder management. The most common urodynamic finding is detrusor hyperreflexia in 62% of these patients, followed by detrusor-sphincter dyssynergia in 25% and hypocontractility in 20%. Less than 1% of patients has renal deterioration and most may be treated with conservative measures. If conservative measures fail, new forms of bladder reconstruction and diversion may be effectively used. The incidence of sexual dysfunction is up to 80% in men and 72% in women, and treatment focuses on improvement of overall disability and erectile or orgasmic function.

Conclusions: Although the genitourinary consequences of MS are rarely life threatening, they can cause significant morbidity and patient frustration. With the rapid advances in the medical management of MS the urologist should be actively involved in multispecialty treatment of these patients.

KEY WORDS: multiple sclerosis; urodynamics; bladder, neurogenic

Multiple sclerosis (MS) is the most common disabling neurological disorder affecting people between 20 and 45 years old. MS involves myelinated white matter pathways in the brain and spinal cord, and can produce many distinct neurological deficits. The primary disease mechanism of MS is related to an autoimmune attack on central nervous system myelin with relative preservation of axon cylinders. Enhanced detection and diagnosis are increasing our awareness of this disease, while immunological research is leading to the development of new therapeutic strategies.

More than 80% of MS patients have symptoms of lower genitourinary tract dysfunction and more than 96% with the disease for longer than 10 years have urological findings.¹⁻⁴ The effects of MS on the genitourinary tract range from bladder and urethral dysfunction to impotence. Urological involvement usually presents as lower urinary tract (bladder and urethral) dysfunction, which can be a source of significant disability and patient frustration. A working knowledge of the pathophysiology, evaluation and treatment of this condition is essential for the urologist who is often asked to manage these severe, debilitating symptoms.

METHODS AND BACKGROUND

MEDLINE, Ovid and Index Medicus databases from 1966 to the present were searched using the key words, multiple sclerosis, multiple sclerosis/neurogenic bladder and multiple

sclerosis/urological treatment. Additional articles were also obtained. Only articles written in English were reviewed unless a translated abstract was available. For meta-analysis series were selected only when the patients were from a well-defined MS population, and urodynamic evaluation was well documented and conformed to International Continence Society standards.⁵

History. Cruveilhier in 1835 and Carswell in 1838 were the first to illustrate clearly the lesions in MS.⁶ In 1868 Charcot published *Sclerose En Plaques* in which he described the multiple areas of sclerosis as brain hardening,⁷ and at the time it represented the most complete clinical and pathological description of MS. However, Frommann identified reactive gliosis as a principal feature of the MS plaque.⁸

Epidemiology. Current prevalence rates for MS are 1/1,000 Americans, 2/1,000 Northern Europeans and 20 to 40/1,000 first degree relatives of patients with MS. Studies have shown that the risk of MS in identical twins, 1 of whom has clinically definite disease, is approximately 30%, representing a 300-fold risk elevation over the general population.⁹⁻¹¹ The incidence of MS in children adopted by parents with the disease is similar to the general population, demonstrating that a shared environment poses no increased risk.^{12,13} MS affects women more commonly than men by 2:1. Most often it is diagnosed in patients between 20 and 45 years old but there are a number of well documented cases of MS in chil-

dren younger than 5 years and in patients 60 to 70 years old.^{14,15} Because many individuals can be afflicted with central nervous system demyelination without clinical evidence of disease, the individual who presents with a new diagnosis of MS at age 70 years may have had subclinical lesions of demyelination for many years.

PATHOLOGY

Immunopathology (fig. 1). MS is caused by an autoimmune attack of central nervous system myelin leading to a loss of saltatory conduction and conduction velocity in axonal pathways. It is characterized by perivenular demyelination with preservation of axons. However, in severe plaque lesions axonal loss may also be observed and there is less potential for myelin repair. The cardinal features of the histopathology of MS plaques include perivenular lymphocytic infiltrates, macrophages within the white matter, gliosis and scarring. The T lymphocyte line is the predominant cell type which is believed to have a pivotal role in the formation of the MS plaque. T cell immune responses are dependent on the interaction of antigen presentation cells and uncommitted T helper (TH)-0 lymphocytes. Uncommitted TH-0 cells can be converted into TH-1 pro-inflammatory lymphocytes which elaborate cytokines, such as interleukin (IL)-2, interferon gamma and tumor necrosis factor- α , or into immunoregulating TH-2 lymphocytes which release IL-4, IL-10 and transforming growth factor- β .¹⁶ The earliest stages of MS plaque development involve migration of T lymphocytes and other

immune cells from the blood compartment into the central nervous system.¹⁷ This migration is likely dependent on a series of enzymes capable of degrading tissue. Interferon- β , an approved treatment for MS, inhibits these enzymes, which could explain the significant reduction in gadolinium enhancing lesions with such treatment. After T lymphocytes migrate in the brain they elaborate a series of cytokines and other factors that contribute to myelin injury.

Animal models. In an animal model of inflammatory demyelination experimental allergic encephalomyelitis, the predominant epitope in myelin basic protein recognized by auto-aggressive lymphocytes, has been identified. Modifications of myelin basic protein can be made using a blocking peptide that inhibits antigen presentation and produces a state of immune tolerance to the development of experimental allergic encephalomyelitis. This anergy response is at least partly mediated through IL-4, thus providing a strong rationale for its use in MS.¹⁸ This response also suggests that modified blocking peptides based on epitopes of myelin basic protein and possibly other myelin proteins, such as myelin oligodendroglial cell glycoprotein and proteolipid protein, may represent other means to combat human demyelinating disease.

Neurological effects and the urinary tract. Although MS plaques can be seen anywhere in the central nervous system, there is a documented prevalence of the disease in the cervical spinal cord, predominantly the lateral corticospinal (pyramidal) and reticulospinal tracts.^{19,20} Because innervation of the detrusor and external urethral sphincter is mediated by these tracts, most MS patients have lower urinary tract dysfunction.²¹

Suprasacral spinal cord effects. Autopsy studies by Oppenheimer indicated that lesions of the suprasacral spinal cord are common in MS patients.²⁰ Cervical cord plaques are the most common, occurring in up to 80% of patients.^{20,21} Thus, patients with MS may lack suprasacral suppression of autonomous bladder contractions, resulting in detrusor hyperactivity and urge incontinence. Spinal lesions may also disrupt reticulospinal pathways from the pons involved in the synergic integration of urethral sphincteric and detrusor activity.²²⁻²⁵ This disruption may result in a continuum of the 3 main abnormalities of detrusor-sphincter dyssynergia, incomplete sphincteric relaxation and sphincteric paralysis.^{23,25,26}

Sacral cord effects. Lower motor neuron symptoms associated with presumed demyelination of the sacral cord/conus medullaris are reported in 0 to 63% of patients.¹⁻³ In contrast, autopsy studies by Philip et al demonstrated only an 18% incidence of sacral plaques.²⁷ Mayo and Chetner reported that 63% of patients had detrusor hypocontractility but only 5% displayed areflexia.²⁸ This finding has led some authors to question the contribution of sacral plaques to overall symptoms of lower urinary tract dysfunction.²⁹⁻³¹ In animal studies Kruse et al demonstrated that intact spinal afferents and efferents are crucial to facilitate sustained detrusor contractions.^{32,33} Plaques in these afferent or efferent pathways may inhibit facilitated contraction thereby causing impaired emptying and urinary retention. Although abnormal sacral nerve function, demonstrated by prolonged reflex latencies, has been documented by several authors and may help confirm the diagnosis of MS, the sole contribution of these reflex pathways to bladder dysfunction remains uncertain.^{1,3,32-34}

Intracranial plaques. Intracranial plaques occur in 60 to 90% of MS patients.³⁵⁻³⁷ Although the most commonly involved area is the periventricular white matter, plaques have been reported in nearly all areas of the intracranial white matter. Thus, disease in the supraspinal central nervous system may account for urological dysfunction (detrusor hyperreflexia). In 90 MS patients studied by Kim et al there was no correlation between magnetic resonance imaging

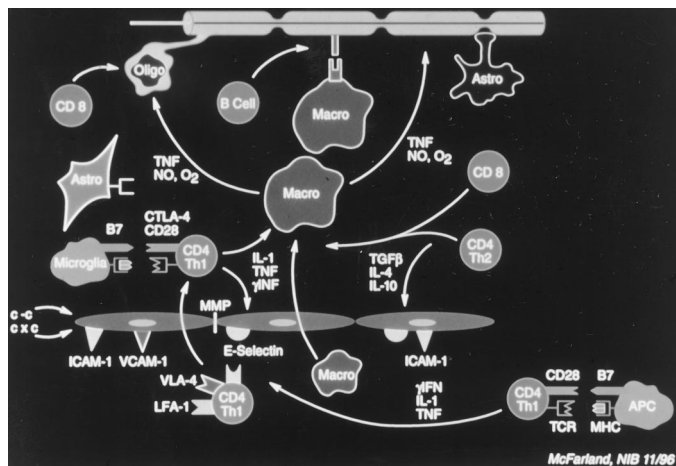


FIG. 1. Pathogenesis of and proposed immunomodulatory networks in MS. At bottom right antigen presentation is depicted. Antigen presenting cell (APC) presents antigen in context of major histocompatibility complex antigens (MHC), which interacts with T cell receptor on CD4 TH-1 pro-inflammatory lymphocytes. CD28 and B7 are co-associational signals important for antigen presentation. Once activated by antigen presentation, CD4/TH-1 cells move to vessel wall and use specific receptors, such as VLA4 and LFA1 to interact with adhesion ligands VCAM-1 and ICAM-1. E-selectin is another cerebrovascular endothelium receptor site. Once bound to vessel wall lymphocytes and macrophages (Macro) can migrate into central nervous system compartment. Lymphocytes can then interact with resident brain microglia (central nervous system macrophages). Macrophages can subsequently mediate tissue damage through elaboration of toxic effector agents, such as tumor necrosis factor (TNF), nitric oxide (NO) and oxygen-free radicals (O₂). Targets for such damage include oligocyte (Oligo) (principal cell that produces and maintains central nervous system myelin), myelin sheath, astrocytic processes at nodes of Ranvier and axon. CD4/TH-2 lymphocytes are immunomodulating cells that elaborate IL-4 and IL-10. These important cytokines likely serve to down regulate pro-inflammatory limb of immune response in MS. In contrast, IL-1, tumor necrosis factor and interferon gamma (IFN- γ) are pro-inflammatory cytokines that likely promote disease activity by enhancing antigen presentation, immunoadhesion and tissue damage. TGF β , transforming growth factor- β . Reprinted with permission from McFarland, Neuroimmunology Branch, National Institutes of Health.

(MRI) findings (atrophy, number of lesions, nature or size of a lesion) and any specific urodynamic parameters.³⁸ However, Pozzilli et al demonstrated a statistically significant correlation ($p < 0.001$) between urinary symptoms and midbrain lesions on T2-weighted imaging.³⁹⁻⁴¹ While lesions in the midbrain highly correlate with urological disease, the urological significance of clinically isolated pontine lesions in the absence of pyramidal findings remains unknown.^{42, 43}

CLINICAL PRESENTATIONS

Diagnosis. MS is generally diagnosed by the occurrence of multiple events of neurological dysfunction during different periods. These events should be separated by at least 1 month and reflect distinct anatomical regions of the central nervous system (multiple events in time and space).¹²⁻¹⁴ Events are defined by clinical history and neurological examination. Diagnosis has become more accurate with the addition of paraclinical investigations of MRI, evoked potentials and cerebral spinal fluid analysis. Diagnostic criteria can be divided into those that confirm clinically definite and those that confirm laboratory supported definite MS (Appendix 1).⁴⁴

Differential diagnosis. When a single lesion has a relapsing-remitting course, other disease entities should be considered, including central nervous system tumors (lymphomas), arterial/venous malformations of the spinal cord and brain stem, primary central nervous system vasculitis, polyarteritis nodosa, sarcoid, Behcet's disease, systemic lupus erythematosus, neurosyphilis, paraneoplastic disorders and mitochondrial cytopathologies. Of note, primary central nervous system lymphomas can strongly mimic demyelinating disease, displaying responsiveness to therapy with corticosteroids only to recur later. Without multifocality of disease a questionable lesion may require biopsy for diagnostic confirmation. When patients present with evidence of multiple lesions that are symmetrically distributed, alternative diagnostic considerations include vitamin B12 deficiency, hereditary spinocerebellar atrophy and infectious myelopathies (human immunodeficiency virus, human T cell leukemia/lymphoma virus-I associated myelopathy).^{6, 10, 12}

Clinical course. MS is generally described as relapsing-remitting or primary progressive.⁴⁴ The former is characterized by episodes of neurological dysfunction followed by remissions, when one notices complete or partial improvement in neurological deficits following each exacerbation and no further progression of neurological decline between attacks. This form of MS affects 85 to 90% of the patients who initially present with the illness. In primary progressive MS patients present with a continuous decline in neurological function that occurs insidiously or rapidly. Often the rate of decline is imperceptible to the patient until significant disabilities emerge. Approximately 30 to 40% of patients with relapsing-remitting MS will subsequently have a more chronic progressive course, which is called secondary progressive MS. Alternatively, patients with primary progressive MS can later experience superimposed exacerbations of neurological dysfunction, a condition referred to as relapsing progressive MS.⁴⁴

Clinical features (Appendix 2). **Optic Neuritis:** By far the most common presentation of optic neuritis is visual loss related to demyelination in the optic nerve. Patients complain of diminished visual acuity, red and green color desaturation, and visual field defects often associated with ophthalmic pain. Typically patients with optic neuritis will have significant if not complete recovery of visual acuity within weeks to months. Treatment of acute optic neuritis generally involves intravenous steroid therapy.⁴⁵ Among patients with isolated optic neuritis 33 to 66% have progression to clinically definite MS.⁴⁶

Ocular Motor Dysfunction: Patients may have gaze palsies, abnormal pursuit and saccadic eye movements, unwanted eye movements during steady fixation or nystagmus.^{47, 48} The

most common oculomotor abnormality in MS is internuclear ophthalmoplegia, which is related to a lesion in the medial longitudinal fasciculus in the pontine or midbrain tegmentum. This abnormality represents a neuro-ophthalmological hallmark of MS. Clinically, internuclear ophthalmoplegia is characterized by a slowing in adduction velocity with or without ocular limitation and nystagmus in the abducting eye.

Vestibular Abnormalities: Disorders of balance are common in the MS patient and thought to be due to somatosensory loss, cerebellar abnormalities, visual decline and vestibular pathology.⁴⁹ However, true vertigo occurs in less than 20% of patients.⁵⁰ Hearing loss, although rare, can occur in MS and generally relates to involvement of the converging auditory pathways in the pons.⁵¹ Approximately 1 to 2% of MS patients have tonic and tonic-clonic seizures, and complex partial seizures, vertigo, visual hallucinations, motor dysfunction or peculiar auras.

Weakness, spasticity and sensory loss are major features that contribute to a decline in ambulation, and are related to interruption in descending inhibitory pathways which regulate motor outflow through the lower motor neuron unit. In the presence of significant lower extremity weakness some degree of spasticity can actually be beneficial as it provides increased stability during standing. Patients with MS have tremors involving the lower extremities as well as trunk and head, which may occur at rest and with volitional movement. The voice can similarly be affected.^{52, 53} Transient neurological symptoms include Lhermitte's sign, an electric shock-like sensation in the arms, back or legs, Uhthoff's phenomenon, which involves a deterioration of symptoms in a hot environment, and trigeminal neuralgia.⁵⁴⁻⁵⁶

Cognitive Dysfunction: An estimated 43 to 65% of MS patients will have cognitive impairment.^{56, 57} In 1 series 50 to 80% of patients were unemployed within 10 years of disease onset and those who were cognitively impaired were most likely to stop working.⁵⁷ Patients may exhibit abnormalities in recent memory, sustained attention, verbal fluency, conceptual reasoning, visual spatial perception and immediate or remote memory. As the lesion burden expands, as measured by the volume of white matter abnormalities on MRI, there is an associated loss of cognitive function.^{56, 58}

Lower Urinary Tract Dysfunction: Lower urinary tract symptoms range from frequency or urgency in 31 to 85% of patients to incontinence in 37 to 72% to obstructive symptoms with urinary retention in 2 to 52%.¹⁻⁹ Although the incidence of lower urinary tract symptoms ranges between 52 and 97%, the presence or absence of symptoms is an unreliable indicator of the extent of vesical dysfunction.^{4, 26, 59, 60} Betts et al reported that only 47% of patients with elevated post-void residual had the sensation of incomplete emptying.²⁹ Conversely, 83% of patients complaining of incomplete emptying had post-void residual greater than 100 cc.⁴² Koldewijn et al noted urodynamic evidence of urinary tract dysfunction in 100% of patients with and 52% without urological symptoms.⁴

Although several studies have demonstrated that duration of disease, older age at diagnosis and degree of motor or sensory dysfunction correlate well with degree of urological impairment, lower urinary tract dysfunction best correlates with pyramidal tract involvement and overall disability as measured by the Expanded Disability Status Scale.^{4, 42, 60-65} In contrast, Awad et al found that pyramidal dysfunction independent of level of disability (Expanded Disability Status Scale) was most closely related to lower urinary tract dysfunction,³⁰ and so a history of ataxia, gait disturbances, unexplained lower extremity weakness, numbness or paresthesias may suggest occult urological dysfunction. Thus, the degree of lower extremity motor dysfunction may be the best

predictor of urological and bladder dysfunction. This correlation is so significant that lower urinary tract dysfunction is rarely seen in the absence of pyramidal dysfunction.^{4,64} Secondary progressive MS is the only course of the disease associated with an increased risk of progressively deteriorating bladder function ($p < 0.05$).⁴

Urinary symptoms may be age related and have a bimodal distribution. Patients younger than 40 years are most bothered by bladder storage and voiding symptoms, although these findings may be related to expectations inherently different from older patients. Patients older than 50 years are also greatly bothered by bladder symptoms, which may be related to the longer duration of disease or cumulative effect of other causes of bladder dysfunction, such as benign prostatic hyperplasia or female stress incontinence.⁶⁰ Although increasing duration of disease is linked to increased frequency of overall symptoms, no 1 symptom is more prevalent in patients with long-standing disease. No significant relationship has been found between the incidence of overall symptoms and gender. However, men with MS have a higher incidence of obstructive symptoms, which may be due to age related changes in the prostate or the severity of detrusor-sphincter dyssynergia in men.⁴

EVALUATION

History. Although only 2 to 2.5% of patients present with urological symptoms, a high level of suspicion for MS should exist in any young patient with unexplained voiding dysfunction even without neurological symptoms.^{1,5,27,65} Patients with unexplained voiding dysfunction who fit the demographic parameters for MS should be questioned about fatigue, heat intolerance (Uhthoff's phenomenon), sensory dysfunction, motor weakness and periods of waxing or waning symptoms. As previously discussed a history of lower extremity sensory or motor loss can be a sign of unrecognized urological pathology. A history of visual disturbance (diplopia, oscillopsia) or dizziness may indicate pontine pathology with concomitant bladder and sphincter effects. Gastrointestinal disturbances, usually constipation, may be reported.

Voiding symptoms should be characterized temporally and spatially. Patients should be questioned about urgency, stress incontinence and emptying. Aggravating and relieving factors should be elicited. Use of protective devices should be determined and a quality of life instrument may be useful to assess the overall daily impact of symptoms.⁶⁶⁻⁶⁸ A history of incontinence or vaginal prolapse surgery may raise suspicion of concomitant anatomical factors affecting continence. Assessment of adequate fluid intake is important as many patients attempt to remedy bladder symptoms by decreasing fluid intake. A current and past medication profile should be obtained as many medications used to treat MS have neuroleptic or anticholinergic side effects (Appendix 3) and some patients have been treated with cyclophosphamide for progressive disease.

Physical examination. A directed neurological examination may help to determine the extent of urological dysfunction. In addition to the high correlation between lower extremity and bladder dysfunction, cerebellar signs, such as ataxia and dysdiadochokinesis, are correlated with detrusor areflexia.²⁹ Extensor plantar responses (positive Babinski reflex) may be evident in 70 to 95% of patients with bladder dysfunction and 70% with detrusor-sphincter dyssynergia but poor specificity limits diagnostic use. Similarly, many patients will display hyperactive deep tendon reflexes but this finding also is a poor specific indicator of detrusor hyperreflexia or bladder dysfunction (sensitivity 76%, specificity 58%).¹

The association between cranial nerve findings and urinary tract abnormalities is not well established. Betts et al reported that internuclear ophthalmoplegia correlated with bladder dysfunction in 16 patients.²⁹ Notably, most of these

patients demonstrated concomitant pyramidal tract dysfunction, raising a question about the significance of isolated internuclear ophthalmoplegia.²⁹ Sensory abnormalities may also be associated with bladder dysfunction, especially those of lower extremity vibratory sensation.⁶⁵

Genitourinary examination should focus on evaluation of sensory and motor function of the pelvic floor and sacral dermatomes (L2-S3). Patients with an indwelling catheter may have traumatic hypospadias (men) or urethral erosion (women). Pelvic examination is important as patients may have concomitant pelvic organ prolapse and urethral hypermobility. Prostate and testicular examinations are also important to aid in cancer screening and diagnosis of concomitant benign prostatic enlargement.

ANCILLARY TESTING

MRI. MRI is the most useful ancillary technique for obtaining supportive evidence of MS. MRI is diagnostic in 70 to 95% of patients with clinically definite MS and supports diagnosis in 65 to 85% with probable MS.⁶⁹ While characteristic MRI abnormalities are not specific for MS, in the proper clinical setting MRI is a useful diagnostic tool. The most common MRI abnormality is a focus of increased signal intensity on T2-weighted scans representing a plaque demyelination. Periventricular white matter is especially predisposed to demyelination. Acute lesions enhance with gadolinium on T1-weighted images due to local breakdown of the blood-brain barrier.⁷⁰ Lesion enhancement generally lasts between 6 weeks and 3 months, and signals recent disease activity. Occasionally lesions are associated with significant edema that may mimic an intracranial mass.⁷¹ Alternatively plaques may be confused with microvascular ischemic disease or other conditions.^{72,73}

However, the absence of MRI lesions does not exclude the diagnosis of MS. Conversely many patients have lesions on MRI without clinical correlation, suggesting that disease activity sufficient to produce signal changes on MRI may be inadequate to produce clinical deficits. Imaging studies of normal controls have revealed that approximately 10 to 15% of the normal population have evidence of nonspecific findings on T2-weighted MRI. Postmortem studies demonstrate that plaques previously detected on MRI may be normal at autopsy, which may be explained by remyelination but more likely represents the difficulty in radiologically differentiating demyelinating lesions from those of edema or inflammation.^{74,75}

Cerebrospinal fluid analysis. Although abnormal findings are common, no characteristic cerebrospinal fluid analysis findings are specific for MS. Similar abnormalities can be seen in various disorders, particularly those of an inflammatory or infectious nature.^{76,77} Mild increases in the cerebrospinal fluid monocyte count and protein may be evident in up to 40% of patients but a markedly elevated level of cerebrospinal fluid protein (greater than 100 mg/dl.) should cause doubts about the diagnosis of MS. The IgG index (a measure of central nervous system antibody synthesis) may be elevated and oligoclonal bands can be demonstrated by gel electrophoresis in 90% of patients. The IgG synthesis rate is also often increased in MS.⁷⁷ Cerebrospinal fluid glucose is generally normal.

Evoked responses. Occasionally patients present with evidence of a single attack of neurological dysfunction but insufficient evidence to confirm a diagnosis of MS. In these cases physiological evoked responses can be a useful diagnostic adjunct. An evoked potential is the neuronal electrical response to stimulation of a sensory pathway recorded through surface electrodes, and amplified and subjected to signal averaging. The 3 responses of clinical use are visual evoked, brain stem auditory evoked and somatosensory evoked responses. Demyelination within these peripheral and central pathways produces

prolongation in the event related response latencies. Abnormalities in these diagnostic studies may identify additional evidence for sites of demyelination, leading to confirmation of multiple neurological events in space.⁷⁸

Upper tract imaging. Baseline radiographic assessment remains an integral part of initial urological evaluation. In a review of 14 series comprising 2,076 patients Koldewijn et al found a 0.34% incidence of hydronephrosis or renal complication.⁴ All 7 affected patients had detrusor-sphincter dyssynergia.⁴ Although there are isolated reports of severe morbidity and mortality from upper tract disease in MS,^{79,80} progression to upper tract deterioration is usually the exception rather than the rule.^{4,31,60} Studies advocating initial surgical intervention for mild hydronephrosis are primarily historical and often antedate the widespread acceptance of clean intermittent catheterization as a treatment alternative.^{79,81} Upper tract deterioration may be linked to several risk factors, including detrusor-sphincter dyssynergia in men and the presence of an indwelling catheter (1.7% of patients).^{3,22,26} In these high risk patients a baseline renal sonogram is advisable as it may diagnose clinically silent calculi, identify parenchymal scarring and provide comparison for longitudinal followup.

Lower tract imaging. In women with incontinence or other lower tract symptoms an initial lateral voiding cystourethrogram or video urodynamics may aid in the assessment of bladder neck support, urethral hypermobility and bladder diverticuli. As patients may have competing symptomatology, such as stress and/or urge incontinence, this type of imaging may be beneficial to determine the relative contribution of anatomical factors (urethral hypermobility or cystocele) relative to voiding dysfunction or incontinence. Video urodynamics may also be useful to determine more accurately Valsalva leak point pressures and as an adjunct in the diagnosis of detrusor-sphincter dyssynergia. Lower tract radiological imaging is not necessary in the patient with no stress incontinence or with good pelvic floor support on physical examination.

URODYNAMIC EVALUATION

Urodynamic evaluation of the patient with MS not only allows proper identification of any underlying bladder and sphincteric abnormalities, but also aids in individualized bladder management. Blaivas et al reported that 73% of MS patients without urodynamic evaluation were treated inappropriately.⁶³ Of patients with symptoms suggestive of ob-

struction 73% had detrusor areflexia.²⁴ In equivocal cases urodynamic evaluation may lend support to a suspected diagnosis of MS in 10 to 14% of patients.^{1,27,65} In the MS patient population the incidence of abnormal urodynamic findings may be as high as 100%.³ In a meta-analysis of 22 series and 1,882 patients the incidence of normal urodynamic findings was 10% (see table). However, because most published series include symptomatic patients referred specifically for urological evaluation, there is a significant reporting bias toward patients with advanced disease and pyramidal dysfunction. To our knowledge there are few prospective studies of MS and asymptomatic bladder dysfunction but in a prospective study by Bemelmans 52% of patients (21 of 40) demonstrated silent urodynamic abnormalities.³⁶ However, the incidence of positive urodynamic findings in patients with lower urinary tract complaints was 98%.³⁶

Detrusor hyperreflexia. Detrusor hyperreflexia, defined as bladder overactivity due a disturbance of nervous control mechanisms, is the most common urodynamic abnormality in MS (see table and fig. 2).⁵ The incidence of detrusor hyperreflexia varies directly with the level of the neurological lesion.²³ In 22 published series of primarily symptomatic MS patients 62% (1,194 of 1,882) had detrusor hyperreflexia as the primary urodynamic diagnosis, which is not surprising given the high incidence of cervical and intracranial plaque formation in MS (see table).^{19,20,24,60} Detrusor hyperreflexia is commonly manifest symptomatically as urgency, frequency and generalized irritative symptoms. Among patients with detrusor hyperreflexia 67% will have synergic voiding and 43% will have detrusor-sphincter dyssynergia.⁸² Patients in the latter group paradoxically may have storage and emptying failure, further complicating treatment.

Detrusor hypocontractility. Although up to 63% of patients with or without associated hyperreflexia may have detrusor hypocontractility, only 20% have areflexia, which may be associated with hesitancy (see table). Hypocontractility may be related to cerebellar plaque involvement, lack of cortical facilitatory input or sacral cord involvement.^{3,27,30} Some evidence suggests that areflexia is a temporary condition that may progress to hyperreflexia in 57 to 100% of patients.^{1,83}

Urethral dysfunction and dyssynergia. Urethral dysfunction (detrusor-sphincter dyssynergia, incomplete sphincteric relaxation or flaccidity) represents a continuum in 12 to 84% of patients (mean 25.4%) (see table and fig. 3).^{24,27,84} Consequently clinical effects range from retention to complete in-

Published series of urodynamic findings in MS

References	No. Pts.	No. Hyperreflexia (%)	No. Detrusor-Sphincter Dyssynergia (%)	No. Hyporeflexia (%)	No. Normal (%)
Anderson and Bradley ²	52	33 (63)	16 (31)	21 (40)	2 (4)
Awad et al ³⁰	57	38 (66)	30 (52)	12 (21)	7 (12)
Beck et al ⁶²	46	40 (87)	— (—)	6 (13)	— (—)
Betts et al ²⁹	70	63 (91)	— (—)	0 (0)	7 (10)
Blaivas et al ²⁴	41	23 (56)	12 (30)	16 (40)	2 (4)
Bradley et al ¹⁷⁶	99	58 (60)	20 (20.2)	40 (40)	1 (1)
Bradley ³	302	127 (62)	— (—)	103 (34)	10 (24)
Eardley et al ¹⁷⁷	24	15 (63)	6 (27)	3 (13)	6 (25)
Goldstein et al ¹	86	65 (76)	57 (66)	16 (19)	5 (5.8)
Gonor et al ⁸⁴	64	40 (78)	8 (12)	13 (20)	1 (2)
Hinson and Boone ³¹	70	44 (63)	15 (21)	20 (28)	6 (9)
Koldewijn et al ⁴	212	72 (34)	27 (12.7)	32 (8)	76 (36)
Mayo and Chetner ²⁸	89	69 (78)	5 (6)	5 (6)	11 (12)
McGuire and Savastano ²⁶	46	33 (72)	21 (46)	13 (28)	0 (0)
Petersen and Pederson ¹⁷⁸	88	73 (83)	36 (41)	14 (16)	1 (1)
Philip et al ²⁷	52	51 (99)	16 (37)	0 (0)	1 (1.9)
Piazza and Diokno ¹⁷⁹	31	23 (74)	9 (47)	2 (6)	3 (9)
Schoenburg et al ¹⁸⁰	39	27 (69)	20 (5)	2 (6)	6 (15)
Sirls et al ⁸⁶	113	79 (70)	15 (27.8)	17 (15)	7 (6)
Summers ¹⁸¹	50	26 (52)	6 (12)	6 (12)	9 (18)
Van Poppel and Baert ¹⁰²	160	105 (66)	38 (24)	38 (24)	16 (10)
Weinstein et al ¹⁸²	91	64 (70)	16 (18)	15 (16)	11 (12)
Total/Total No. (%)	1,882	1,194 (62.10)	373/1,464 (25.40)	394 (20.1)	188 (10)

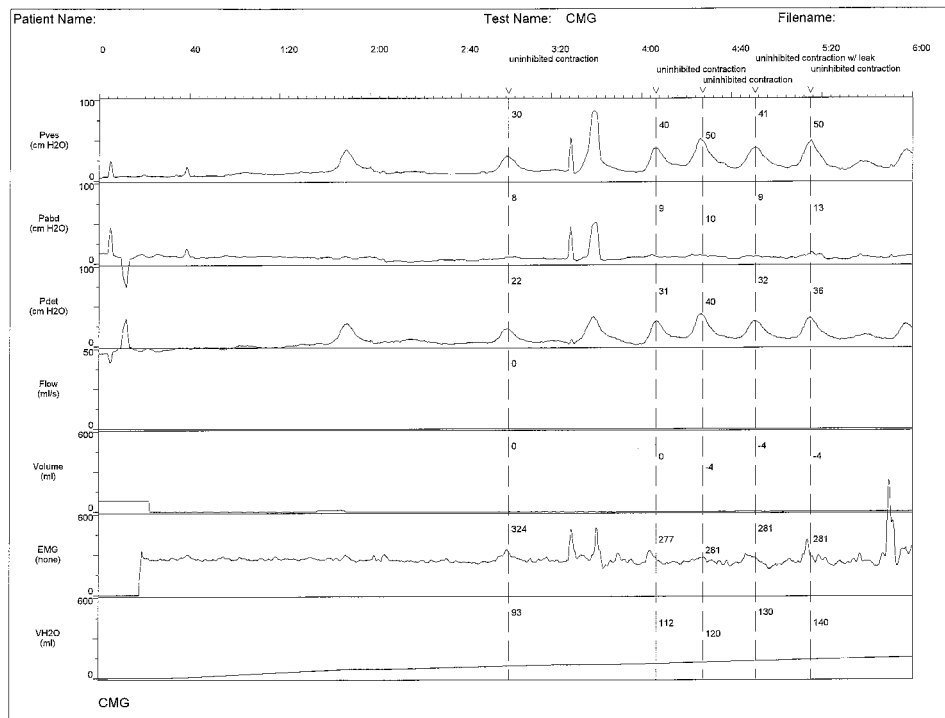


FIG. 2. Detrusor hyperreflexia. Urodynamic evaluation of 55-year-old man with MS and urge incontinence. Detrusor hyperreflexia begins at 50 cc of filling and continues to 150 cc. Amplitude of unstable contractions is between 22 and 40 cm. water. *CMG*, cystometrogram. *VH20*, vol. water. *Pves*, bladder pressure. *Pabd*, abdominal pressure. *Pdet*, detrusor pressure. *EMG*, electromyography.

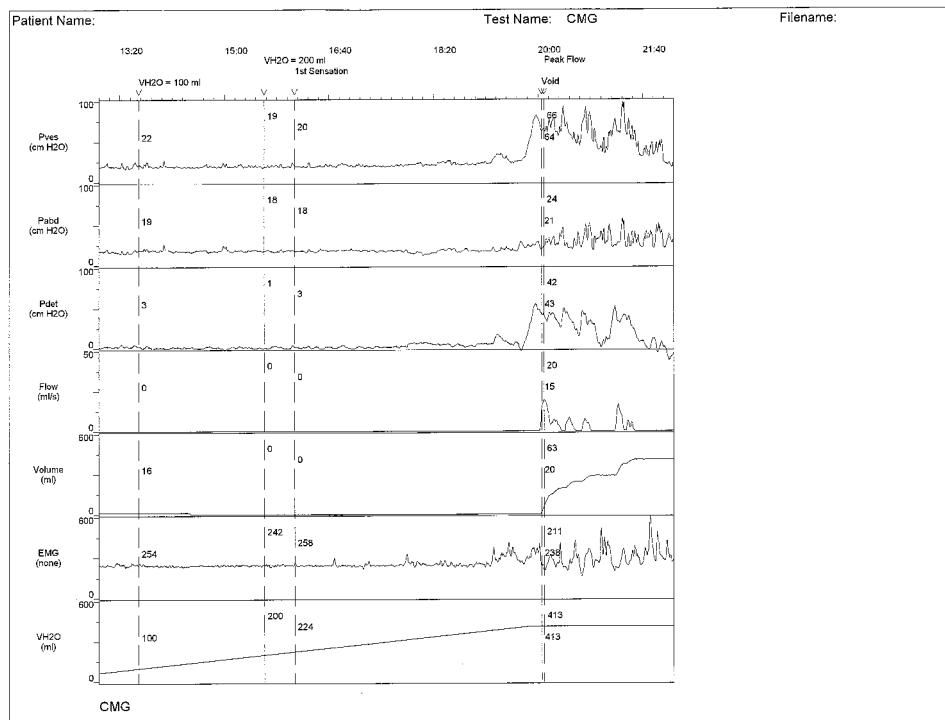


FIG. 3. Detrusor-sphincter dyssynergia. Urodynamic evaluation of 51-year-old man with MS, hesitancy and weak intermittent urinary stream. Filling is stable to 380 cc at which patient senses strong urge to void. External sphincter is active during voiding and flow tracing demonstrates characteristic stop/start pattern typical of detrusor-sphincter dyssynergia. *CMG*, cystometrogram. *VH20*, vol. water. *Pves*, bladder pressure. *Pabd*, abdominal pressure. *Pdet*, detrusor pressure. *EMG*, electromyography.

continence. Detrusor-sphincter dyssynergia highly correlates with cervical plaque formation as well as increased cerebrospinal fluid myelin basic protein ($p < 0.05$).^{1,4,23} Detrusor-sphincter dyssynergia usually presents with incomplete emptying and stranguria, which are also seen with

hypocontractility. Detrusor-sphincter dyssynergia is the most extreme defect in this continuum and is evident when a detrusor voiding contraction is accompanied by concomitant internal and/or external sphincter contraction.²⁴ In sharp contrast to dyssynergia in spinal cord injury patients

detrusor-sphincter dyssynergia in the MS population is rarely associated with upper tract dysfunction but rather with local symptoms of incomplete emptying, elevated post-void residuals, bladder calculi and infection.^{4,24,62,80,84,85} The reason for this distinction is unclear but may be related to the protective effect of poorly sustained detrusor contractions in up to 50% of MS patients with detrusor hyperreflexia. Alternatively, the hyperreflexia and degree of external sphincter spasm in MS may be less severe than those in spinal cord injury.⁸⁴⁻⁸⁶

Although the diagnosis of detrusor-sphincter dyssynergia is typically made with electromyography, the proper method for diagnosis is unclear. The use of urethral versus anal electromyography, wire or patch electrodes, urethral pressure gradients and video urodynamic urethral assessment is also debated.^{24,25,87} Urethral pressure profilometry has a limited role in the assessment of detrusor-sphincter dyssynergia. Studies using profilometry have demonstrated urethral pressures which have failed to correlate reliably with neurological dysfunction in MS.^{61,84} However, the necessity for sphincteric assessment and diagnosis of detrusor-sphincter dyssynergia is debated.^{22,24,26,62} Sirls et al noted that sphincteric evaluation (electromyography) was not useful in the treatment of 15 patients with detrusor-sphincter dyssynergia and believed that it was useful only to confirm the diagnosis of MS.⁶⁰

Incomplete sphincteric relaxation, while similar to detrusor-sphincter dyssynergia, is of lesser magnitude and less commonly associated with lower urinary tract complications. Instead incomplete sphincteric relaxation may be manifested as weak force of stream or stranguria. Sphincteric paralysis (flaccidity) is demonstrated in less than 15% of patients and may manifest as sphincteric incontinence.²

Like neurologically intact patients, those with MS may have various degrees of sphincteric insufficiency or stress incontinence. Sphincteric insufficiency may be assessed with urethral profilometry or Valsalva leak point pressures.⁸⁸⁻⁹¹ Although these studies may discern better the effects of urethral function, the exact technique for determining Valsalva leak point pressure is not standardized and remains investigator dependent.⁹²

Stability of urodynamic findings. As MS is a dynamic disease characterized by exacerbations and remissions, changes in lower urinary tract function with time and in response to therapy can occur. In select patients 15 to 55% demonstrate changes on repeat urodynamic testing.⁸³ Of note, once detrusor-sphincter dyssynergia is revealed on urodynamic evaluation it rarely remits.^{24,83} However, few studies to our knowledge have evaluated the natural progression of urological findings in mildly symptomatic or asymptomatic patients. Furthermore, longitudinal studies following MS patients with time and in response to systemic treatment are currently lacking.

MANAGEMENT OF MS

Neurological management (see table). Traditionally MS exacerbations have been treated with corticosteroids which have diverse effects, including a decrease in capillary dilation, decreasing vasogenic edema and diminished leukocyte migration into the central nervous system.^{93,94} Although steroids have not been demonstrated to influence the overall course of MS, they do appear to accelerate the recovery from each attack by diminishing cerebral edema and inflammation. Broad immunosuppression strategies have been used in the treatment of MS, including azathioprine, total body irradiation, cyclophosphamide and cyclosporine, but overall these agents have provided little long-term benefit. The most important advance has been that interferon- β 1A decreases the number of exacerbations by approximately a third and significantly slows the progression of disease related disability.

ity.⁹⁵⁻⁹⁷ Recently the Food and Drug Administration (FDA) approved interferon- β 1B, which is administered as a weekly intramuscular injection. Methotrexate has been shown to have anti-inflammatory properties, including a decrease in cytokine release, and to be associated with a modest improvement in upper extremity function in ambulatory patients with progressive MS.⁹⁴ Copolymer 1, which has recently been approved by the FDA for the treatment of MS, is an amino acid polymer patterned after the amino acid composition of myelin basic protein that may confuse the targeting of the immune system against central nervous system myelin. Like the 2 forms of interferon, copolymer 1 decreased the number of MS exacerbations compared to placebo.⁹⁸

Symptomatic treatments. Many MS patients have significant weakness, especially in the lower extremities, and intensive physical therapy and rehabilitation represent the cornerstone of therapy. While some patients with MS have diminished exercise tolerance, all should routinely engage in some physical activity. Recent investigations have provided substantial support for the favorable effects of exercise on the clinical course of MS.⁹⁹ The consequences of inactivity include deconditioning, muscle atrophy, loss of postural tone, osteoporosis and thrombophlebitis.

Spasticity. The standard first line drug for spasticity is baclofen, and effective agents include diazepam, gabapentin, dantrolene and quinine. Recently the FDA approved tizanidine, which reduces spasticity without significant weakness. The main side effects are light-headedness and hypotension secondary to the α -2 agonist action of the drug.¹⁰⁰ In patients with excessive tone that is focal in distribution botulin injections may be beneficial. Severe refractory spasticity can be treated with an intrathecal baclofen pump and occasionally contracture or tendon release procedures.

Fatigue. Fatigue is among the most tenacious and disabling symptoms of MS. Although different factors, including stress, depression, bladder dysfunction with nocturia and infection, can produce fatigue, many MS patients have fatigue without these other features. Amantadine, pemoline and fluoxetine have improved fatigue in some patients. The potassium channel antagonist 4-aminopyridine has resulted in improved exercise and heat tolerance in some patients, and is under investigation.¹⁰¹

Developing neurological therapies. The myelin epitope(s) and specific type of T cell receptor(s) involved in MS are still unknown. Identification of the T cell receptor(s) would enable the development of anti-idiotypic antibodies or anti-idiotypic T cells that could produce a clonal abortion of auto-aggressive lymphocytes. Similarly, knowledge of the T cell receptor, which mediates disease in humans, could provide an opportunity to produce tolerance induction with antigens or peptides based on the T cell receptor structure. Clinical vaccine trials are using native and substituted versions of T cell receptor peptides. These vaccines may promote immune responses to particular regions of the T cell receptor, thereby rendering pro-inflammatory T cells anergic.

Urological treatment and therapeutic guidelines. In low risk patients, those without indwelling catheters or detrusor-sphincter dyssynergia, most authors cite a low incidence of renal complications and upper tract deterioration.^{4,29,60,65} These findings may support a conservative approach to upper tract management, discouraging the routine use of yearly upper tract monitoring except in high risk patients and those with a changing clinical course or progression of disease.^{27,31,60,61} Aggressive surgical management for mild hydronephrosis, as practiced in the past, has been primarily replaced with clean intermittent catheterization.^{79,81} Although pyelonephritis is not common, treatment may be complicated by atypical organisms, including *Pseudomonas* in 34%, *Proteus* in 31% and *Providencia* in 25% of cases.¹⁰²

In making treatment decisions one should consider patient disability, ability to function independently, manual dexter-

ity, competing medical problems and social support networks. A team approach involving the treating neurologist, urologist and rehabilitation specialist is essential to optimize care. An empirical trial and error method is discouraged as it may be time-consuming and costly, and leaves many patients improperly treated and at risk for complications.^{22,24} Instead a clear understanding of the underlying pathology of each patient should be based on objective parameters, such as flow rate, residual urine and urodynamic evaluation. For treatment purposes patients may be classified as those with storage and/or emptying problems. In most patients conservative measures are effective for primary management.

Conservative therapy for bladder storage disorders. Symptoms of frequency, urgency, nocturia and incontinence comprise the most common cause for urological consultation. As nearly two-thirds of patients have detrusor hyperreflexia, treatment involves pharmacological therapy to suppress uninhibited bladder contractions. Traditionally atropine-like drugs, which competitively bind the acetylcholine receptor thereby blocking muscarinic effects, have represented the cornerstone of treatment. Various drugs can be used, including propantheline, imipramine, oxybutynin, hyoscyamine and methantheline bromide.^{26,102-106} Dosages may be titrated to therapeutic response or until anticholinergic side effects become intolerable.¹⁰⁷ The use of imipramine in MS may be tempered by its α agonistic properties, thus impairing bladder emptying in patients with detrusor-sphincter dyssynergia.¹⁰⁸ Concomitant use of other antidepressants in the MS population also limits the effective use of imipramine. When monotherapy fails to improve detrusor storage, medications with pure anticholinergic properties (hyoscyamine, propantheline) may be combined with those having additional direct smooth muscle relaxant properties (oxybutynin, flvoxate).^{103, 104, 109-111}

Oxybutynin chloride is among the most widely prescribed of these medications and has demonstrated fair to good response in 67 to 80% of MS patients. Because anticholinergic side effects of decreased salivation, blurred vision and constipation occur in 57 to 94% of patients, long-term compliance is a problem. Attrition rates of up to 50% have been reported in long-term studies.¹¹²⁻¹¹⁴ These side effects are especially troublesome in the MS population as blurry vision may be mistaken for deterioration due to optic neuritis, and for most MS patients constipation is a significant problem.¹¹⁵

New selective muscarinic receptor blockers, such as tolterodine, may have promise in relieving these symptoms with a lower incidence of anticholinergic side effects.^{116, 117} In some patients clean intermittent catheterization may be combined with anticholinergic therapy, and may be especially beneficial in those with storage and emptying failure. In these patients urinary retention is promoted by anticholinergics, thus alleviating storage problems, while emptying is provided solely by intermittent catheterization.

To avoid anticholinergic side effects from oral medications intravesical verapamil, lidocaine and oxybutynin have been tested for treatment of detrusor hyperreflexia.¹¹⁸⁻¹²⁴ Oxybutynin, the most commonly used intravesical agent, has demonstrated an 86% therapeutic response in MS patients in select studies. However, the inconvenience of this route of administration has contributed to a high attrition rate and has tempered enthusiasm.¹²⁴ Nevertheless, in select patients already on intermittent catheterization intravesical oxybutynin may lead to a significant improvement in continence but with fewer side effects.

Newer intravesical medications, resiniferatoxin and capsaicin, also show promise. These compounds exert a selective action on C sensory fiber axons, which are thought to have an important role in bladder reflex pathways following spinal cord insult. Intravesical capsaicin exerts a neurotoxic effect on afferent C fiber axons, causing depletion of substance P and calcitonin gene-related peptide.¹²⁵⁻¹³¹ In a study of 18

patients by Fowler et al 61% treated with capsaicin had excellent results and 17% had clinical improvement for 3 to 6 months.¹²⁹ Optimism for capsaicin has been tempered by the pungent effects and pain on instillation. Since resiniferatoxin lacks these side effects and is 1,000-fold more potent than capsaicin, it may represent a more attractive form of intravesical therapy. In studies of resiniferatoxin mean bladder volume at initial urge was not affected, although total bladder capacity was increased by an average of 105 cc ($p < 0.001$).¹³¹ These preliminary results suggest a difference in the urodynamic effect between resiniferatoxin and capsaicin that merits further evaluation. As capsaicin and resiniferatoxin are not FDA approved drugs but industrial reagents, use is currently limited to investigational protocols.

Detrusor hyperreflexia, especially nocturia, may also be treated effectively by decreasing urine production. In multiple placebo controlled trials of MS patients desmopressin nasal spray (1 desamino-8-D-vasopressin) has shown significant efficacy in reducing the incidence of nocturia and nocturnal enuresis, and increasing sleep time.¹³²⁻¹³⁵ Desmopressin may be especially useful in treating patients with detrusor hyperreflexia who cannot tolerate anticholinergic medication, or who have concomitant emptying failure due to detrusor-sphincter dyssynergia or hypocontractility. In a phase I trial by Eckford et al doses of 10 to 20 μ g. significantly decreased nocturnal urinary volumes without hyponatremia. Increased dosages to 60 μ g. were no more efficacious and were accompanied by a trend toward lower serum sodium.¹³⁴

Conservative therapy for emptying failure (hypocontractility and sphincter dyssynergia). Despite problems encountered with storage failure (detrusor hyperreflexia), 42% of MS patients may also have emptying difficulties due to detrusor-sphincter dyssynergia or detrusor hypocontractility (see table). In a select small group of patients timed or double voiding may be sufficient for adequate emptying but in most intervention is required to prevent infections, calculi or overflow incontinence. Treating these patients conservatively with α -1 blocking agents (prazosin) and muscle relaxants (diazepam, baclofen, dantrolene) has had mixed results.^{136, 137} Anecdotal success has been reported with tizanidine, a new spasmolytic with centrally acting α -2 adrenergic properties. Clean intermittent catheterization has been the primary treatment for patients with emptying difficulties and may aid in bladder rehabilitation.¹³⁸ Urodynamic evaluation may facilitate the decision for clean intermittent catheterization by defining bladder storage capabilities and selecting the optimum catheterization interval.

Surgical management of bladder dysfunction. When conservative management fails in lower urinary tract dysfunction, more aggressive surgical treatments may be necessary. The degree of manual dexterity, social support systems, disability status, life expectancy and urodynamic parameters should be considered. For most patients long-term management plans should be based on a life expectancy of 20 to 30 more years. Thus, short-term solutions may need to be dismissed in favor of a more comprehensive long-term approach. Surgical options include suprapubic cystostomy, sphincterotomy, sphincteric stents, augmentation cystoplasty with or without a catheterizable limb, incontinent vesicostomy and suprapubic diversion.^{79, 139-141}

Suprapubic cystostomy is an attractive initial plan for patients when conservative treatment fails as it has several distinct advantages over a conventional indwelling catheter. Urethral erosion in women and traumatic hypospadias in men, often occurring in patients with chronic Foley catheterization (prompted by using successively larger catheters), are avoided. Personal hygiene and catheter care are simplified as the catheter position is readily accessible and remote from vaginal/perineal soilage. Usually the tube can be placed percutaneously with local anesthesia. This decision is reversible

as the tube may be removed without difficulty. Suprapubic cystostomy may not be a good long-term option for younger patients because of the risk of bladder calculi, infection and squamous cell carcinoma.¹⁴²⁻¹⁴⁴

In men with detrusor hyperactivity and detrusor-sphincter dyssynergia who cannot be treated with conservative measures an outlet reducing procedure, such as sphincterotomy or urethral stent, may be effective to facilitate bladder emptying. In both treatment options a condom catheter is necessary to manage the resulting incontinence. These procedures are best reserved for the patient with limited hand function for whom clean intermittent catheterization is not an option. Documentation of adequate detrusor contractility is imperative as patients with hypocontractile bladders may have an unacceptably high residual even after the procedure.^{140, 141}

Surgical augmentation for detrusor dysfunction is usually reserved for the patient in whom all other conservative options have been exhausted. As the course of MS is by nature dynamic and progressive, permanent procedures using intestinal segments should be performed only after careful consideration of the course of disease (relapsing or progressive) and overall prognosis. Patients undergoing augmentation cystoplasty should be assessed for manual dexterity as most will continue to require some intermittent catheterization.¹⁰⁷

When neither the patient, family member nor caretaker can perform intermittent catheterization and conservative management has failed, cutaneous ileovesicostomy has been used successfully for storage and emptying abnormalities. In this procedure a segment of ileum is used to construct a chimney emanating from the bladder to allow cutaneous drainage to an external collection device.¹³⁹ The advantages of this procedure over supraventricular diversion are preservation of the bladder and ureterovesical junction (if competent), lack of a defunctionalized bladder, decreased blood loss and absence of a ureteroenteric anastomosis. A psoas hitch may be used with this procedure to aid in tubularizing the bladder and promoting more effective drainage.¹⁴⁵ Ileovesicostomy in combination with bladder neck closure or retropubic urethral hypersuspension may provide effective treatment for detrusor hyperreflexia with additional urethral incompetence. Although some patients are reluctant to undergo major surgical intervention, most are pleasantly surprised after surgery with the improvement in quality of life and daily management of incontinence. Despite the prevalence of chronic constipation among the majority of MS patients, prospective candidates and families should be made aware of the possible risk of diarrhea or malabsorption, which may accompany the use of intestinal segments for urinary tract reconstruction.

Urethral incompetence. The treatment for urethral incompetence includes the use of injectable bulking agents (collagen, polytetrafluoroethylene, fat), urethral inserts, conventional suspension procedures and compressive slings.^{89, 146, 147} In surgical intervention for urethral insufficiency voiding efficiency, ability to perform intermittent catheterization, stability of disease and general overall health should be considered. Patients should be informed of the risk for postoperative urinary retention, which may adversely affect the amount of required nursing care and quality of life.

The artificial urinary sphincter has had a limited role in the management of incontinence in MS, which is primarily due to the significant incidence of detrusor hyperreflexia in MS and its association with upper tract deterioration in patients undergoing artificial urinary sphincter placement.¹⁴⁸ Before any outlet enhancing procedure is performed adequate bladder storage and voiding function should be assessed, since patients with poorly sustained voiding contractions may be at increased risk for postoperative urinary retention. In patients with adequate bladder storage who use clean intermittent catheterization for emptying postoperative urinary retention is not a concern and an artificial uri-

nary sphincter may be an acceptable treatment for urinary leakage.

BOWEL AND SEXUAL DYSFUNCTION

Bowel dysfunction. Most patients with bladder symptoms also have bowel dysfunction and, therefore, a careful history regarding bowel habits (constipation, diarrhea and fecal incontinence) should be completed.^{61, 149-152} Constipation is by far the most common bowel complaint. Many drugs used to treat MS can exacerbate constipation, including diuretics, opiate analgesics, antidepressants, anticholinergic agents and calcium or aluminum antacids. Constipation may also be related to an alteration in neurogastrointestinal signaling and the gastrocolic reflex, which involves the urge to defecate following a meal. Other factors contributing to constipation include weak abdominal musculature, pelvic muscle spasticity, reduced fluid intake and a decrease in physical activity, which increases gastrointestinal transit time of fecal matter. By far the most important strategy for the treatment of constipation in MS patients involves the use of supplemental fiber and adequate hydration. Occasionally patients will benefit from suppositories and mini-enemas. Fecal incontinence has been reported in 30 to 50% of patients but there is a paucity of information on its proposed mechanisms. Abnormal colonic activity, laxative abuse, anorectal dyssynergia and decreased sensation have all been speculated to be causes but there is no consensus on the exact mechanisms involved.¹⁵² However, adherence to a bowel regimen which includes fiber therapy and avoidance of fecal impaction can significantly improve this problem.

Sexual dysfunction. As MS affects patients in midlife, issues concerning sexual dysfunction become an increasingly important factor in enhancing quality of life. MS adversely affects sexual functioning in up to 91% of men and 72% of women, and sexual activity ceases or is unsatisfactory in 64% and 39%, respectively.¹⁵³⁻¹⁵⁶ In addition to physiological disturbances, psychosocial stressors can influence sexual functioning. Mattson et al found associated marital relationship problems in 71% of MS patients with primary sexual dysfunction.¹⁵⁷

Male Sexual Dysfunction: Men with MS have adverse symptoms, including erectile dysfunction, decreased sensation, fatigue and decreased libido resulting in orgasmic dysfunction.¹⁵⁸ The onset of erectile dysfunction has been reported 3.7 to 9 years after diagnosis.^{154, 155} Yet despite an incidence of impotence as high as 80%, more than 75% of patients have continued interest in sexual activity.¹⁵³ Some authors have shown that sexual dysfunction parallels the level of overall disability^{153, 158, 159} but others have demonstrated that erectile dysfunction is independent of disability, and more closely relates to bladder and pyramidal dysfunction alone.^{155, 156, 160} In a study by Betts et al 100% of 48 patients with erectile dysfunction had concomitant bladder dysfunction.¹⁵⁵ However, the absence of bladder or pyramidal dysfunction did not ensure adequate sexual function as up to 50% of patients without pyramidal symptoms had sexual impairment.¹⁵⁸ Several authors have studied the physiological basis of erectile dysfunction using pudendal reflex latencies, and tibial, pudendal and cortical evoked potentials. These studies have demonstrated consistent deficits in cortical and pudendal evoked potentials without consistent changes in sacral reflex latencies (bulbocavernosus).^{155, 156, 160} Thus, it is thought that MS related impotence is related to suprasacral mechanisms. Abnormal pudendal evoked potentials were also predictive of ejaculatory dysfunction.¹⁵⁵ In addition to neurophysiological abnormalities, nocturnal tumescence studies have demonstrated a significant psychogenic component in more than 50% of patients,¹⁵⁶ who may benefit from marital and sexual counseling.

In treating erectile dysfunction in MS the degree of manual dexterity, stability of the relationship of the patient, degree

of disability and course of disease should be considered. The approach to treatment should involve the neurologist, rehabilitation physician and urologist. An initial course of sexual counseling may help treat any psychological factors and develop a better understanding between partners, thereby promoting intimacy. To our knowledge there are few studies of impotence treatment in the MS patient and much of what is known is extrapolated from general studies of neurogenic impotence.^{161, 162} Because the possibility for recovery of erectile dysfunction is low (2%), nonsurgical options, such as vacuum erection devices, intracorporeal pharmacotherapy and sildenafil, have a more prominent role than prosthetic implantation, and most MS patients are reluctant to undergo surgery for impotence.¹⁵⁸ Interestingly despite a better than 95% success rate with injection therapy, the attrition rate at 2 years in MS patients is 39%.¹⁵⁵

Female Sexual Dysfunction: Although the majority of women with MS want to remain sexually active, sexual dysfunction is a significant problem for 56 to 72%.^{158, 163} The most common problems are fatigue in 68%, decreased sensation in 48%, decreased or absent orgasm in 72%, difficulty with arousal in 35% and frequent urinary tract infections in 21% of women.¹⁵⁸ Vaginal dryness is also a frequent complaint, which may be related to anticholinergic medications, and may be effectively treated with vaginal lubricants. For patients with orgasmic dysfunction vibratory stimuli may help decrease the orgasmic threshold. In patients with decreased mobility sexual positioning may be altered for greater comfort. Involvement of the neurologist and careful attention to overall systemic treatment can alleviate many somatic symptoms related to sexual dysfunction (fatigue,

spasticity). Finally, marital or sexual counseling may significantly help the patient and partner to foster a healthier relationship.

Pregnancy. Women with MS are frequently of reproductive age and, thus, pregnancy becomes a significant issue. The effect of pregnancy on MS has been evaluated in retrospective studies which demonstrate a reduction in the relapse rate during pregnancy and a sharp increase during the first 3 months postpartum, thus supporting the notion of pregnancy induced immunosuppression.¹⁶⁴⁻¹⁷¹ However, recent prospective studies have questioned the protective effect of gestation as relapse rates during pregnancy did not differ significantly from those in controls.^{170, 172} Despite an increased incidence and severity of postpartum relapses, pregnancy does not appear to affect overall disability.^{168-170, 173}

CONCLUSIONS

MS is a devastating disease affecting 0.1% of the population in the prime of life. During the course of this disease nearly all patients have lower urinary tract symptoms and/or sexual dysfunction.^{174, 175} Although these symptoms are rarely life threatening, they have a significant impact on quality of life. Consequently the urologist may be asked to assist in the care of these patients. To treat these problems effectively and intelligently the urologist must have a fundamental working knowledge of the disease process and the effects on the genitourinary system. Using this knowledge a logical and individualized treatment plan can be formulated, thus making the urologist an integral part of the MS management team.

APPENDIX 1: DIAGNOSTIC CRITERIA FOR MS

Clinically Definite MS	Laboratory Supported MS
Two attacks plus clinical evidence of 2 lesions	Two attacks with clinical or paraclinical evidence of 1 lesion and cerebrospinal fluid analysis abnormalities
Two attacks plus clinical evidence of 1 lesion and paraclinical evidence of another lesion	One attack, clinical evidence of 2 separate lesions plus oligoclonal bands and evidence of elevated IgG index
	One attack, 1 lesion, paraclinical evidence of another lesion and oligoclonal bands with elevated IgG index

APPENDIX 2: CLINICAL FEATURES OF MS

	Plaque Site	Symptom	Management
Optic neuritis	Optic nerve	Visual loss (fundi normal), color blind	Intravenous steroids (methylprednisolone)
Ocular motor dysfunction	Cranial nerve III, IV, VI, pons	Diplopia, internuclear ophthalmoplegia (30-50%), nystagmus	Baclofen, gabapentin
Vestibular dysfunction	Vestibular nuclei, cranial nerve VIII	Loss of balance (greater than 50%), vertigo (20%)	Clonazepam, diazepam
Seizures	Cerebral cortex	Generalized tonic-clonic seizures (1-2%)	Carbamazepine, phenytoin
Ambulation dysfunction	Corticospinal tracts	Spasticity, weakness	Baclofen, tizanidine
Transverse myelitis	Spinal cord	Sensory loss, paresthesias, weakness, spasticity	Steroids (acute), tricyclic antidepressants, anticonvulsants
Tremor	Cerebellum	Upper extremity tremor (intention), pendular nystagmus	Thalamotomy, gabapentin
Cognitive dysfunction	Frontal lobes	Intellectual decline, dementia (30%), attention deficit, verbal expressivity	Rule out depression, effect of medication, metabolic abnormality, sleep dysfunction/nocturia
Transient symptoms:			
Lhermitte's sign	Spinal cord	Electric shocking sensation	Carbamazepine, phenytoin
Trigeminal neuralgia	Cranial nerve V3	Facial pain (may be bilat.)	Carbamazepine, phenytoin
Uhthoff's phenomenon	Spinal cord	Heat sensitivity	Avoid heat, 4-aminopyridine, cooling vest/cap

APPENDIX 3: TREATMENTS FOR MS

Drug	Use	Route	Side Effects/Complications
Acute Episodes: Corticosteroids	Acute exacerbations, optic neuritis	Oral, intravenous (daily)	Glucose intolerance, infection, gastrointestinal bleeding
Systemic Therapy:			
Azathioprine	Relapse prevention	Oral (daily)	Leukopenia
Methotrexate	Upper extremity disability, systemic disease	Oral (weekly)	Bone marrow suppression, secondary malignancy
β -Interferon 1a	Relapse prevention	Subcutaneous (every other day)	Erythema at injection site (1b, 90%), malaise, flu-like syndrome (1b, 70%), headache (1b, 1a), depression (1b, 1a), abnormal liver function tests (1b, 1a)
β -Interferon 1b	Relapse prevention, decreased disability	Intramuscular (weekly)	
Intravenous Ig	Relapse prevention	Intravenous	Hyperviscosity, pulmonary edema
Copolymer 1	Relapse prevention	Subcutaneous (daily)	Erythema at injection site, dyspnea

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