Multiple sclerosis is a common neurologic disorder that often affects the genitourinary system. One of the most common symptoms of multiple sclerosis is the hyperactive bladder. These patients will have symptoms that may affect their lifestyle, such as urinary incontinence, urgency, and frequency. They may also suffer from debilitating bladder dysfunction associated with multiple sclerosis can be treated with a reasonable chance of success. With proper treatment, related symptoms may be brought under control, allowing the physician to concentrate on the more debilitating aspects of this disease.

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Fingerman and Finkelstein • The overactive bladder in multiple sclerosis

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Multiple sclerosis is a common neurologic disorder that often affects the genitourinary system. One of the most common symptoms of multiple sclerosis is the hyperactive bladder. These patients will have symptoms that may affect their lifestyle, such as urinary incontinence, urgency, and frequency. They may also suffer from debilitating bladder dysfunction associated with multiple sclerosis can be treated with a reasonable chance of success. With proper treatment, related symptoms may be brought under control, allowing the physician to concentrate on the more debilitating aspects of this disease.

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For illustrative purposes, we describe the case of a 36-year-old woman who was seen in the urologist’s office complaining of urinary urge incontinence. Three years earlier, multiple sclerosis was diagnosed after she had had visual changes and ataxia.

History revealed that she soaked three to four pads a day, with significant social impact. Occasional stress incontinence occurred in which a cough or Valsalva maneuver would promote a complete micturition episode. She was able to ambulate without significant difficulty, so there was minimal functional component attributing to her incontinence.

During a recent hospitalization for rehabilitation, an indwelling catheter was placed and later left in place to control her socially debilitating incontinence.

The initial urologic workup revealed normal findings on urinalysis and negative findings on renal ultrasound examination were also normal, without evidence of renal scarring or hydronephrosis.

Flexible cystoscopy and urodynamic evaluation (Figure 1) revealed a first sensation to void at 30 mL and an uninitiated detrusor contraction at 80 mL. There was no involuntary sphincter contraction at the time of detrusor contraction. These findings were consistent with bladder hyperactivity without detrusor-sphincter dysynergia.

The patient was started on oxybutynin chloride (Ditropan) therapy (2.5 mg orally three times a day), and she was followed up closely for evidence of urinary retention. She was placed on a timed voiding regimen five times a day. Although her incontinence resolved, close follow-up revealed an increased postvoid residual urine volume of 100 mL, which eventually normalized. She is presently continent with oxybutynin and is catheter free.

Multiple sclerosis

Multiple sclerosis is the most common neurologic disorder in the 20- to 45-year-old age group. There is a 2:1 female-to-male predilection, and a genetic and environmental component has also been established. People descended from Scandinavian countries and colder climates in general have been reported to have a higher incidence of multiple sclerosis. This debilitating neurologic disease affects 1 of 1000 Americans. Most patients present in the most productive years of life, therefore making multiple sclerosis even more devastating.

Multiple sclerosis has been related to an autoimmune attack on the myelin-producing oligodendrocytes of the central nervous system, causing demyelination of the affected nerve. Although there is preservation of the axon, this demyelination results in decreased conduction through the nerve. The demyelination most often affects the posterior and lateral columns of the cervical spinal cord, but the lumbar and sacral cords as well as the optic nerve, cerebrum, cerebellum, and brainstem are also commonly involved. The clinical course of multiple sclerosis is one of relapses and remissions with distinct neurologic deficits related to the various regions affected.

Bladder overactivity

Bladder overactivity is a common disorder. It is characterized by involuntary detrusor contractions that may occur spontaneously or may be provoked (such as by rapid filling, changes in posture, coughing, walking, and jumping) while the person is attempting to suppress them. The overactive bladder is referred to as unstable when the etiology is nonneurogenic, and as hyperreflexic when the etiology is neurogenic. The term overactive bladder refers to the storage phase of the bladder only, not to micturition (the voiding phase), and is diagnosed by the filling cystometry phase of urodynamics. Unlike other human visceral systems that require an intact autonomic nervous system (such as the gastrointestinal and cardiovascular systems), the lower urinary tract depends partly on the voluntary central nervous system to function in the storage and evacuation of urine. Micturition is under voluntary control and depends on learned behavior that develops during maturation of the nervous system. Damage to the brain and spinal cord can induce bladder overactivity by reducing the parasympathetic inhibition that normally allows the bladder to fill. It has also been noted that damage to the inhibitory axonal pathways in the spinal cord can lead to the emergence and unmasking of
primitive spinal bladder voiding reflexes. Upper motor neuron lesions affecting the genitourinary system can result in bladder hyperactivity and hyperreflexia.

The hyperreflexic bladder is one of the most common symptoms of multiple sclerosis. Lower urinary tract symptoms occur in up to 90% of patients with multiple sclerosis at some time in the course of their disease. They occur primarily because the neural control system for the urinary bladder is distributed throughout the central nervous system. Therefore, clinically, multiple sclerosis can manifest itself urologically in many ways.

Clinical relevance
Between 50% and 90% of all patients with multiple sclerosis complain of voiding symptoms at some time in their life. Often, voiding dysfunction is part of the presenting symptom complex (between 2% and 15%), but the number of those patients with urinary tract symptoms increases as the duration of disease increases.

Bladder overactivity is the most common urodynamic abnormality detected. It is present in 50% to 99% of patients. A recent meta-analysis of 1882 patients revealed that 62% of symptomatic patients with multiple sclerosis had detrusor hyperreflexia as the primary urodynamic diagnosis. This hyperreflexia commonly manifests symptomatically as urgency, frequency, and generalized "irritative" symptoms. Very often, there is associated sphincter dyssynergia, defined as simultaneous contractions of the bladder and urethral sphincter. This dyssynergia can lead to more serious complications, as the unstable bladder will contract against a closed urethral sphincter. It can be stated with moderate assurance that any patient whose symptom complex consists of hyperreflexia with an increased postvoid residual urine volume has evidence of dyssynergia.

The urinary tract symptoms associated with multiple sclerosis vary widely. They can present along the spectrum from detrusor hyperactivity and urinary retention to detrusor hyperactivity, incontinence, and generalized irritative symptoms. Therefore, the treatment must be tailored appropriately to each individual patient. This necessity is exemplified by the fact that the volume of postvoid residual urine varied widely in one recent study from 50 mL to 900 mL in patients with multiple sclerosis. Therapy is further complicated by the fact that the urodynamic findings change as the disease waxes and wanes.

As the majority of patients have overactive bladder contractions, the incontinence associated with hyperactivity may represent the most socially disabling symptom of the disease. Aside from the social aspects of bladder overactivity, it is imperative to effectively treat the neurogenic bladder and the resulting urinary tract infections. Many patients with multiple sclerosis are treated with immunosuppressive medications, and these infections can lead to devastating complications and sepsis. It is therefore quite important that physicians diagnose and treat these disabling and potentially dangerous conditions.

Treatment
As already mentioned, the wide array of urologic symptoms and abnormalities associated with multiple sclerosis poses a therapeutic dilemma. Each patient must have a specific treatment plan aimed toward his or her own objective urodynamic abnormalities. It has been noted recently that as many as 73% of patients with multiple sclerosis without undergoing urodynamic evaluation were treated inappropriately. As stated earlier, the majority of patients with multiple sclerosis will demonstrate detrusor hyperreflexia on cystometric evaluation, but some may demonstrate the opposite.

The goals of therapy of the neurogenic bladder in multiple sclerosis are continence and, when sphincter dyssynergia is present, reduction of residual urine. A high residual urine volume may cause cystitis, and the upper urinary tract is at risk. The use of indwelling urethral or suprapubic catheters should only be the treatment of last resort, as indwelling catheters produce chronic irritation and predispose the patient to infection, erosion or stricture of the urethra, bladder stone formation, and possibly malignancy.

Because of acetylcholine-induced stimulation of detrusor receptor cells, it would seem logical that anticholinergic agents be considered the medications of choice for treatment of bladder overactivity. This hypothesis has, in fact, proved to be true. Oxybutynin or tolterodine tartrate (Detrol) should be the first line of treatment (Figure 2). Oxybutynin has shown moderate potency as an anticholinergic agent, and it has also been shown to possess local anesthetic activity. The recommended dosage is 2.5 mg to 5.0 mg two to four times daily.
daily. It has recently been released in extended-release form that has significantly fewer side effects.\textsuperscript{11} Tolterodine is a newly approved and similar medication that has proven effective; it also appears to have fewer side effects.\textsuperscript{12-20} The optimal dosage is 1 mg to 2 mg twice daily.\textsuperscript{14,15,17,18} Tolterodine is a competitive muscarinic receptor antagonist. It has been shown that urinary bladder contraction is mediated via cholinergic muscarinic receptors.

Another well-tolerated anticholinergic agent is propantheline bromide (Pro-Banthine). It is considered the second-line anticholinergic medication for bladder hyperactivity.\textsuperscript{9} The dosage is 7.5 mg to 30 mg three to five times a day. Hyoscyamine sulfate (Levsin) is another commonly used second-line anticholinergic and antispasmodic medication (0.125 mg to 0.375 mg orally or sublingually every 4 hours as needed). This medication has the added benefit of rapid sublingual onset of action.

A notable study reported in 1991 showed increased bladder volume at the first involuntary contraction of 51 mL with oxybutynin, compared with 11.2 mL with propantheline. Mean cystometric bladder capacity increased by 80.1 mL with oxybutynin and 48.9 mL with propantheline.\textsuperscript{21}

All anticholinergic agents have the potential side effects related to their anticholinergic mechanism of action. These side effects include dry mouth, blurred vision, tachycardia, drowsiness, and constipation. Usually, these side effects are well tolerated.

It should be mentioned that anticholinergic agents do not increase the time between sensation to void and actually voiding. There are also often an increase in the patient’s residual urine and a decrease in detrusor pressure. Therefore, these agents can be used with a timed voiding or timed catheterization regimen if excess residual urine warrants.

The next line of treatment, in patients who have no contraindications to them, are tricyclic antidepressants, imipramine hydrochloride (Tofranil) in particular. These drugs have shown central and peripheral anticholinergic effects, and they have proven useful in facilitating bladder storage. They decrease bladder contractility and simultaneously increase bladder outlet resistance. This class of pharmaceutical agents blocks the active reuptake of serotonin and norepinephrine. The exact mechanism of action on the lower uri-
nary tract remains a topic of debate.9

In addition to the pharmacologic therapy for bladder overactivity, clean intermittent catheterization (CIC) is essential if residual urine is a problem. Clean intermittent catheterization has been proven to reduce the residual urine volume, thereby reducing the risk of infection. It has also been shown to improve continence. As already stated, these are the two main goals of treatment.

Depending on the patient’s general medical status, CIC is performed by the patient or the patient’s caretaker. It is usually performed four to five times a day. Clean intermittent catheterization allows regular emptying of the bladder, leading to a lower incidence of cystitis, and no residual urine.8 The lack of an indwelling catheter also decreases the risk of bladder carcinoma and stone formation associated with the resultant chronic irritation from such a catheter.

It has been shown that the treatment of neurogenic bladder in patients with multiple sclerosis is effective, beneficial, and cost-effective. It is recommended that all patients with multiple sclerosis with lower urinary tract symptoms be appropriately evaluated and treated.

Comment

Detrusor hyperreflexia is common in patients with multiple sclerosis. The pathophysiologic process that causes multiple sclerosis often causes detrusor hyperreflexia. The resultant symptoms can be very distressing and socially unacceptable for the patient with multiple sclerosis. After a thorough urologic evaluation and the exclusion of other causes, appropriate treatment can be planned.

Bladder overactivity often responds well to pharmacologic therapy. If there is a component of sphincteric dysynergia and there is a high postvoid residual urine volume, it may be necessary to include CIC in the treatment regimen. These modalities have proven to be effective in relieving the most distressing urologic symptoms of multiple sclerosis.

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