Differential Diagnosis and Treatment of Impaired Bladder Emptying

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Although much attention is paid to urinary incontinence, the condition of incomplete bladder emptying is becoming more common with the aging of the US population and the widespread use of anticholinergic drugs to treat overactive bladder. This disorder can often be silent until end-stage presentation of overflow incontinence. In this article, we review the pathophysiologic conditions of the bladder and urethra that can cause impaired bladder emptying and discuss how to evaluate and screen the patient with a bladder that does not empty. In addition, we provide an overview of treatment options available for impaired bladder emptying and consider the research that is under way to find the best therapies for the failing bladder.

[Rev Urol. *2004;6(suppl 1):S24-S31*]

Key words: Bladder • Urethra • Urinary retention • Ultrasound • Bethanechol

We have heard a great deal about "overactive" bladder recently. But what if your patients have the opposite problem—a bladder that "won't go"? How do you evaluate the patient whose bladder does not empty? What are the most common and effective forms of therapy for impaired bladder emptying?

Urinary retention and incomplete bladder emptying can be caused by an inadequately contractile bladder, urethral sphincter obstruction, or both. Because prostate enlargement has been addressed in a previous article in this supplement (see Lepor, p. S8), this article focuses on bladder dysfunction. The one unique case of urethral obstruction that is discussed is function retention due to non-neurogenic detrusor-sphincter dyssynergia, also referred to as shy bladder syndrome.

Micturition Reflexes

Normal micturition is completely dependent on neural pathways in the central nervous system. These pathways perform 3 major functions: amplification, coordination, and timing.[1] The nervous control of the lower urinary tract must be able to amplify weak smooth-muscle activity to provide sustained increases in intravesical pressures sufficient to empty the bladder. The bladder and urethral sphincter function must be coordinated to allow the sphincter to open during micturition but remain closed at all other times.

Timing represents the voluntary control of voiding in the normal adult and the ability to initiate voiding over a wide range of bladder volumes. In this regard, the bladder is a unique visceral organ that exhibits predominantly voluntary rather than involuntary (autonomic) neural regulation. A number of important reflex mechanisms contribute to the storage and elimination of urine and modulate the voluntary control of micturition.

Guarding Reflexes Against Stress Urinary Incontinence

There is an important bladder-to-urethra reflex that is mediated by sympathetic efferent pathways to the urethra. This is an excitatory reflex that contracts the urethral smooth muscle and, thus, is called a guarding reflex. The positive reflex is not activated during micturition but activates when bladder pressure is increased, such as during a cough or exercise.

A second guarding reflex is triggered by activation of sacral motoneurons that, in turn, activate urethral external sphincter efferent neurons, which send axons into the pudendal nerves and the nerves innervating the pelvic floor.[2] This somatic guarding reflex is activated by bladder afferents and/or directly by stress such as sneezing.[3] The activation of somatic urethral and pelvic floor efferent pathways contracts the external urinary sphincter and the pelvic floor muscle, thus preventing stress urinary incontinence. The brain inhibits the guarding reflexes during micturition.

Causes of Incomplete Bladder Emptying

Urinary retention and incomplete emptying can result from a number of causes (Table 1). In some cases, the flow of urine is blocked, for example, in men with benign prostatic hyperplasia. This causes obstruction. Another form of impaired emptying is nonobstructive, that is, there is no problem with the urethra but the bladder muscle is less able to adequately contract. When the bladder cannot contract properly, some or all of the urine remains in the bladder. If left untreated, this condition can lead to urinary tract infection and damage to the kidneys.[4]

Urethral Obstruction

Functional obstruction at the pelvic floor external sphincter, sometimes called shy bladder syndrome, can cause just as much distress as prostatic mechanical obstruction of the urethra. At the University of Pittsburgh, we have seen a number of patients in end-stage renal failure resulting from the inability to relax the external sphincter over decades. The condition is believed to be an abnormal, learned, and upregulated guarding reflex. Before these patients are put on the transplant list, they are taught intermittent self-catheterization.

Bladder Dysfunction

Detrusor areflexia is defined as acontractility due to an abnormality of nervous control. In detrusor areflexia, the bladder cannot be demonstrated to contract during urodynamic studies. Detrusor areflexia can develop from various conditions in which the neurologic pathways innervating the bladder are damaged. However, the contribution of myogenic factors should not be ignored.

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Common Neurologic Causes of Impaired Bladder Emptying

Spinal cord injury. Any injury to the spinal cord, including blunt, degenerative, developmental, vascular, infectious, traumatic, and idiopathic injury, can cause voiding dysfunction. Injury to the cauda equina and peripheral sacral nerves can have devastating effects on bladder and urethral sphincter function. The true incidence of lower urinary tract dysfunction as a result of cauda equina and pelvic plexus injury is unknown, mainly because of the lack of prospective studies with preoperative and postoperative neurourologic evaluation of patients.

Pelvic surgery. The incidence of

Table 1
Diagnosis, Evaluation, and Treatment of Impaired Bladder Emptying

Causes

- Urethral obstruction
  - Mechanical: benign prostatic hyperplasia and urethral stricture
  - Functional obstruction at the pelvic floor external sphincter: shy bladder syndrome
- Bladder: detrusor muscle areflexia or impaired centricity
  - Motor: neurologic diseases damaging the nerves that innervate the bladder, detrusor muscle damage, and anticholinergic drugs used to treat overactive bladder can induce high residual urine and impaired bladder emptying
  - Sensory: the bladder gradually expands to large capacity due to sensory deficit seen commonly in patients with diabetic neuropathy

Evaluation

- Urinalysis: rule out infection
- Residual urine screening: noninvasive ultrasonographic assessment of residual urine volume (preferred over catheterization for residual urine)
- Uroflow: noninvasive private test to screen for diminished flow rate that may predict impaired contractility, bladder outlet obstruction, or both
- Urodynamics: catheter-based test that can measure bladder sensation and contractility power

Treatment

- Catheterization: indwelling urethral or suprapubic catheters or clean intermittent catheterization
- Biofeedback to teach the patient to relax his or her spastic sphincter muscle
- Drug: bethanechol chloride, 25 mg tid/qid, is the only drug approved for urinary retention
- Urethral sphincter botulinum toxin injection
- Neuromodulation with sacral nerve stimulation
- Basic research
  - Muscle cell transplantation to reengineer the failing bladder
  - Gene therapy to repair the damaged nerve to the bladder

vesicourethral dysfunction has been reported to be 20% to 68% after abdominal perineal resection, 16% to 80% after radical hysterectomy, 10% to 20% after proctocolectomy, and 20% to 25% after anterior resection.[5]

Pelvic and sacral fractures. Pelvic trauma can result in cauda equina and pelvic plexus injury. The frequency of neurologic injury after pelvic fracture is estimated to be between 0.75% and 11%.[5] The injury most closely correlated with neurologic damage is transverse sacral fracture. Approximately two thirds of these patients will have neurogenic bladder.[5] Because most of the injuries are incomplete, the majority of patients with neurourologic injury after pelvic and sacral fractures will improve over time.

Herniated disc. Some reports indicate that the incidence of voiding dysfunction in patients with disc prolapse may approach 20%. Data have demonstrated that, once patients show evidence of bladder dysfunction following lumbar disc prolapse, detrusor recovery with treatment is uncommon.[5] Therefore, cauda equina syndrome from lumbar disc herniation should be considered a surgical emergency.

Infectious neurologic processes. There are a number of infectious causes of incomplete emptying of the bladder:

- Acquired immune deficiency syndrome (AIDS): Neurologic complications, involving both the central and peripheral nervous systems, occur in as many as 40% of patients with AIDS.[5] Urinary retention is the most common presenting symptom.
- Neurosyphilis (tabes dorsalis): Neurosyphilis has long been recognized as a cause of central and peripheral nerve abnormalities. Voiding dysfunction related to neurosyphilis was common in the era before penicillin use.
- Herpes zoster and herpes simplex: Herpes zoster is an acute, painful mononeuropathy associated with a vesicular eruption in the distribution of the affected nerve. The viral activity is predominantly located in the dorsal root ganglia of the cranial nerves. However, sacral nerve involvement may be associated with loss of bladder and anal sphincter control.
- Lyme disease: Caused by the spirochete *Borrelia burgdorferi*, Lyme disease is associated with a variety of neurologic sequelae. Urologic manifestations of Lyme disease can be primary or late manifestations of disease and affect both sexes and persons of all ages. Urinary urgency, nocturia, and urge incontinence are the most common urologic symptoms.[6]

Myogenic Failure

Degeneration of or damage to bladder smooth muscle can also induce detru-

Table 2
Symptoms of Impaired Bladder Emptying

- Fullness in the bladder area
- Straining to urinate
- Difficulty in starting the stream
- Inability to maintain a steady stream
- Sensation of incomplete emptying at end of micturition
- Discomfort in the lower abdomen
- Feeling of "having to go now" without being able to
- Constant dribbling
- Recurrent urinary tract infections

sor hyporeflexia or areflexia. Chronic overdistension can result in detrusor myogenic failure, even if the neurologic disease is treated or reversed. Bladder management to avoid overdistension, such as institution of intermittent catheterization after spinal cord injury, may protect the bladder from permanent myogenic damage.

Overactive Bladder Link to Impaired Bladder Emptying

Anticholinergic drugs are now widely used to treat overactive bladder. A potential side effect of all anticholinergic agents is high residual urine volume and impaired bladder emptying. This can occur soon after initiation of therapy and is especially worrisome in the frail elderly and men with concomitant prostate hypertrophy.[7] A simple ultrasound check of residual urine after initiation of anticholinergic therapy can rule out potential problems.

Sensory Uropathy

It is widely accepted that diabetes results in sensory and autonomic polyneuropathy. When sensory and/or autonomic neurons innervating the bladder are damaged, bladder dysfunction, characterized by impaired sensation of bladder fullness, increased bladder capacity, reduced bladder contractility, and increased residual urine volume, can be observed.[8] The prevalence of diabetic cystopathy is related to the duration of diabetes and not to the sex and age of the patient.

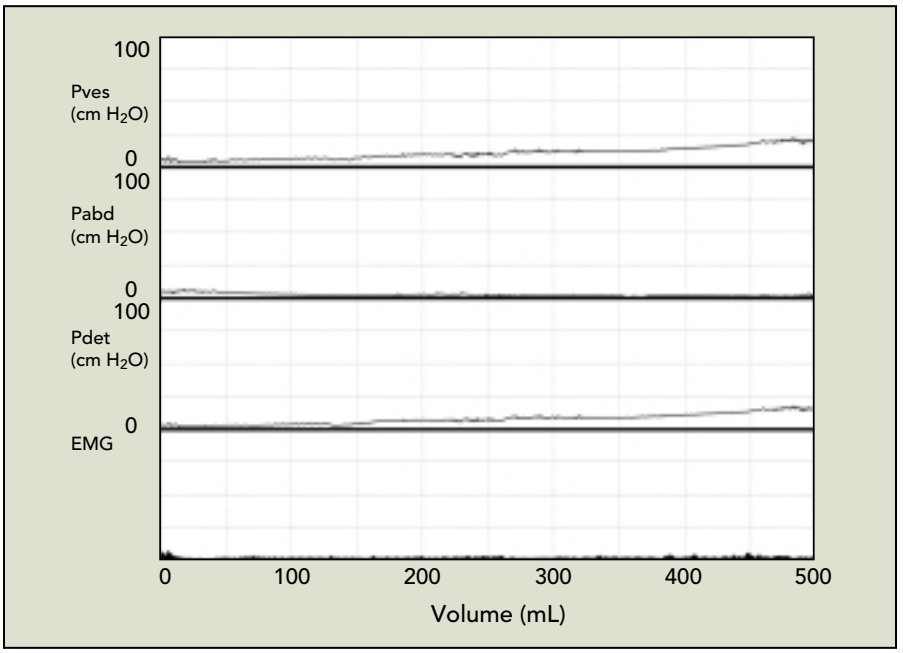
It has also been reported that diabetic cystopathy can occur silently and early in the course of diabetes.[8] In such cases, the bladder dysfunction is often detected only after careful questioning and/or urodynamic testing. Thus, urodynamic testing in patients with diabetes is often key to the early diagnosis of bladder dysfunction.

Diagnosis

Table 2 lists some of the general symptoms of impaired bladder emptying. Patients with known or suspected neurologic damage due to pelvic or sacral injury should have a careful physical examination. The integrity of the sacral dermatomes is tested by assessing perianal sensation, anal sphincter tone, and control of the bulbocavernosus reflex.

Many patients complain of straining to urinate, incontinence, and a sensation of incomplete bladder emptying. The urinary stream may be diminished and interrupted, since many of these patients rely on abdominal straining to urinate. On occasion, symptoms of voiding dysfunction may be the only initial clinical manifestation of a cauda equina lesion.[9] The varied and

Figure 1. *Detrusor areflexia without any voluntary or involuntary detrusor contraction to 500 mL volume on urodynamic study in a 61-year-old insulin-dependent diabetic woman. The patient is receiving intermittent catheterization approximately 4 times per 24 hours. Pves, intravesical pressure; Pabd, abdominal pressure; Pdet, detrusor pressure; EMG, electromyography.*



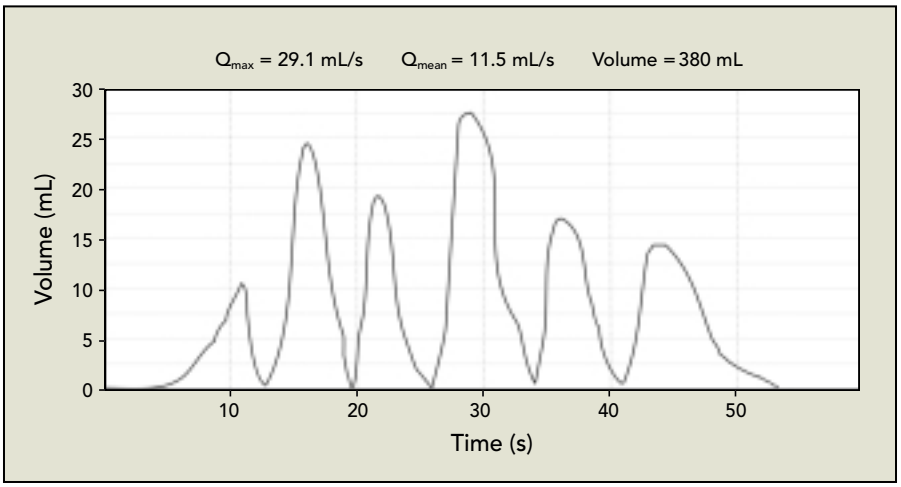


Figure 2. *Straining uroflowmetry of the diabetic woman in Figure 1. The patient complained of the sensation of incomplete emptying post-micturition, occasional incontinence, and straining to urinate. Although her maximum flow rate is normal (29.1 mL/s), the voiding pattern is classic for Valsalva voiding without true detrusor contractility.*

mixed symptomatologies emphasize the need for a complete neurourologic evaluation.

The physical examination may reveal a distended bladder, but the most characteristic features are elicited by a careful neurologic examination. Sensory loss in the perineum or perianal area is associated with the S2 through S4 dermatomes. The extent of perineal anesthesia can be a useful predictor in patients with lumbar disc prolapse. If "saddle" anesthesia of the S2 through S4 dermatomes continues after surgical laminectomy and decompression, the urinary bladder rarely recovers. A unilateral or mild sensory disturbance indicates a better prognosis. Deep tendon reflexes in the lower extremities, clonus, and plantar responses, as well as the bulbocavernosus reflex, should be routinely evaluated.

Urodynamic Findings

The typical cystometrogram finding of cauda equina injury is detrusor areflexia (Figure 1). On the uroflowmetry, an abdominal straining, sawtooth pattern is generally seen (Figure 2). Urodynamic abnormalities may be the only aberration documented, with no other overt neurologic manifestations, in some patients with cauda equina injury. In cases of herniated disc not induced by trauma or acute conditions, the protrusion is usually slow and progressive and may result in nerve irritation and, consequently, detrusor hyperreflexia.[10]

The integrity of the sacral reflex in men may be further studied with evaluation of the latency time of the sacral evoked potentials by stimulating the penile skin and recording the response with a needle electrode in the bulbocavernosus muscle.[11] In patients with complete cauda equina lesions, the sacral evoked response is either absent or significantly prolonged; this represents a more sensitive indicator of neuropathy than the classic electromyographic changes.

In conclusion, the major urodynamic features in patients with cauda equina injury are an absent or diminished bulbocavernosus reflex, detrusor areflexia, neuropathic changes on perineal floor electromyography, and absent evoked electromyographic responses.

Risks of Catheterization

When evaluating impaired bladder emptying, it is important to avoid catheterizing a patient who has a large residual urine volume. Even with a sterile technique, it is difficult to avoid introducing bacteria into the bladder with catheterization. This is of little concern in the normal patient; however, in a patient with high residual urine, just a few bacteria can quickly multiply in the warm and wet environment of the bladder and can overgrow and become stagnant. Therefore, not only does an ultrasonographic residual urine check avoid the pain and irritation of urethral catheterization, it is medically safer. Use of the portable bladder ultrasound machine, rather than catheterization, is recommended for routine residual urine check (Figure 3).

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Treatment

Catheterization

Indwelling urethral or suprapubic catheters and clean intermittent

Figure 3. *Checking residual urine volume is quicker, less irritating, and safer with a bladder scanner.*

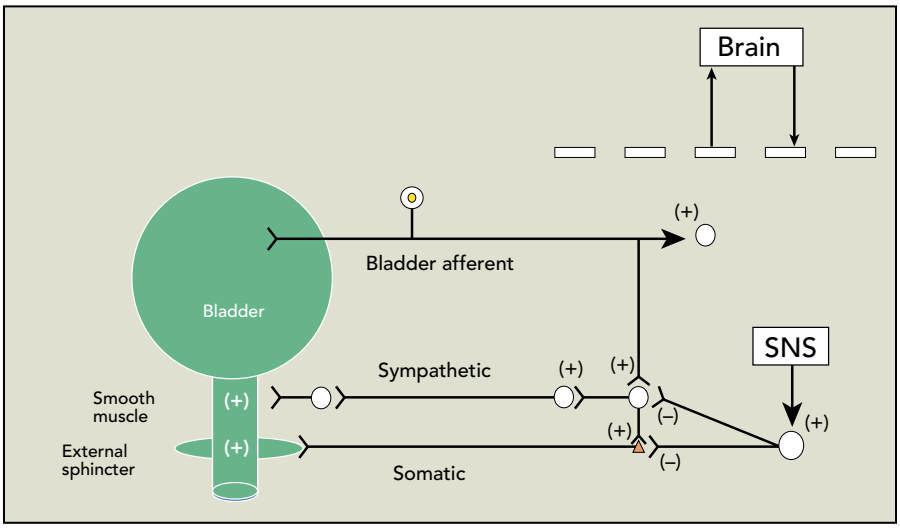

Figure 4. *In cases of neurologic disease, the brain cannot turn off the guarding reflex and retention can occur. Sacral nerve stimulation (SNS) restores voluntary micturition in cases of voiding dysfunction and urinary retention by inhibiting the guarding reflex.*

catheterization are the options available when the bladder must be drained. Both urethral and suprapubic catheterization achieve this end; however, if long-term catheterization is required, most patients prefer a minor surgical procedure to place a suprapubic catheter. Suprapubic catheterization is more comfortable than urethral catheterization, allows the patient to have sexual intercourse, and is easier to change. Long-term urethral catheterization should especially be avoided in women, because of risk of chronic catheter pressure causing erosion damage and fistula formation to the vagina. Without question, if the patient can perform clean intermittent self-catheterization, it is almost always preferred over indwelling catheterization.

Biofeedback

Bladder retraining and biofeedback can help the patient with a spastic pelvic floor and external urinary sphincter to relearn how to relax during micturition. This technique is typically performed with perineal electromyographic electrodes connected to an electronic biofeedback machine. Over several sessions, patients get visual and auditory signals of what it feels like when they contract the pelvic floor muscles. Positive and negative feedback then can be used to teach the patient to relax specific muscles.

Drug Treatment

Bethanechol chloride, 25 mg tid/qid, is the only drug available for the treatment of urinary retention. Bethanechol is an agonist for the parasympathetic nerve–mediated, acetylcholine-mediated detrusor muscle contraction.[12,13] It helps to increase bladder muscle tone and contractility.

Bethanechol works within an hour after the pill is administered. Therefore, it takes only a few days to determine whether the medication is effective for a particular patient. Because of absorption issues, bethanechol generally should be taken on an empty stomach. Adverse effects include upset stomach, vomiting, dizziness, wheezing, sweating, and flushing.

Urethral Botulinum Toxin Injection

Another method of treating refractory sphincter spasticity is injection of botulinum toxin into the spastic pelvic floor. Although this technique may sound highly unusual, we have had great success with it at our institution. Botulinum toxin is a powerful site-specific muscle relaxant. We have employed the injection of botulinum toxin A in the lower urinary tract, as an FDA off-label use, in more than 125 patients since 1998. This therapy should not be used as first-line treatment; however, it can avoid the need for lifelong catheterization in patients who are refractory to therapy.[14] The technique is simple to perform and has been described in a previous issue of *Reviews in Urology*.[15]

Sacral Nerve Stimulation

Why would sacral nerve neuromodulation promote voiding in patients with voiding dysfunction? To understand this, it should be recognized that, in adults, functioning of brain pathways is necessary to turn off sphincter and urethral guarding reflexes and allow efficient bladder emptying. Spinal cord injury produces bladder sphincter dyssynergia and inefficient bladder emptying by interfering with these brain mechanisms (Figure 4). This may also occur with more subtle neurologic lesions in patients with idiopathic urinary retention; for example, after a bout of prostatitis or a urinary tract infection.

It has been demonstrated in animals that, before the development of brain control of micturition, stimulation of somatic afferent pathways passing through the pudendal nerve to the perineum can initiate efficient voiding by activating bladder efferent pathways and turning off the excitatory pathways to the urethral outlet.[1] Tactile stimulation of the perineum in the cat also inhibits the bladder sympathetic reflex component of the guarding reflex mechanism. Sacral nerve stimulation can elicit similar

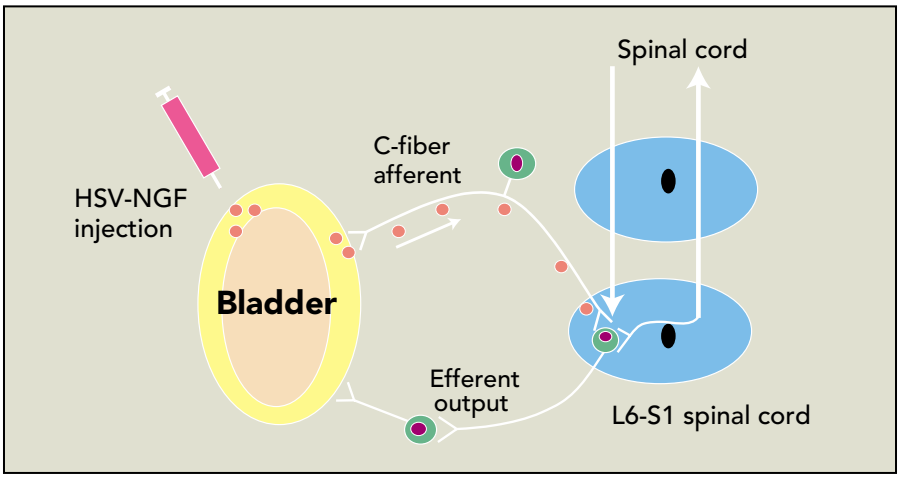

Figure 5. *Herpes vector neurotrophic factor gene therapy: the herpes vector for nerve growth factor (HSV-NGF) is injected into the bladder and taken up by the sensory C-fiber afferent nerves.*

responses in patients with urinary retention, turning off excitatory outflow to the urethral outlet and promoting bladder emptying.[16] Because sphincter activity can generate afferent input to the spinal cord that can, in turn, inhibit reflex bladder activity, an indirect benefit of suppressing sphincter reflexes would be a facilitation of bladder contraction.

Research

Muscle Cell Transplantation

The aim of stem cell tissue engineering is to replace, repair, or enhance the biologic function of damaged tissue or organs. The process involves harvesting cells from patients or donors, isolating stem cells from the sample, expanding the cell number through cell culture techniques, and subsequently injecting or implanting the cells into the patient. One particular advantage of muscle stem cell transplantation is that it may augment impaired detrusor muscle function. It has been demonstrated that skeletal muscle stem cells, when injected into the failing bladder, can improve detrusor contractility and may be able to differentiate into bladder smooth muscle.[17] This treatment offers the only hope for patients with detrusor myogenic failure.

Gene Therapy

What can you do when the impaired bladder emptying is caused by damage to the nerve that innervates the bladder? We are studying the feasibility of gene therapy using a replication-deficient herpes simplex viral vector encoding neurotrophic factors that is injected into the bladder wall.[18] The herpes vector would hone in on the nerves that innervate the bladder. It is hoped that the payload it delivers, the transcription of neurotrophic factor proteins, will help improve nerve function. Thus, in the future, neurotrophic factors or other growth factors combined with targeted gene therapy techniques may be beneficial for patients with diabetic cystopathy or other forms of urologic nerve damage (Figure 5).

Conclusion

Impaired bladder emptying is a common and underdiagnosed condition.

Main Points

- Urinary retention and incomplete bladder emptying can result from urethral obstruction (such as in men with benign prostatic hyperplasia), shy bladder syndrome, or detrusor areflexia (acontractility of the bladder due to an abnormality of nervous control).
- Incomplete bladder emptying is often neurologic in nature, as in patients who have had spinal cord injury, pelvic surgery or trauma, or herniated disc; it can also result from an infectious cause, presenting as a neurologic sequela of AIDS, Lyme disease, herpes zoster, or neurosyphilis.
- Patients with incomplete bladder emptying should undergo a careful physical and neurologic examination to assess for distended bladder, sensory loss in the perianal and perineal areas, deep tendon reflexes in the lower extremities, clonus, plantar responses, and bulbocavernosus reflex.
- Catheterization to evaluate impaired bladder emptying is not recommended in patients with a large residual urine volume because of the risk of bacteriuria. Ultrasonographic residual urine check, which is safer and more comfortable for the patient, should be employed in this population.
- Treatment options for patients with urinary retention include biofeedback to teach muscle relaxation, drug therapy with bethanechol chloride, and sacral nerve neuromodulation. In addition, injection of botulinum toxin to suppress pelvic floor spasticity has shown success in patients refractory to first-line therapy. Stem cell transplantation and gene therapy for impaired bladder emptying are also being investigated.

With overactive bladder being treated more often, physicians should especially be on the lookout for impaired bladder emptying. Screening is simple and safe with portable bladder ultrasound scanners. Treatment ranges from bethanechol for stimulation of detrusor contraction to clean intermittent self-catheterization.

Injection of botulinum toxin and acupuncture, like sacral nerve neuromodulation, can help a number of patients with refractory impaired bladder emptying. Exciting research on muscle stem cell transplantation and neurotrophic gene therapy is under way. ■

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