CHAPTER e35 Interstitial Cystitis/Painful Bladder Syndrome

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Most clinicians with outpatient practices see undiagnosed cases of interstitial cystitis/painful bladder syndrome (IC/PBS). This chronic condition is characterized by pain perceived to be from the urinary bladder, urinary urgency and frequency, and nocturia. As currently diagnosed, the great majority of cases occur in women. Symptoms wax and wane for months or years or possibly even for the patient's lifetime. The spectrum of symptom intensity is broad. The pain can be excruciating, urgency can be distressing, frequency can be up to 60 times per 24 h, and nocturia can be causative of sleep deprivation. These symptoms can be disabling in terms of daily activities, work schedules, and personal relationships; patients with IC/PBS report less life satisfaction than do those with end-stage renal disease. The etiology of IC/PBS is unknown. It is not a new disease, having first been described in the late nineteenth century in a patient with the symptoms described above and a single ulcer visible on cystoscopy (now called Hunner's ulcer after the urologist who first reported it). Over the ensuing decades, it became clear that many patients with similar symptoms had no ulcer. It is now appreciated that ≤10% of patients with IC/PBS have a Hunner's ulcer.

The definition of IC/PBS, its diagnostic features, and even its name continue to evolve. The International Continence Society, a body devoted to studying disorders of the lower urinary tract and pelvic floor, has defined PBS as "the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology." In practice, clinicians have interpreted this definition to include any chronic pelvic pain that increases with bladder filling and/or decreases with voiding and that cannot be explained by reference to another identifiable disease.

Many patients with IC/PBS also have other syndromes, such as fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, vulvodynia, and migraine. These syndromes collectively are known as functional somatic syndromes (FSSs): chronic conditions in which pain and fatigue are prominent features but laboratory tests and histologic findings are normal. Like IC/PBS, the FSSs often are associated with depression and anxiety. The majority of cases affect women, and more than one FSS can affect a single patient. Because of its similar features and comorbidity, IC/PBS sometimes is considered an FSS.

EPIDEMIOLOGY

Contemporary population studies of IC/PBS in the United States indicate prevalences of 2–3% among women and 1–2% among men. For decades, it was thought that 90% of IC/PBS cases occurred in women. These prevalence findings, however, have generated research aimed at determining the proportion of men with symptoms usually diagnosed as chronic prostatitis (now known as chronic prostatitis/chronic pelvic pain syndrome) who actually have IC/PBS. Well-designed studies of the incidence of IC/PBS have not been reported.

Among women, the average age at onset of IC/PBS symptoms is the early forties, but the range is from childhood through the early sixties. Risk factors (antecedent features that distinguish cases from controls) primarily have been FSSs. Indeed, the odds of IC/PBS increase with the number of such syndromes present. Surgery was long thought to be a risk factor for IC/PBS, but analyses adjusting for FSSs refuted that association. A minority of patients have a bacterial urinary tract infection (UTI) at the onset of IC/PBS.

The natural history of IC/PBS is not known. Although studies from urology and urogynecology practices have been interpreted as showing that IC/PBS lasts for the lifetime of the patient, population studies suggest that some individuals with IC/PBS do not consult specialists and may not seek medical care at all, and most prevalence studies do not show an upward trend with age—a pattern that would be expected with incident cases throughout adulthood followed by lifetime persistence of a nonfatal disease. It may be reasonable to conclude that patients in a urology practice represent those with the most severe and recalcitrant IC/PBS.

PATHOLOGY

For the ≤10% of IC/PBS patients who have a Hunner's ulcer, the term *interstitial cystitis* may indeed describe the histopathologic picture. Most of these patients have substantive inflammation, mast cells, and granulation tissue. However, in the 90% of patients without such ulcers, the bladder mucosa is relatively normal, with scant inflammation.

ETIOLOGY

Numerous theories about the pathogenesis of IC/PBS have been put forward. It is not surprising that most early theories focused on the bladder. For instance, IC/PBS has been investigated as a chronic bladder infection. Sophisticated technologies have not identified a causative organism in urine or in bladder tissue; however, the patients studied by these methods had IC/PBS of chronic duration, and the results do not preclude the possibility that infection may trigger the syndrome or may be a feature of early IC/PBS. Other inflammatory factors, including a role for mast cells, have been postulated, but as was noted above, the 90% of patients without a Hunner's ulcer have little bladder inflammation and do not exhibit a prominence of mast cells. Autoimmunity has been considered, but autoantibodies are low in titer, nonspecific, and thought to be a result rather than a cause of IC/PBS. Increased permeability of the bladder mucosa due to defective epithelium or glycosaminoglycan (the bladder's mucous coating) has been studied frequently, but the findings have been inconclusive.

Investigations of causes outside the bladder have been prompted by the presence of comorbid FSSs. Many patients with FSSs have abnormal pain sensitivity as evidenced by (1) low pain thresholds in body areas unrelated to the diagnosed syndrome, (2) dysfunctional descending neurologic control of tactile signals, and (3) enhanced brain responses to touch in functional neuroimaging studies. Moreover, in patients with IC/PBS, body surfaces remote from the bladder are more sensitive to pain than is the case in individuals without IC/PBS. All these findings are consistent with upregulation of sensory processing in the brain. Indeed, the prevailing theory is that these concomitantly occurring syndromes have in common an abnormality of brain processing of sensory input. However, antecedence is a critical criterion for causality, and no study has demonstrated that abnormal pain sensitivity precedes either IC/PBS or FSSs.

CLINICAL PRESENTATION

In some patients, IC/PBS has a gradual onset and/or the cardinal symptoms of pain, urgency, frequency, and nocturia appear

sequentially in no consistent order. Other patients can identify the exact date of onset of IC/PBS symptoms. More than half of the latter patients describe burning or pain with urination beginning on that date. This symptom, usually termed *dysuria*, is characteristic of a UTI. As was stated above, only a minority of IC/PBS patients who obtain medical care soon after symptom onset have uropathogenic bacteria or leukocytes in urine. These patients and many others with new-onset IC/PBS are treated with antibiotics for a presumptive UTI. Men presenting with such symptoms generally are treated for chronic bacterial prostatitis. Persistent or recurring symptoms without bacteriuria eventually prompt a differential diagnosis, and IC/PBS is considered. Traditionally, the diagnosis of IC/PBS has been delayed (sometimes for years), but recent interest in the disease has shortened this interval.

The pain of IC/PBS includes suprapubic prominence and changes with the voiding cycle. Two-thirds of women with IC/PBS report two or more sites of pain. The most common site (involved in 80% of women) and generally the one with the most severe pain is the suprapubic area. About 35% of female patients have pain in the urethra, 25% in other parts of the vulva, and 30% in nonurogenital areas, mostly the low back and also the anterior or posterior thighs or the buttocks. The pain of IC/PBS most commonly is described as aching, pressing, throbbing, tender, and/or piercing. What may distinguish IC/PBS from other pelvic pain is that in 95% of patients bladder filling exacerbates the pain and/or bladder emptying relieves it. Almost as many patients report a puzzling pattern in which certain dietary substances worsen the pain of IC/PBS. Smaller proportions—but still the majority—of patients report that their IC/PBS pain is worsened by menstruation, stress, tight clothing, exercise, and riding in a car as well as during or after vaginal intercourse.

The urethral and vulvar pain of IC/PBS merits special mention. In addition to the descriptive adjectives for IC/PBS mentioned above, this pain commonly is described as burning, stinging, and sharp and as being worsened by touch, tampons, and vaginal intercourse. Patients report that urethral pain increases during urination and generally lessens afterward. These characteristics have commonly caused the urethral pain of IC/PBS to be diagnosed as chronic urethral syndrome and the vulvar pain as vulvodynia.

In many patients with IC/PBS, there is a link between pain and urinary urgency; that is, two-thirds of patients describe the urge to urinate as a desire to relieve pain. Only 20% report that the urge stems from a desire to prevent incontinence; indeed, very few patients with IC/PBS are incontinent. Urinary frequency can be severe, with ~85% of patients voiding >10 times per 24 h and some as often as 60 times. Voiding continues through the night, and nocturia is common, frequent, and often associated with symptoms of sleep deprivation.

Beyond these common symptoms of IC/PBS, additional urinary and other symptoms may be present. Among the urinary symptoms are difficulty in starting urine flow and perceptions of difficulty in emptying the bladder and bladder spasms. Among the other symptoms are the manifestations of comorbid FSSs as well as symptoms that do not constitute recognized syndromes, such as numbness, muscle spasms, dizziness, ringing in the ears, and blurred vision.

The pain, urgency, and frequency of IC/PBS can be debilitating. Proximity to a bathroom is a continuous focus, and patients report difficulties in the workplace, leisure activities, travel, or simply leaving home. Familial and sexual relationships can be strained.

DIAGNOSIS

Traditionally, IC/PBS has been considered a rare condition that is diagnosed by urologists at cystoscopy. However, this disorder is much more common than once was thought; it is now being considered earlier in its course and is being diagnosed and managed more often by primary care clinicians. Results of physical examination, urinalysis, and urologic procedures are insensitive and/or nonspecific. Thus, diagnosis is based on the presence of appropriate symptoms and the exclusion of diseases with a similar presentation.

Three categories of disorders can be considered in the differential diagnosis of IC/PBS. The first represents other identifiable diseases that manifest as pelvic pain and/or urinary symptoms, including common infections (recurrent UTI, vaginitis, genital herpes); cystitis caused by irradiation, cyclophosphamide treatment, or tuberculosis; neurogenic bladder, bladder stones, or urethral diverticulum; cancer of the bladder, uterus, cervix, vagina, or urethra; and, in men, prostate cancer. Overactive bladder is a chronic condition of women and men that manifests as urgency and frequency and that can be distinguished from IC/PBS by the patient's history: pain is not a feature of overactive bladder, and its urgency arises from the need to avoid incontinence. Endometriosis is a special case: it can be asymptomatic or can cause pelvic pain, dysmenorrhea, and dyspareunia—i.e., types of pain that mimic IC/PBS. Endometrial implants on the bladder (although uncommon) can cause urinary symptoms, and the resulting syndrome can mimic IC/PBS. Even if endometriosis is identified, it is difficult in the absence of bladder implants to determine whether it is causative of or incidental to the symptoms of IC/PBS in a specific woman.

The second category of disorders encompasses the FSSs that can accompany IC/PBS. IC/PBS can be misdiagnosed as chronic pelvic pain, irritable bowel syndrome, or fibromyalgia. The correct diagnosis may be entertained only when changes of pain with altered bladder volume or urinary symptoms appear or become more prominent.

The third category involves syndromes that IC/PBS mimics by way of its referred pain. These syndromes include vulvodynia and chronic urethral syndrome. In studies of adults with chronic urinary symptoms, the distribution of symptoms is similar in men and women, a finding that calls into question the distinctions among IC/PBS, overactive bladder, benign prostatic hyperplasia, and chronic prostatitis /chronic pelvic pain syndrome.

Therefore, IC/PBS should be considered in the differential diagnosis of persistent or recurrent "UTI" but sterile urine cultures; "overactive bladder" with pain; chronic pelvic pain, endometriosis, vulvodynia, or FSSs with urinary symptoms; and "chronic prostatitis." As was mentioned above, important clues to the diagnosis of IC/PBS are the exacerbation of pain with bladder filling or with the consumption of certain foods or drinks and the alleviation of pain after urination.

Cystoscopy under anesthesia formerly was thought to be necessary for the diagnosis because of its capacity to reveal a Hunner's ulcer or—in the 90% of patients without an ulcer—petechial hemorrhages after bladder distention. However, because these findings are nonspecific, many experts find this procedure unnecessary. Because other urologic diagnostic procedures are not particularly helpful, the indications for urologic referral have evolved toward the need to rule out other diseases or administer more advanced treatment.

A typical patient presents to the primary clinician after days, weeks, or months of pain, urgency, frequency, and/or nocturia. The presence of urinary nitrites, leukocytes, or uropathogenic bacteria should prompt treatment for a UTI and bacterial prostatitis in women and men, respectively. Persistence or recurrence of symptoms in the absence of bacteriuria should prompt a pelvic examination for women, an assay for serum prostate-specific antigen for men, and urine cytology and inclusion of IC/PBS in the differential diagnosis in both sexes.

In the diagnosis of IC/PBS, inquiries about pain, pressure, and discomfort are useful; IC/PBS should be considered if any of those sensations are noted in one or more anterior or posterior sites between the umbilicus and the upper thighs. Nondirective questions about the effect of bladder volume changes include "As your

next urination approaches, does this pain get better, get worse, or stay the same?" and "After you urinate, does this pain get better, get worse, or stay the same?" Establishing that the pain is exacerbated by the consumption of certain foods and drinks can not only support the diagnosis of IC/PBS but also serve as the basis for one of the first steps in managing this syndrome. A nondirective way to ask about urgency is to describe it to the patient as a compelling urge to urinate that is difficult to postpone; follow-up questions can determine whether this urge is intended to relieve pain or prevent incontinence. To assess severity and provide quantitative baseline measures, pain and urgency should be estimated by the patient on a scale of 0–10, with 0 being none and 10 the worst imaginable. Frequency per 24-h period should be determined and nocturia assessed as the number of times per night the patient is awakened by the need to urinate.

About half of patients with IC/PBS have intermittent or persistent microscopic hematuria; this manifestation and the need to exclude bladder stones or cancer require urologic or urogynecologic referral. Initiation of therapy for IC/PBS does not hamper subsequent urologic evaluation.

TREATMENT

The goal of therapy is to relieve the symptoms of IC/PBS; the challenge lies in the fact that no treatment is uniformly successful. However, most patients eventually obtain relief, generally with a multifaceted approach. The correct strategy is to begin with less invasive therapies and move to more invasive measures only if necessary and under the supervision of a urologist or urogynecologist. Tactics include education, dietary changes, medications, pelvic-floor physical therapy, and treatment of associated FSSs.

Months or even years may have passed since the onset of symptoms, and the patient's life may have been disrupted continually, with repeated medical visits provoking frustration and dismay in both the patient and physicians. In this circumstance, simply giving a name to the syndrome is beneficial. The physician should discuss the disease, the diagnostic and therapeutic strategies, and the prognosis with the patient and with the spouse and/or other pertinent family members, who may need to be made aware that although IC/PBS has no visible manifestations, the patient is undergoing substantial pain and suffering. This information is particularly important for sexual partners, as exacerbation of pain during and after intercourse is a common feature of IC/PBS. The Interstitial Cystitis Association (*http://www.ichelp.com*) and the Interstitial Cystitis Network (*http://www.ic-network.com*) can be useful in this educational process.

Over time, many patients identify particular foods and drinks that exacerbate their symptoms. Common among these are chilies, chocolate, citrus fruits, tomatoes, alcohol, caffeinated drinks, and carbonated beverages; full lists of common trigger foods are available at the websites cited above. To construct a benign diet, some patients find it useful to exclude all possible offenders and add those items back into the diet one at a time to identify the ones that worsen IC/PBS symptoms. Patients also should experiment with fluid volumes; some find relief with less fluid, others with more.

Among oral medications, nonsteroidal anti-inflammatory drugs are commonly used first but are often unsuccessful. A small randomized controlled trial suggested that amitriptyline is a reasonable choice for the next agent. This drug is used not for its antidepressant activity but because of its proven effects on neuropathic pain. The initial dose of 25 mg at bedtime is increased weekly by 25 mg up to 100 mg (or less if adequate relief of symptoms is obtained with a lower dose). Side effects can be expected and include dry mouth, weight gain, sedation, and constipation. If this regimen does not control symptoms adequately, pentosan polysulfate, a semisynthetic polysaccharide, can be added at a dose of 100 mg three times a day. Its theoretical effect is to replenish a possibly defective glycosaminoglycan layer over the bladder mucosa, but randomized clinical trials suggest only a modest benefit over placebo. Adverse reactions are uncommon and include gastrointestinal symptoms, headache, and alopecia. Pentosan polysulfate has weak anticoagulant effects and perhaps should be avoided by patients with coagulation abnormalities.

Tenderness of the pelvic floor often is reported by IC/PBS patients. A small but cleverly designed randomized clinical trial suggested that weekly physical therapy directed at muscles and soft tissues of the pelvis yields significantly more relief than a similar schedule of general body massage. This intervention can be initiated under the direction of a knowledgeable physical therapist while trials of medications are under way.

Anecdotal reports suggest that successful therapy for one FSS is accompanied by diminished symptoms of other FSSs. As has been noted here, IC/PBS often is associated with one or several FSSs. Thus, it seems reasonable to hope that, to the extent that accompanying FSSs can be treated successfully, the symptoms of IC/PBS may be relieved as well.

If several months of these therapies in combination do not relieve symptoms adequately, the patient should be referred to a urologist or urogynecologist who has access to additional modalities. Cystoscopy under anesthesia allows distention of the bladder with water, a procedure that provides ~40% of patients with several months of relief and can be repeated. For those few patients with a Hunner's ulcer, fulguration may offer relief. Bladder instillation of solutions containing lidocaine can be repeated. A small randomized clinical trial indicates that bladder instillation of dimethyl sulfoxide is effective in significantly more patients than is placebo. Physicians experienced in the care of IC/PBS patients have used anticonvulsants, narcotics, and cyclosporine as components of therapy. Pain specialists can be of assistance. Sacral neuromodulation can be tested with a temporary percutaneous electrode and, if effective, can be administered with an implanted device. In a very small number of patients with recalcitrant symptoms, surgeries, including cystoplasty, partial or total cystectomy, and urinary diversion, can be valuable.

FURTHER READINGS

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