Interstitial Cystitis-Painful Bladder Syndrome

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Interstitial cystitis (IC) is a chronic, debilitating disease of the urinary bladder characterized by urinary frequency, nocturia, urgency, and frequently pain. It affects more females than males by a ratio of approximately 10:1.1 Recently, the International Continence Society has developed a somewhat broader term for IC described as “IC-painful bladder syndrome.” This new term is defined as the complaint of suprapubic pain related to bladder filling, and is accompanied by other symptoms, such as increased daytime and nighttime frequency in the absence of proven urinary infection or other obvious pathology.2 The true prevalence of IC is not determined and it may be underestimated. In 1997, Jones and Nyberg3 estimated that up to one million patients had IC, many of them unable to cope with day-to-day activities. In Finland, Oravisto4 estimated the incidence as 18.6 out of 100,000 in 1975. Another Finnish study in 2002 used a wider definition and found 450 out of 100,000 had IC.5 There is little international agreement on the epidemiology of IC; it varies as the diagnostic tools vary.

Etiology and Pathogenesis

Interstitial cystitis is an indolent bladder disorder that has continued to be a challenging concern in urology. Despite aggressive investigation in the past two decades, the cause and pathophysiology of the disease remain elusive. Several theories of its pathogenesis have been proposed, but none fully account for the manifestation of the disease. Although the specific etiology of IC is unknown, many mechanisms may be involved.

Occult Infection

Attempts to show an infectious etiology go back to the dawn of the disease, but the case has never been a strong one. Bacterial, viral, and fungal studies were performed on IC patients, and they failed to substantiate an infectious etiology. Infection with “atypical” or fastidious organisms has been proposed by numerous investigators. Some studies showed isolation of fastidious bacteria and Ureaplasma urealyticum.6–8 Although absence of bacterial DNA was reported, presence of bacterial 16Sr RNA was found in the bladder biopsies of some IC patients.9,10 Domingue and Ghoniem11 suggested that even if the organisms are not causative agents, their presence might lead to immune and host-cell responses that could initiate or exacerbate an inflammatory state.

Defective Mucosal Layer (Epithelial Dysfunction)

The healthy bladder surface is coated by a thin mucinous substance, termed bladder surface mucin (BSM), which is composed of numerous sulfonated glycosaminoglycans (GAGs) and glycoprotein. This mucus lining prevents urine and its contents from leaking through the urothelium and damaging the underlying nerves and muscles. In IC patients, this layer is defective and the epithelium is abnormally permeable. As a result, potentially toxic substances in urine are permitted to permeate the bladder muscle, depolarizing sensory nerves and causing the symptoms of IC. One of the urine constituents is potassium (K+), which is highly toxic to the bladder muscularis. Therefore, investigators have developed the potassium sensitivity test to support this theory.12,13 Based on this, GAG agents such as heparin and pentosan polysulfate have been used to treat IC.14,15

Mast Cell Involvement

Simmons16 (1961) was the first to suggest mast cells as a cause of IC. Mast cells contain cytoplasmic granules, which in turn contain substances such as histamine, leukotrienes, prostaglandins, and tryptases. All these substances are capable of stimulating inflammation. Degranulation or activation of mast cells can occur as a part of an immunoglobulin E-mediated hypersensitivity reaction or...
in response to multiple other stimuli including neurotransmitters substance P, cytokines, anaphylatoxins (complement: C3a, 4a, 5a), bacterial toxins, and stress.17,18 Mastocytosis has been reported in the bladders of 30% to 65% of patients with IC.19,20 Increased substance P-containing fibers were found adjacent to mast cells in the bladder biopsies of IC patients.21 Elevated levels of histamine and its metabolites, in the urine of IC patients, were reported by some investigators. Others found overlap or no difference in urinary histamine excretions in IC patients and controls.22,23 Whether mast cells have a primary or secondary role in the etiology of IC is not exactly known.

**Neurogenic Mechanism**

Neurogenic inflammation is a process by which nerves may secrete inflammatory mediators, resulting in local inflammation and/or hyperalgesia. This pathogenesis is described in IC as well as in other painful syndromes. One central component of this mechanism is substance P, a short chain peptide that functions as a nociceptive neurotransmitter in the central and peripheral nervous system and as an inflammatory mediator. When released by peripheral nerves (C fibers or fibers associated with pain transmission), an inflammatory cascade occurs that results in processes such as mast cell degranulation and activation of nearby nerves. Supporting the role of neurogenic inflammation in IC is the finding of increased numbers of substance P-containing nerve fibers in the bladders of IC patients.24 Likewise, an increased concentration of substance P has been found in the urine of patients with IC, and the concentration of substance P is affected by the patient’s degree of pain.25

**Autoimmunity and Inflammation**

The exact role of autoimmunity in IC remains controversial, with no clear indication of a primary role for autoimmunity as the cause of IC. Urothelial activation in IC may result in aberrant immune responses and immune activation within the bladder wall that could relate to the pathogenesis of the disease.

Numerous inflammatory mediators have been studied with regard to their relation to IC. Bladder inflammation is categorized by elevated urinary interleukin-6 and activation of the kallikrein-kinin system.26 Abdel-Mageed and Ghoniem27 were the first to find activated nuclear factor-kappa B in the bladder biopsies of IC patients. This nuclear factor was also found in other inflammatory diseases including rheumatoid arthritis, inflammatory bowel disease, and bronchial asthma. Activation of this nuclear factor was found to be responsible for production of proinflammatory cytokines.28

**Toxic Substances in Urine**

The idea that the urine of IC patients carries a pathologic substance accounting for the disorder has been suggested. The initial observation that the urine of IC patients may contain pathologic substances was suggested when it was found that it inhibits the proliferation of cultured human transitional cells. Keay et al.29 determined that the urine of IC patients specifically contains a low-molecular-weight protein factor that inhibits bladder epithelium proliferation, an antiproliferative factor (APF).

**Clinical Picture**

Patients can present with many symptoms. These symptoms include urgency, frequency, pelvic pain, pelvic pressure, bladder spasm, dyspareunia, dysuria, awakening at night with pain, and pain that persists for many days after intercourse. The location of pain includes the vaginal area, the lower abdomen, suprapubic area, groin, or low back. Many symptoms are aggravated by menstruation and most of the patients believe that sexual intercourse exacerbates their symptoms.

To confirm bladder origin of pain, the patient is asked whether pain worsens if the bladder is full and if it improves with voiding. Bladder pain of IC is experienced suprapubically, in the perineum, vulva, vagina, or in the back or medial thigh. Most patients will also have nocturia, at least one to two times per night.

**Symptoms Scores**

In 1997, O’Leary et al.30 developed a questionnaire specifically to assess IC patients. The questionnaire is composed of two sections, including symptoms and problem indices. The maximum scores are 20 and 16, respectively. A second questionnaire, the University of Wisconsin IC Scale (UW-ICS), includes 7 points, with a 0 (not at all) to 6 (a lot) rating scale. The summed scale ranges from 0 to 42.31 Both questionnaires are validated and either can be given to the IC patient for quantitative evaluation of their symptoms during the course of treatment. We evaluate our patients with the O’Leary questionnaire.

**Voiding Diary**

The number of daily voidings and average volume can be determined from a voiding diary, whereby each voiding is recorded and measured by the patient. At our institution, a 3-day voiding diary is used. Patients with IC void an average of 16 times per day. A baseline voiding diary is obtained at the initial patient visit. Subsequent voiding diaries are then used during and after the treatment for comparison and to determine the progress in therapy.