

Interstitial Cystitis and Related Pain Syndromes: Overlap of Bladder and Bowel Dysfunction

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Interstitial cystitis (IC) and irritable bowel syndrome (IBS) may be classified as functional medical disorders,¹ in which obvious pathophysiological abnormalities cannot explain the signs observed.^{2,3} Despite distinct differences, patients with IC and IBS share many epidemiological, clinical, pathophysiological findings. These disorders also can occur in the same individual. This overlap has resulted in the concept that both disorders share enhanced stress responsiveness as an important underlying mechanism.

Epidemiological similarities:

Approximately 700,000 women in the US suffer from IC (NIDDK), whereas the prevalence of IBS in the United States recently was estimated to be 10-15%.⁴ As mentioned, IC and IBS can occur together in the same patient. For example, Koziol⁵ reported that IBS occurred in 22.5% of 565 IC patients vs. 6.7% of 171 control subjects studied. Frequent stools and "spastic colon" were found in 20 and 18.4% of patients vs. 2.4 and 3% % of controls, respectively. Clauw, et al.,⁶ found significant increases in bloating, and changes in stool consistency, form and passing of stool in 30 IC patients compared with 30 control subjects. In a study of 2862 IC patients from the national database of the Interstitial Cystitis Association, IBS was the second most common co-morbid disease (allergies were the most common) reported, having been diagnosed in 30.2%⁷ of patients.⁸

Patients with IBS frequently report urinary symptoms such as nocturia, frequency, urgency and incomplete bladder emptying; these symptoms may be present in more than half of IBS patients, but most IBS patients do not appear to be evaluated for IC by a urologist.² Both IC and IBS are more common in women than in men. The ratio of females:males in IBS is ~3:2, whereas in IC it is reportedly closer to 10:1. This apparent difference occurs without inclusion of men with nonbacterial prostatitis (CPPS III) and bladder lesions compatible with IC.⁹ If these men are included in the definition of IC, the proportion of affected women and men would be similar. Patients with both syndromes frequently report symptoms of pain and discomfort of other organ systems,^{2,10} and commonly show comorbidity with anxiety disorders. Additionally, the severity of IBS,¹¹ IC,¹² and CPPS III⁷ is significantly exacerbated by low socioeconomic status, further supporting a connection between stressful circumstances and expression of clinical signs.

Clinical similarities:

Both disorders are characterized by chronic pain/discomfort associated with bowel/bladder function, which in the majority of patients is stress-sensitive and not associated with detectable evidence for organic disease. Current symptom criteria probably include a heterogeneous population of patients. Many patients respond to CNS-targeted therapies such as tricyclic antidepressants and cognitive behavioral approaches.

Quality of life of patients with these disorders also is compromised, as shown in Figure 1. The QOL of patients with IBS,^{13, 14} IC¹⁵ and CPPS III⁷ are significantly and comparably degraded compared with healthy individuals. Common co-morbid disorders, including fibromyalgia (FM),¹⁶ chronic fatigue syndrome (CFS),¹⁷ panic disorder,¹⁴ and migraine¹⁴ are included for comparison

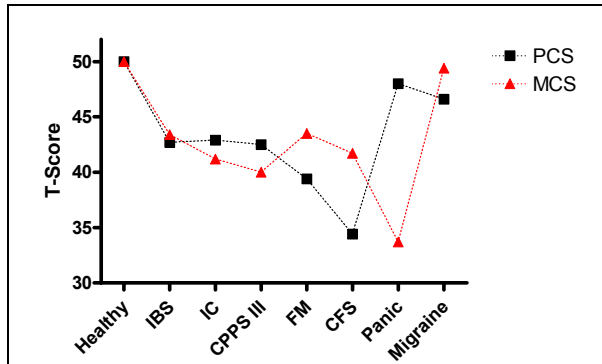


Figure 1. Physical (PCS) and mental component summary (MCS) of quality of life assessments from the RAND Health Surveys. Details and references in text.

Pathophysiological similarities: The urinary bladder and the distal colon share autonomic (sympathetic, sacral parasympathetic) and visceral afferent innervation. IC and IBS patients exhibit visceral hypersensitivity to mechanical stimuli and there is evidence for increased mucosal/urothelial permeability in both syndromes. Animal models for both conditions suggest involvement of the corticotropin releasing factor (CRF) and the CRF1 receptor (CRF/CRF1R) and the substance P (SP) and neurokinin 1 receptor (SP/NK1R) systems. Current evidence also suggests autonomic dysregulation of visceral function with near normal functioning of the hypothalamic pituitary adrenal (HPA) axis, suggesting the possibility of uncoupling of the integration of these systems.

A variety of physiological abnormalities have been identified in some humans with IC that also can occur in patients with IBS. These include abnormalities of the epithelium, sensory (afferent) neuron function, and the sympathetic (efferent) nervous system. Increased urothelial permeability has been identified in both humans and cats with IC,¹⁸ and increased mucosal permeability has been reported in some patients with IBS.¹⁹ Intestinal permeability in humans has been measured using differential urinary excretion of sugars such as lactulose/mannitol²⁰ or lactulose/L-rhamnose.²¹ Such tests, however, assume an impermeable bladder wall, a circumstance that may not be present in patients with co-morbid IC. These tests may thus underestimate the degree of intestinal permeability in some IBS patients.²²

Other reported epithelial abnormalities include increased numbers of mast cells identified in some patients with IC^{23, 24} and IBS²⁵, and increased inducible nitric oxide synthase (iNOS) in the bowel of humans with IBS²⁶ and iNOS generated NO in the bladder of cats with FIC.²⁷ Mast cells are an integral part of the body's defense system,²⁸ and may be activated by both interoceptive and exteroceptive events. Although increased mast cell degranulation in the bladder of IC patients and the bowel of IBS patients has been reported, the finding has not been consistent and may not be specific. The central nervous system can respond to perceived exteroceptive stresses by inducing mast cell degranulation in a variety of tissues in addition to the bladder and bowel, including brain, skin, and lung.²⁹ In previous studies of mast cell involvement in IC and IBS, other tissues were not evaluated to permit assessment of the specificity of the response and potential for exteroceptive activation. Given the overlap of symptoms in this patient population, such studies seem indicated.

Increased iNOS expression and activity have been identified in patients with IBS²⁶ and in models of intestinal inflammation. In one such study, increased iNOS was associated with hypermotility of the small intestine.³⁰ Preliminary data in urinary bladder of cats with FIC²⁷ suggests that there is a high level of continuous basal release of NO due to activation of iNOS, and that NO release due to constitutive NOS activity is depressed. Suppressed phasic and elevated basal NO release could disrupt the epithelial barrier and lead to increased afferent excitability. Increased expression of iNOS also has been identified in enteric nerves in the later stages of inflammation, during the beginning of tissue repair and re-innervation and compensatory growth of nerves, suggesting it also may play a role in tissue repair.³¹ Further studies in patients will be necessary to determine the etiopathogenic significance of these observations.^{32, 33}

Patients with IC and IBS both appear to be more sensitive to visceral stimulation than healthy people are. In patients with IBS, this sensitivity has been documented throughout the gastrointestinal tract.³⁴ In humans with IC, awareness of bladder filling at occurs an smaller volumes than in normal individuals, an observation confirmed by urodynamic studies.³⁵ In cats with FIC, increased sensitivity to bladder filling in both anesthetized³⁶ and awake³⁷ cats has been observed. Increased pelvic nerve activity to bladder distention also has been identified in cats with FIC,³⁸ and lumbosacral dorsal root ganglion cells from cats with FIC exhibit abnormal firing properties and responses to stimulation with capsaicin, a vanilloid receptor agonist. The latter may be due to enhanced endogenous activities of protein kinase C.³⁹

In addition to increased afferent sensitivity to bladder filling, urothelial cells from cats with FIC also exhibit an increased sensitivity to the “mechanical” stimulation of hypotonic stretch.⁴⁰ Similar to results in humans with IC,⁴¹ urothelial cells from FIC respond to hypotonic stretch by releasing more ATP. This increased ATP could stimulate both afferent neurons and other urothelial cells. ATP also participates in the transduction of sensory stimuli from the gut lumen and in the subsequent initiation and propagation of enteric reflexes,⁴² but to our knowledge abnormalities of mucosal ATP production have not yet been investigated in patients with IBS. In summary, current evidence is consistent with the concept that the overlap between the two syndromes is best explained by the presence of hyperresponsiveness of central stress circuits, mediating altered autonomic regulation and altered perceptual responses to visceral stimuli.

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