COMORBIDITY OF INTERSTITIAL CYSTITIS WITH OTHER UNEXPLAINED CLINICAL CONDITIONS

C. A. TONY BUFFINGTON

From the Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Ohio State University, Columbus, Ohio

ABSTRACT

Purpose: The aims of this review are 1) to consider the hypothesis that interstitial cystitis (IC) is not a single disease entity in all patients by reviewing the evidence for the presence of IC subtypes and for the comorbidity of various unexplained clinical conditions in some patients with IC, and 2) to describe recent results obtained in humans and in cats with severe feline IC (FIC) that suggest the presence of an underlying neuroendocrine abnormality.

Materials and Methods: The IC literature concerning comorbidity with other disorders was reviewed and these findings were compared with those of investigators studying the comorbid disorders and comparable data on cats with FIC.

Results: A significant overlap of symptoms exists among a number of unexplained clinical conditions and a common stress response pattern of increased sympathetic nervous system function in the absence of comparable activation of the hypothalamic-pituitary-adrenal axis occurs in a subset of patients with many of these conditions. A comparable pattern exists in cats with FIC, which also includes increased corticotropin releasing factor activity and decreased adrenocorticosteroid reserve.

Conclusions: Further investigation of the stress response system of patients with IC seems merited, which may provide novel approaches to therapy in some patients.

KEY WORDS: bladder; cystitis, interstitial; adrenal cortex; neurosecretory systems; cat diseases

Interstitial cystitis (IC) is a chronic pelvic pain syndrome of unknown cause and no generally accepted treatment. IC symptoms include variable combinations of pain referable to the bladder, and increased frequency and urgency of urination. IC may affect more than 700,000 American women and a significant proportion of men diagnosed with sterile prostatitis or prostatodynia. The quality of life of patients with IC is significantly degraded. In 1 study they scored much lower than healthy control subjects in all 8 domains of health (p < 0.001), as assessed by the Medical Outcomes Study Short Form-36 Health Survey. The aims of this review are 1) to consider the hypothesis that IC is not a single disease entity in all patients by reviewing the evidence for the presence of IC subtypes and for the comorbidity of various unexplained clinical conditions in some patients with IC, and 2) to describe recent results obtained in humans and in cats with severe feline IC (FIC) that suggest the presence of an underlying neuroendocrine abnormality.

Two subtypes of IC are currently recognized based on cystoscopic evaluation of the bladder. In most patients only submucosal petechial hemorrhages (glomerulations) are observed (type I), whereas Hunner’s ulcers with or without glomerulations are identified in a minority (type II). These ulcers were described by Hunner in 1914 (although they had been reported before) as located within the dome and lateral walls of the bladder rather than the trigone, and occurring in the presence of areas of mucosal congestion adjacent to the ulcers. The cystoscopic appearance of the ulcer was later described by Johansson and Fall as "displaying single or multiple patches of reddened bladder mucosa. The redness... is shown to be caused by erythema of the mucosa with small vessels radiating to a central, pale scar, fibrin deposit or coagulum..." In most studies type II IC occurs in 15% to 20% of patients, although some investigators have reported an incidence as high as 50%. The 2 types also appear to differ in patient demographics, histological findings and response to treatment, further suggesting that they may be distinct entities. As others have argued, the differences between types I and II disease require that published reports of studies of IC identify the proportion of each in the subject population. This is particularly important for studies of therapy since the 2 forms appear to respond differently to various treatments. For example, sodium pentosan polysulfate and analgesic doses of tricyclic antidepressants are reportedly more effective in patients with type I vs II disease, whereas patients with type II IC appear to respond more favorably to treatment with transcutaneous electrical nerve stimulation. Patients with type II IC also appear to achieve significant symptomatic relief after supratrigional cystectomy and cystoplasty, whereas the pain in patients with type I IC is not usually decreased by this procedure. This difference may provide important clues to an improved understanding of the underlying causes of pain associated with IC, in that the differential response to surgical therapy suggests that the cause of pain in patients with type II disease may be nociceptive, whereas pain in patients with type I IC may be neuropathic. Nociceptive pain arises from persistent stimulation of sensory afferent fibers and it is relieved by removal of the...
stimulus. Examples of nociceptive pain include the pain of toothache, which is relieved by extraction of the affected tooth, and that associated with severe osteoarthritis of the hip joint, which is relieved by hip replacement.\textsuperscript{11} In contrast, neuropathic pain arises from the central nervous system and, although it is generally attributed to a body structure, it can remain after removal of that structure.\textsuperscript{12}

In addition to the likelihood of the presence of 2 IC subtypes, the syndrome is increasingly considered to be 1 variant of chronic pelvic pain (CPP).\textsuperscript{13, 14} For example, Gunter recently proposed that patients with CPP should be investigated for the presence of IC as well as for various gynecologic, gastrointestinal, musculoskeletal and neurological disorders.\textsuperscript{14} The comorbidity of some of these diseases was suggested by the results of a recent mail questionnaire survey in England, which found that 24% of women 18 to 49 years old reported CPP during the previous 3 months. Of these women 52% had CPP only, 24% had CPP and irritable bowel syndrome, 9% had CPP and urinary frequency and urgency, and 15% had all 3 disorders.\textsuperscript{15} These results suggest that patients with CPP have variable combinations of organ involvement, raising the question of whether a different or a common etiology affects each organ, which then responds in its characteristic way.

Moreover, 4 studies have been published that describe symptoms affecting other organ systems in patients with IC.\textsuperscript{16–19} Tables 1 and 2 list these symptoms by organ system. Some symptoms were reported to be significantly more common in patients with IC than in controls. For other symptoms no difference was identified. However, no statistical power calculations were provided, so that it is possible that a type II statistical error may have occurred for some parameters. In addition to the identified body systems, the presence of headache, abdominal pain, the many cardiopulmonary symptoms and cold sensitivity also suggests a relative sympathetic dominance of the autonomic nervous system,\textsuperscript{20, 21} reported by others based on studies of responses to provocative stimuli,\textsuperscript{22, 23} neurovascular abnormalities\textsuperscript{24} and urine norepinephrine concentrations.\textsuperscript{25}

Erickson et al also investigated the potential subtype specificity of comorbidities.\textsuperscript{19} Five of the 9 symptoms that were significantly increased in patients with IC as a whole were significantly increased in patients with type I disease, whereas none was significantly increased in patients with type II IC. Although many of these differences may have been explained by low statistical power due to small sample size, at least headache and joint aches appeared to be increased only in the type I group.

In addition to these studies by IC researchers and those by gynecologists already mentioned, IC has been reported to be over represented in patients with irritable bowel syndrome by gastroenterologists\textsuperscript{26} and in patients with chronic fatigue syndrome/fibromyalgia by rheumatologists.\textsuperscript{17, 27} A clinical

\begin{table}
\centering
\caption{Symptoms affecting body systems in patients with interstitial cystitis}
\begin{tabular}{|c|c|c|c|c|}
\hline
\textbf{Body System} & \textbf{Symptom} & \textbf{No. IC} & \textbf{No. Control} & \textbf{IC vs Control} \\
\hline
\hline
Genitourinary: & Hysterectomy & 44.1/17.5 & 13 & 44.1/17.5 \textsuperscript{*} \\
 & Vaginal pain & 23/3 & 30 & 23/3 \textsuperscript{*} \\
 & Premenstrual syndrome & 63/53 & 30 & 63/53 \textsuperscript{*} \\
 & Menstrual pain & 50/27 & 30 & 50/27 \textsuperscript{*} \\
 & Endometriosis & 15.3/9.7 & 30 & 15.3/9.7 \textsuperscript{*} \\
 & Incontinence & 9.7/3.2 & 30 & 9.7/3.2 \textsuperscript{*} \\
 & Other pelvic discomfort & 49/6 & 30 & 49/6 \textsuperscript{*} \\
\hline
Musculoskeletal: & Arthritis & 32.7/21.8 & 30 & 32.7/21.8 \textsuperscript{*} \\
 & Muscle spasms & 60/13 & 30 & 60/13 \textsuperscript{*} \\
 & Morning stiffness & 60/21 & 30 & 60/21 \textsuperscript{*} \\
 & Muscle pain & 57/17 & 30 & 57/17 \textsuperscript{*} \\
 & Swollen joints & 27/7 & 30 & 27/7 \textsuperscript{*} \\
 & Fibromyalgia & 18.7/3.2 & 30 & 18.7/3.2 \textsuperscript{*} \\
 & Backache & 57/17 & 30 & 57/17 \textsuperscript{*} \\
 & Joint aches & 63/29 & 30 & 63/29 \textsuperscript{*} \\
 & Swollen ankles & 29/9 & 30 & 29/9 \textsuperscript{*} \\
\hline
Dermatological (sensitive skin) & Numbness & 28.3/15.2 \textsuperscript{*} & 30 & 28.3/15.2 \textsuperscript{*} \\
 & Memory problems & 47/7 \textsuperscript{*} & 30 & 47/7 \textsuperscript{*} \\
 & Concentration problems & 43/13 & 30 & 43/13 \textsuperscript{*} \\
 & Dizziness & 36/7 & 30 & 36/7 \textsuperscript{*} \\
 & Tension headache & 27/3 & 30 & 27/3 \textsuperscript{*} \\
 & Migraine headache & 63/36 & 30 & 63/36 \textsuperscript{*} \\
 & Headache & 40/13 & 30 & 40/13 \textsuperscript{*} \\
 & Vision problems & 29/9 & 30 & 29/9 \textsuperscript{*} \\
 & Ringing in ears & 26/6 & 30 & 26/6 \textsuperscript{*} \\
 & Gastrointestinal: & Abdominal cramps & 30.7/9.0 & 30 & 30.7/9.0 \textsuperscript{*} \\
 & Irritable bowel syndrome & 22.5/6.7 & 30 & 22.5/6.7 \textsuperscript{*} \\
 & Frequent stools & 29.9/2.9 & 30 & 29.9/2.9 \textsuperscript{*} \\
 & Spastic colon & 18.4/3.0 & 30 & 18.4/3.0 \textsuperscript{*} \\
 & Diverticulitis & 9.9/3.0 & 30 & 9.9/3.0 \textsuperscript{*} \\
 & Bloating & 63/21 & 30 & 63/21 \textsuperscript{*} \\
 & Stool consistency changes & 43/7 & 30 & 43/7 \textsuperscript{*} \\
 & Stool form changes & 36/10 & 30 & 36/10 \textsuperscript{*} \\
 & Stool passage changes & 33/7 & 30 & 33/7 \textsuperscript{*} \\
 & Pain relieved by defecation & 53/17 & 30 & 53/17 \textsuperscript{*} \\
 & Pain with stool change & 50/10 & 30 & 50/10 \textsuperscript{*} \\
 & Nausea or vomiting & 27/10 & 30 & 27/10 \textsuperscript{*} \\
 & Mucus in feces & 36/0 & 30 & 36/0 \textsuperscript{*} \\
 & Colitis/Crohn’s disease & 7.8/0.07 & 30 & 7.8/0.07 \textsuperscript{*} \\
\hline
\end{tabular}
\end{table}

\textsuperscript{*} IC vs controls statistically significantly different.
and genetic link between IC and panic disorder has also been identified in patients with by epidemiologists. \(^{28}\)

Many investigators have observed and reported these co-morbidities but have drawn differing conclusions. For example, while some investigators concluded that the commonalities suggest a single underlying pathophysiological model, \(^{29-31}\) others concluded that such models may hamper research into the pathogenetic mechanisms specific to each conditions. \(^{32}\) These conclusions are not mutually exclusive. Wessely et al also concluded that the overlap could result from similarities in symptom definitions of the different syndromes, \(^{29}\) although the presence of overlap with IC in the absence of inclusion of urinary symptoms in the case definition of many comorbid disorders argues against this hypothesis. Some investigators have also suggested that bodily symptoms are the result of somatization of psychiatric disorders, although there is no obvious reason why the symptoms of depression, anxiety and irritability in some patients are the cause rather than another comorbidity or the result of somatic diseases. \(^{33}\)

One commonality among some patients with various unexplained clinical conditions and in healthy subjects subjected to chronic stress appears to be enhanced activation of the stress response system with a relative predominance of sympathetic nervous system (SNS) to hypothalamic-pituitary-adrenal (HPA) activity. \(^{34}\) Figure 1 shows a schematic diagram of some features of part of this complex system. \(^{35}\) After stimulation by central nervous system structures responding to the perception of a threat corticotropin releasing factor (CRF) is released from the hypothalamus, which acts as a hormone to stimulate the anterior pituitary and as a neurotransmitter to activate neurons in the pontine locus coeruleus and brainstem nuclei. SNS outflow is normally restrained by cortisol, \(^{36}\) which also inhibits its own release by feedback inhibition at the level of the anterior pituitary and hypothalamus to terminate the response. However, in some patients the SNS response appears to be uncoupled from the HPA axis, in that SNS outflow increases in the absence of HPA axis activation.

Although neuroendocrine features of the stress response have not been thoroughly studied in humans with IC, available data support the presence of a comparable abnormality in at least a subset of these patients. Although plasma catecholamine concentrations have yet to be reported, abnormal vasomotor tone, \(^{23}\) increased bladder sympathetic neuron density, \(^{26,37}\) and increased urine norepinephrine excretion \(^{25}\) found in patients with IC suggest increased SNS activity. In addition, Lutgendorf et al recently reported that, although mean urinary or salivary cortisol did not differ between patients with IC and controls, patients with higher morning cortisol had significantly less pain and urgency, while those with higher urinary free cortisol reported less overall symptomatology (\(p < 0.05\)). \(^{38}\)

This relationship was also observed when comorbid conditions such as fibromyalgia, chronic fatigue syndrome (CFS) and rheumatoid arthritis were controlled for. Patients with morning cortisol less than 12.5 nmol/l (0.45 \(\mu g/dl\)) were 12.8

<table>
<thead>
<tr>
<th>% IC/Control</th>
<th>Koziol(^{16})</th>
<th>Clauw et al(^{17})</th>
<th>Alagiri et al(^{18})</th>
<th>Erickson et al(^{19})</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. IC</td>
<td>565</td>
<td>30</td>
<td>2,682</td>
<td>35</td>
</tr>
<tr>
<td>No. controls</td>
<td>171</td>
<td>30</td>
<td>Varied</td>
<td>35</td>
</tr>
<tr>
<td>Cardiopulmonary:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinusitis*</td>
<td>31.9/13.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>8.2/4.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent upper respiratory infections*</td>
<td>17.2/4.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart palpitations*</td>
<td>30/7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shortness of breath when hurrying*</td>
<td>60/13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shortness of breath when walking*</td>
<td>33/3</td>
<td>26/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased heart rate*</td>
<td>23/0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shortness of breath*</td>
<td>43/13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shortness of breath when dressing</td>
<td>20/14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stop for breath when walking</td>
<td>13/3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart pounding*</td>
<td></td>
<td></td>
<td>35/6</td>
<td></td>
</tr>
<tr>
<td>Nasal congestion</td>
<td></td>
<td></td>
<td>49/37</td>
<td></td>
</tr>
<tr>
<td>Coughing</td>
<td></td>
<td></td>
<td>23/11</td>
<td></td>
</tr>
<tr>
<td>Suffocation</td>
<td></td>
<td></td>
<td>9/0</td>
<td></td>
</tr>
<tr>
<td>Allergic/immune:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug allergy*</td>
<td>36.9/13.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hay fever*</td>
<td>23.3/12.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food allergies*</td>
<td>22.6/7.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epstein-Barr virus*</td>
<td>9.6/0.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swollen lymph nodes</td>
<td></td>
<td></td>
<td>27/7</td>
<td></td>
</tr>
<tr>
<td>Recurrent fever</td>
<td></td>
<td></td>
<td>23/3</td>
<td></td>
</tr>
<tr>
<td>Allergies*</td>
<td></td>
<td></td>
<td>42.1/22.2</td>
<td></td>
</tr>
<tr>
<td>Lupus*</td>
<td>2.0/0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td></td>
<td></td>
<td>46/0</td>
<td></td>
</tr>
<tr>
<td>Endocrine:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroid*</td>
<td>8.1/3.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthyroid</td>
<td>5.0/3.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>4.0/5.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IC family history</td>
<td>16.3/17.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue*</td>
<td>77/13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth*</td>
<td>36/10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry eyes*</td>
<td>36/10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold sensitive fingers*</td>
<td>33/10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balance problems*</td>
<td>27/7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus pain</td>
<td>50/21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear pain</td>
<td>46/10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear blockage or fullness</td>
<td>49/3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hearing loss</td>
<td>23/3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hands turn white in cold</td>
<td>35/3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic fatigue syndrome</td>
<td>10.4/8.5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* IC vs controls statistically significantly different.
times more likely to report high urinary urgency than those with values above this cutoff. Increased adrenocorticotropic hormone (ACTH)/cortisol has also been reported in women with IC by Lutgendorf et al. Hypocortisolism has also been described in women with CPP, CFS and various other disorders, of which many have been related to increased adrenocortical activity. The primary abnormality identified was decreased size of the fasciculata and reticularis zones. When combined with our observations of increased concentrations of CRF and ACTH in patients with IC, these results suggest the presence of mild primary adrenal insufficiency or decreased adrenal reserve in cats with FIC.

The most parsimonious explanation that I have been able to identify for the combination of increased CRF, ACTH and SNS activity in the presence of a decreased adrenocortical response, and small adrenal fasciculata and reticularis zones without other apparent abnormalities is a genetic disorder and/or developmental accident. Figure 2 shows these relationships. When a pregnant female is exposed to a sufficiently harsh stressor, the hormonal products of the ensuing stress response may cross the placenta and affect the course of fetal development. Matthews recently suggested that the biological purpose of transmitting this response to the fetus is to program the development of the fetal stress response and associated behaviors toward enhanced vigilance to increase the probability of survival. Prenatal and postnatal stressors can result in persistently increased central CRF activity in animals. For example, in continuous and last trimester paradigms prenatal dexamethasone (0.1 mg/kg) treatment increased CRF mRNA levels specifically in the hypothalamus and central nucleus of the amygdala, which are key loci for the effects of the neuropeptide on the expression of fear and anxiety. The effects of stressors on the fetal HPA axis seem to depend on the timing and magnitude of exposure to products.
of the maternal stress response in relation to developmental programs that determine the maturation of the various body systems during gestation and early postnatal development. If exposed before initiation of a developmental program, there may be no effect. However, during the critical period, while the adrenocortical maturation program is running, studies in rodents, foxes, rhesus monkeys, and baboons have shown that adrenal size in the developing fetus may be reduced. If a sufficiently severe stress response occurs after the critical period of adrenocortical development, subsequent adrenocortical responses to stress and adrenal size may be increased.

However, in either case the biological outcome might be similar. Raison and Miller recently concluded from a review of the pertinent literature that inadequate biological activity of glucocorticoids can occur as a result of decreased hormone bioavailability or decreased hormone sensitivity due to agonist mediated receptor desensitization. Regardless of the cause, decreased biological activity of adrenocortical steroids may have various adverse effects on bodily function, possibly related to their role in restraining activation of the immune system and other components of the stress response, including the SNS and CRF.

The lack of a long-term benefit of glucocorticoid therapy in patients with IC suggests that inadequate production of other steroids might also have a role in the pathophysiology of IC. Evidence suggests that part of the stress response may include maintaining cortisol production (Δ-4 pathway) and the expense of the 17, 20 lyase (Δ-5 pathway) products of the 17α-hydroxylase enzyme (fig. 3), such as dehydroepiandrosterone (DHEA) sulfate (DHEAS), the longer lived metabolite of DHEA, when the stressor is severe or the adrenocortical reserve is inadequate.

We recently measured serum free cortisol and DHEAS concentrations in patients with moderate to severe IC during flare and remission. Blood samples were collected from patients in the follicular phase of the menstrual cycle between 8:00 and 10:00 a.m. Patients with a history of use of any corticosteroid containing product within the previous month were excluded. During flare the concentration of serum free cortisol was half and that of DHEAS was 20% of the concentrations found in patients not in a flare (table 3). During flare 2 patients were deficient in serum free cortisol and 4 patients were deficient in DHEAS (adjusted for age). In addition to suggesting that neuroendocrine function may be altered in IC, the results of studies in patients with IC and other unexplained clinical conditions document that neuroendocrine abnormalities may not be identifiable by an evaluation of baseline neuroendocrine function and may only be unmasked by appropriate provocative testing paradigms.

Adrenocortical function also has been evaluated in patients with CFS by measuring the cortisol-to-DHEAS ratio, which was 2 to 3 fold higher in patients with CFS than in controls. Kizildere et al have suggested that serum levels of DHEAS may be low in patients with inflammatory and noninflammatory diseases due to an activated SNS. They concluded that sympathetic hyperactivity may be a common denominator for low levels of DHEAS in inflammatory and noninflammatory diseases. These abnormalities also suggest that some patients may have decreased availability of adrenocortical steroids and neurosteroids (fig. 3), which could adversely affect normal neural function.

One important challenge to any hypothesis for an underlying role for neuroendocrine abnormalities in the pathophysiology of IC is, “Why are symptoms related to the bladder?” The bladder may be affected because of the central role of the SNS in micturition and arousal. Urination is a common physiological response to severe stress, possibly mediated via the pontine micturition center through the activation of sympathetic outflow. Overlap between the micturition and fear pathways may place the bladder at increased risk for activation during stress responses. Documentation of widespread involvement of other organ systems also suggests a role for neuroendocrine involvement. In particular the prominence of autonomic symptoms in some patients with IC provides compelling evidence for the presence of persistently increased SNS activity in these patients. Even the somewhat unusual bladder histopathology found in patients with IC, that is vasodilatation and vascular leakage in the absence of any significant mononuclear infiltrate, could be the result of high local concentrations of noradrenaline, and dopamine.

**TABLE 3. Adrenocortical function in women with IC**

<table>
<thead>
<tr>
<th>Flare</th>
<th>Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pts</td>
<td>10</td>
</tr>
<tr>
<td>Mean age ± SD</td>
<td>44 ± 7.8</td>
</tr>
<tr>
<td>Mean body mass index ± SD</td>
<td>26 ± 6</td>
</tr>
<tr>
<td>Free cortisol:</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD (μg/dl)</td>
<td>0.55 ± 0.14</td>
</tr>
<tr>
<td>No. pts</td>
<td>9</td>
</tr>
<tr>
<td>DHEAS:</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD (μg/dl)</td>
<td>49 ± 16</td>
</tr>
<tr>
<td>No. pts</td>
<td>10</td>
</tr>
</tbody>
</table>
IC and the other unexplained clinically conditions with which it can be comorbid are so complex that it seems unlikely that all or even most cases will be explained by a single underlying etiology. Separating type I from type II patients in data analyses appears to be an important distinction and it may suggest different underlying neuroendocrine abnormalities. However, even if a neuroendocrine imbalance only explains a subset of these cases of IC, it could result in improved care for these patients.

For example, clinically if these findings are validated by other investigators, it may be prudent to assess adrenocortical function in patients with IC prior to elective surgical procedures or after significantly stressful experiences and consider providing replacement therapy as indicated.  

Although to our knowledge adverse Addisonian-like events have not been reported in patients with IC, studies in other patient populations have suggested that inadequate adrenocortical function in stressed patients may predispose some individuals to post-traumatic stress disorder.  

We believe it may suggest different underlying neuroendocrine abnormalities which it can be comorbid are so complex that is seems unlikely that all or even most cases will be explained by a single underlying etiology. Separating type I from type II patients in data analyses appears to be an important distinction and it may suggest different underlying neuroendocrine abnormalities. However, even if a neuroendocrine imbalance only explains a subset of these cases of IC, it could result in improved care for these patients.

For example, clinically if these findings are validated by other investigators, it may be prudent to assess adrenocortical function in patients with IC prior to elective surgical procedures or after significantly stressful experiences and consider providing replacement therapy as indicated.  

Although to our knowledge adverse Addisonian-like events have not been reported in patients with IC, studies in other patient populations have suggested that inadequate adrenocortical function in stressed patients may predispose some individuals to post-traumatic stress disorder.  

We believe it may suggest different underlying neuroendocrine abnormalities which it can be comorbid are so complex that is seems unlikely that all or even most cases will be explained by a single underlying etiology. Separating type I from type II patients in data analyses appears to be an important distinction and it may suggest different underlying neuroendocrine abnormalities. However, even if a neuroendocrine imbalance only explains a subset of these cases of IC, it could result in improved care for these patients.

For example, clinically if these findings are validated by other investigators, it may be prudent to assess adrenocortical function in patients with IC prior to elective surgical procedures or after significantly stressful experiences and consider providing replacement therapy as indicated.  

Although to our knowledge adverse Addisonian-like events have not been reported in patients with IC, studies in other patient populations have suggested that inadequate adrenocortical function in stressed patients may predispose some individuals to post-traumatic stress disorder.  

We believe it may suggest different underlying neuroendocrine abnormalities which it can be comorbid are so complex that is seems unlikely that all or even most cases will be explained by a single underlying etiology. Separating type I from type II patients in data analyses appears to be an important distinction and it may suggest different underlying neuroendocrine abnormalities. However, even if a neuroendocrine imbalance only explains a subset of these cases of IC, it could result in improved care for these patients.
COMORBIDITY OF INTERSTITIAL CYSTITIS WITH OTHER UNEXPLAINED CLINICAL CONDITIONS


44. Dinan, T. G.: personal communication, 2003


70. Straub, L. R., Riley, H. S. and Wolf, S.: Disturbances in bladder function in association with varying life situations and emotional stress. JAMA, 141: 1139, 1949


77. Straub, L. R., Riley, H. S. and Wolf, S.: Disturbances in bladder function in association with varying life situations and emotional stress. JAMA, 141: 1139, 1949

