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Review Articles

COMORBIDITY OF INTERSTITIAL CYSTITIS WITH OTHER UNEXPLAINED CLINICAL CONDITIONS

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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 adrenocortical 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.[1] 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[2] and a significant proportion of men diagnosed with sterile prostatitis or prostatodynia.[3] 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.[1]

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.[1] 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. . .."[4]

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.[5] As others have argued,[6] 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[7] and analgesic doses of tricyclic antidepressants[8] 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.[9] Patients with type II IC also appear to achieve significant symptomatic relief after supratrigonal cystectomy and cystoplasty, whereas the pain in patients with type I IC is not usually decreased by this procedure.[10] 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

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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.[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.[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).[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.[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.[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.[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,[20,21] reported by others based on studies of responses to provocative stimuli,[22,23] neurovascular abnormalities[24] and urine norepinephrine concentrations.[25]

Erickson et al also investigated the potential subtype specificity of comorbidities.[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[26] and in patients with chronic fatigue syndrome/fibromyalgia by rheumatologists.[17,27] A clinical

TABLE 1. *Symptoms affecting body systems in patients with interstitial cystitis*

	% IC/% Control			
	Koziol[16]	Clauw et al[17]	Alagiri et al[18]	Erickson et al[19]
No. IC	565	30	2,682	35
No. controls	171	30	Varied	35
Genitourinary:				
Hysterectomy*	44.1/17.5			
Vaginal pain*		23/3		
Premenstrual syndrome		63/53		
Menstrual pain		50/27		
Endometriosis			15.3/20.7	
Incontinence			9.7/13.3	
Other pelvic discomfort*				49/6
Musculoskeletal:				
Arthritis*	32.7/21.8			
Muscle spasms*		60/13		
Morning stiffness*		60/21		
Muscle pain*		57/17		
Swollen joints*		27/7		
Fibromyalgia*			18.7/3.2	
Backache*				57/17
Joint aches*				63/29
Swollen ankles				29/9
Dermatological (sensitive skin)			24.6/10.6*	
Neurological:				
Numbness	28.3/15.2*	47/7*		46/14
Memory problems*		43/13		
Concentration problems*		36/7		
Dizziness*		27/3		31/0
Tension headache		63/36		
Migraine headache		40/13	20.6/18	
Headache*				41/17
Vision problems				26/6
Ringing in ears				20/9
Gastrointestinal:				
Abdominal cramps*	30.7/9.0			38/0
Irritable bowel syndrome*	22.5/6.7		29.9/2.9	
Frequent stools*	20.0/2.4			
Spastic colon*	18.4/3.0			
Diverticulitis*	9.9/3.0			
Bloating*		63/21		
Stool consistency changes*		43/7		
Stool form changes*		36/10		
Stool passage changes*		33/7		
Pain relieved by defecation		53/17		
Pain with stool change		50/10		
Nausea or vomiting		27/10		26/3*
Mucus in feces		36/0		
Colitis/Crohn's disease*			7.8/0.07	

* IC vs controls statistically significantly different.

TABLE 2. *Symptoms affecting body systems in patients with IC*

	% IC/% Control			
	Koziol[16]	Clauw et al[17]	Alagiri et al[18]	Erickson et al[19]
No. IC	565	30	2,682	35
No. controls	171	30	Varied	35
Cardiopulmonary:				
Sinusitis*	31.8/13.9			
Asthma	8.2/4.8		9.5/6.1	
Frequent upper respiratory infections*	17.2/4.8			
Heart palpitations*		30/7		
Shortness of breath when hurrying*		68/13		
Chest pain*		33/7		26/0
Shortness of breath when walking*		33/3		
Increased heart rate*		23/0		
Shortness of breath*		43/13		
Shortness of breath when dressing		20/14		
Stop for breath when walking		13/3		
Heart pounding*				35/6
Nasal congestion				49/37
Coughing				23/11
Suffocation				9/0
Allergic/immune:				
Drug allergy*	36.0/13.2			
Hay fever*	23.3/12.6			
Food allergies*	22.6/7.8			
Epstein-Barr virus*	9.6/0.0			
Swollen lymph nodes		27/7		
Recurrent fever		23/3		
Allergies*			42.1/22.5	
Lupus*			2.0/0.05	
Influenza				6/0
Endocrine:				
Hypothyroid*	8.1/3.6			
Hyperthyroid	5.0/3.0			
Diabetes	4.0/5.4			
Other:				
IC family history	16.3/17.3			
Fatigue*		77/13		
Dry mouth*		36/10		
Dry eyes*		36/10		
Cold sensitive fingers*		33/10		
Balance problems*		27/7		
Sinus pain		50/21		
Ear pain		46/10		
Ear blockage or fullness		40/3		
Hearing loss		23/3		
Hands turn white in cold		33/3		
Chronic fatigue syndrome			10.4/8.5	

* 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 comorbidities 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[20,37] 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 μg/dl) were 12.8

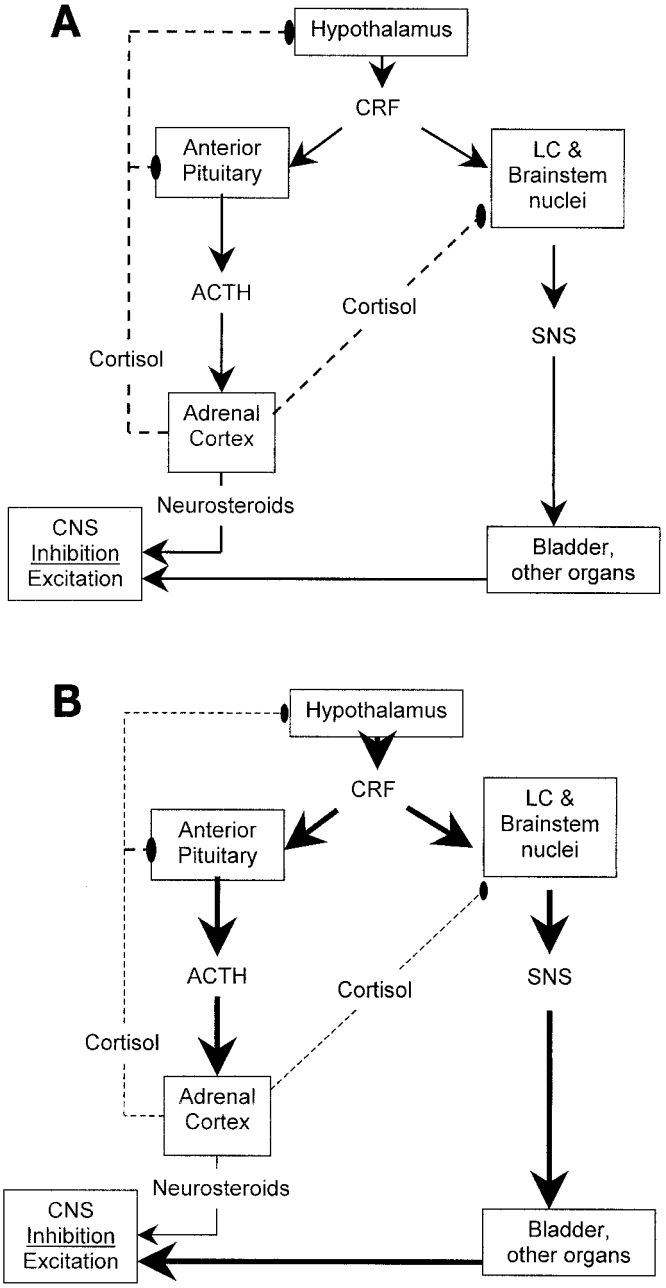

FIG. 1. *A*, normal stress response system. Activation of hypothalamus results in CRF release, which activates anterior pituitary and excitatory SNS outflow from locus coeruleus (*LC*) and brainstem nuclei. System is normally restrained by cortisol at brainstem, anterior pituitary and hypothalamus. Solid lines indicate stimulation. Dotted lines indicate inhibition. Both sets of lines are of equal size. *B*, imbalanced stress response system of IC. In this case excitatory SNS outflow is inadequately restrained by cortisol. This enhanced activity can increase tissue permeability, resulting in increased sensory afferent activity. Feedback inhibition at level of anterior pituitary and hypothalamus is also decreased, which tends to perpetuate CRF output. Sex and neurosteroid production by adrenal cortex, which generally enhances CNS inhibitory tone during chronic stress, also may be decreased.

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.[39] Hypocortisolism has also been described in women with CPP, CFS and various other disorders, of which many have been related to increased activity of the stress response system.[40] The causes of the decrease in cortisol have yet to be identified in patients with IC but they have been investigated in patients with CPP[40,41] and CFS. For example, after comprehensive study of the HPA axis in patients with CFS Demitrack et al concluded that the data were most compatible with a mild central adrenal insufficiency secondary to a CRF deficiency (although this was not identified) or some other central stimulus to the pituitary-adrenal axis.[42]

Scott et al later reported that the adrenal glands of patients with CFS were some 50% smaller than those of control subjects based on computerized tomography.[43] Although they studied patients with low cortisol responses to ACTH, they subsequently found comparable results in patients with CFS and with normal cortisol responses to ACTH.[44] Additionally, Kizildere et al recently identified β-adrenoceptor mediated inhibition of CRF stimulated adrenal steroid secretion.[45] They found that administration of 10 mg propranolol (a nonspecific β-adrenoceptor antagonist) 2 hours prior to administration of 100 μg human CRF decreased heart rate and diastolic blood pressure by 20%. Propranolol treatment also decreased plasma ACTH concentrations by about 40% and increased serum cortisol by about 70%, which decreased the ACTH-to-cortisol ratio by about 2-fold. These results suggest that increased sympathetic tone may also decrease adrenocortical responsiveness to ACTH. Moreover, ACTH release can be enhanced by α-adrenergic receptor activation as well as by vasopressin, which also can modulate stress response system activity.[46]

Recent findings in cats with FIC, a common lower urinary tract disorder of domestic cats that provides a naturally occurring model of type I IC,[1,47] are consistent with and extend the neuroendocrine abnormalities identified in humans with IC. Based on some anomalous results obtained during experiments with a CRF receptor antagonist in cats with FIC[48] we began to look more closely at the adrenal glands of these cats. We found that the cortisol response to ACTH stimulation during stressful circumstances was decreased and adrenal gland size was smaller in cats with FIC than in healthy cats.[49] Microscopic examination of the glands by a board certified veterinary pathologist did not reveal any obvious hemorrhage, inflammation, infection or necrosis as causes of the reduced size. The primary abnormality identified was decreased size of the fasciculata and reticularis zones of the adrenal cortex. When combined with our observations of increased concentrations of CRF[50,51] and ACTH[48] in response to stress in the absence of a comparable increase in plasma cortisol concentrations, 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.[52] Prenatal and postnatal stressors can result in persistently increased central CRF activity in animals.[53] 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.[54]

The effects of stressors on the fetal HPA axis seem to depend on the timing and magnitude of exposure to products

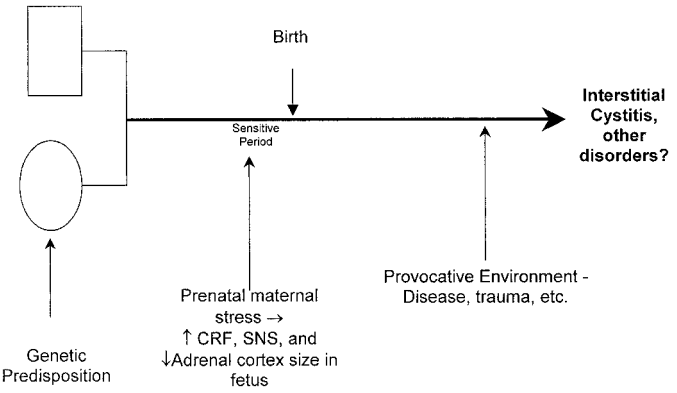

FIG. 2. Hypothesized trajectory to type I IC. Variable combinations of genetic susceptibility, and severity and timing of developmental influences could result in differences in disease severity among patients. Decreased adrenocortical function may only occur if mother experiences severe stressor during sensitive period of adrenocortical development.

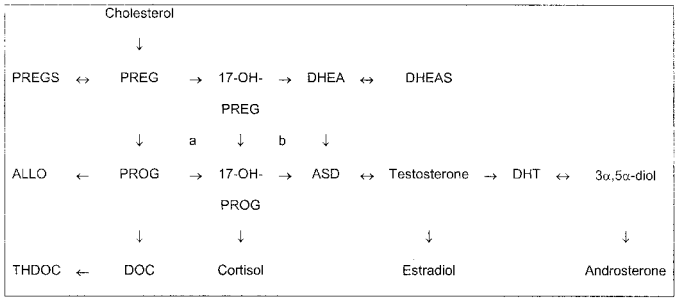

FIG. 3. Some major recognized pathways of adrenocortical steroid synthesis. Other intermediate and products also occur (data not shown). P450c17 enzyme (*a*) performs 17α-hydroxylase reaction equally well using pregnenolone (*PREG*) and progesterone (*PROG*) as substrates but 17,20 lyase reaction occurs 50 to 100 times more efficiently using 17-hydroxy-pregnenolone (*17-OH-PREG*) as substrate rather than 17-hydroxy-progesterone (*17-OH-PROG*). Thus, conversion of 17-hydroxy-progesterone to androstenedione (*ASD*) is minimal and DHEA is principal precursor of sex steroid synthesis.[76] *PREGS*, pregnenolone sulfate. *ALLO*, 3α,5α-tetrahydroprogesterone. *DHT*, dihydrotestosterone. *3α,5α-diol*, 3α-androstanediol. *THDOC*, 3α,5α-tetrahydrodeoxycorticosterone. *DOC*, 11-deoxycorticosterone.

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,[55,56] foxes,[57] rhesus monkeys[58] and baboons[59] 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.[52]

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.[60] 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 17-α hydroxylase enzyme (fig. 3), such as dehydroepiandrosterone (DHEA) sulfate (DHEAS), the longer lived metabolite of DHEA,[45] when the stressor is severe or the adrenocortical reserve is inadequate.[61,62]

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).[63] 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[64] 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.

TABLE 3. *Adrenocortical function in women with IC*

	Flare	Remission
No. pts	10	3
Mean age ± SD	44 ± 7.8	51 ± 18
Mean body mass index ± SD	26 ± 6	24 ± 2
Free cortisol:		
Mean ± SD (μg/dl)	0.55 ± 0.14	1.06 ± 0.48
No. pts	9	3
DHEAS:		
Mean ± SD (μg/dl)	49 ± 16	219 ± 52
No. pts	10	2

Adrenocortical function also has been evaluated in patients with CFS by measuring the cortisol-to-DHEAS ratio,[65] 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.[45] 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 sex steroids and neurosteroids (fig. 3),[66] which could adversely affect normal neural function.[67,68]

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,[69,70] possibly mediated via the pontine micturition center through the activation of sympathetic outflow.[71] 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[16–19] 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 norepinephrine.[72,73]

IC and the other unexplained clinically conditions with 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.[74] 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.[60,75]

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