ORIGINAL ARTICLE

Interstitial Cystitis and Panic Disorder

A Potential Genetic Syndrome

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Background: Evidence from a genetic linkage study had suggested a possible syndrome in some families with panic disorder (PD). This syndrome includes bladder problems (possibly urinary interstitial cystitis [IC]), thyroid disorders, chronic headaches/migraine, and/or mitral valve prolapse. In 19 multiplex families with PD, one marker (*D13S779*) on chromosome 13 gave a logarithm of odds score of more than 4 when individuals with any of the syndrome conditions were analyzed as affected. Families with the bladder problems yielded the highest logarithm of odds scores. These findings were replicated in an extended sample of 60 families. Whereas PD had been well characterized by direct interview, the urologic problems had been found only via medical history checklists and records. A case review by a board-certified urologist suggested they could be IC.

Objective: To determine whether patients diagnosed as having IC by urodynamics and/or cystoscopy and their first-degree relatives (FDRs) have increased rates of the syndrome conditions, thus validating that the bladder problems observed in the linkage study could be IC and providing further support for the panic syndrome.

Design: Case-control and family history study.

Setting: Two metropolitan urology clinics.

Participants: One hundred forty-six probands (67 with IC and 79 with other urologic disorders) and 815 FDRs.

Main Outcome Measures: Lifetime rates of syndrome conditions in probands and FDRs who were blind to urologic or psychiatric diagnoses in the proband.

Results: Compared with patients without IC, patients with IC had a significantly higher lifetime prevalence of PD (controlling for age and sex) (odds ratio, 4.05; 95% confidence interval, 1.22-13.40; $P=.02$) and a higher lifetime prevalence of any of the syndrome disorders (controlling for age and sex) (odds ratio, 2.22; 95% confidence interval, 0.89-5.54; $P=.09$). First-degree relatives of probands with (vs without) IC were significantly more likely to have PD, thyroid disorder, urologic problems, and any of the syndrome disorders (controlling for age and sex of the relative and sex of the proband) (adjusted odds ratio, 1.95; 95% confidence interval, 1.13-3.38; $P=.02$). These results in relatives were not influenced by PD in probands, and did not change substantially when controlling for the proband-relative relationship, modeling age as a categorical (vs continuous) variable, or excluding FDRs with PD. There were no interactions between proband IC status and sex of the relative.

Conclusions: The increased frequency of seemingly disparate disorders in patients with IC and their FDRs is consistent with the genetic linkage findings in families with PD. These findings suggest that the bladder problems observed in the linkage study may be IC. The hypothesis that there is a familial, possibly pleiotropic, syndrome that may include IC, PD, thyroid disorders, and other disorders of possible autonomic or neuromuscular control deserves further investigation.

Arch Gen Psychiatry. 2004;61:273-279

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We report results from a study designed to follow up genetic linkage findings of a previously unidentified syndrome in some multiplex families with panic disorder (PD).[1] This syndrome included PD, various urinary problems (possibly interstitial cystitis [IC]), thyroid disorders, mitral valve prolapse (MVP), and/or chronic headaches/migraine in some family members. The genetic linkage study had selected the families based on initial evidence of at least 3 family members affected with PD.[2,3] While the information on PD was obtained from careful interviews, information on the bladder problems and other medical conditions was obtained only through medical records and history checklists. By using these less-than-definitive methods for the medical condi-

tions, logarithm of odds scores of 4.2 on chromosome 13 (marker *D13S779*) were obtained in the first 19 multiplex families with PD and these other medical conditions.[1] These findings were further supported in a genome scan performed on an extended sample that included the initial 19 families and an additional 41 families, for a total of 60 multiplex families with 587 individuals.[4]

We present findings from a new study aimed to follow up the bladder/kidney problems. The bladder/kidney problems yielded the highest logarithm of odds scores in the genetic linkage study, but the diagnostic meaning was unclear. Our records were reviewed by a urologist (S.A.K.) who believed that they could be IC. We examined the rate of PD and the other syndrome disorders in a sample of patients diagnosed as having IC by urologists using urodynamics and/or cystoscopy with bladder distention.

The specific hypothesis tested is that probands with IC and their first-degree relatives (FDRs), compared with control subjects and their FDRs, will have an increased rate of the syndrome disorders, including PD, thyroid disorders, MVP, and/or severe headaches/migraine. These findings would partially validate that the bladder problems seen in the linkage study could be IC and also add further support for the panic syndrome identified in the linkage study.

There are several hypotheses implicating various neurobiological mechanisms, such as autonomic dysregulation, in the cause of PD.[5,6] It is possible from a developmental perspective that a putative gene(s) would give rise to additional dysfunctions in other areas, such as the bladder, in which regulation involves smooth muscle function or corticotropin-releasing hormone (CRH). Therefore, these seemingly unrelated conditions might be explained by mutations in certain genes that exert effects on multiple aspects of physiological and anatomical features and lead to pleiotropic phenotypes in probands and their families. Pleiotropy is defined as the phenomenon by which a single gene is responsible for several distinct and seemingly unrelated phenotypic effects.[7]

Panic disorder is a highly familial complex genetic disorder[8] with heritability, based primarily on twin studies, of about 49%.[9] The lifetime prevalence of PD is about 1% to 3% cross-nationally, with a mean age of onset in early adulthood. Women have higher rates of PD than men, and the clinical manifestation of PD is similar across diverse cultures.[10] Symptoms include recurrent episodes of sudden unpredictable apprehension and associated autonomic manifestations involving the cardiorespiratory system (shortness of breath, chest pain, and palpitations), neurologic symptoms (dizziness, paresthesias, and trembling), gastrointestinal symptoms (nausea and abdominal distress), other autonomic symptoms (hot flashes, chills, and sweating), and cognitive symptoms such as fear of dying. Treatment established through controlled clinical trials includes a range of pharmacological agents, most commonly selective serotonin reuptake inhibitors, and behavioral approaches.[11] None are fully effective, and PD is associated with increased rates of medical use and suicide attempts.[12]

Interstitial cystitis is a chronic debilitating bladder syndrome of unknown cause, and there is no generally accepted treatment.[13] There have been several attempts to estimate the prevalence of IC in the United States.[14] The largest most systematic set of data, based on self-report from the National Household Interview Study, shows a lifetime prevalence of 0.5% after weighting of the US population by age, race, and sex.[15] It is more commonly found in females, with a median age of onset at 40 years.[16,17] The role of genetic susceptibility has not been thoroughly investigated. One small twin study[18] found considerably higher concordance in monozygotic vs dizygotic twins. Five of the 8 monozygotic and none of the 26 dizygotic twins had confirmed IC.[18] Preliminary findings from a family study[18] suggest higher rates of IC in the FDRs of IC patients vs population controls.

Interstitial cystitis symptom presentation varies, but most commonly includes urinary frequency and urgency, nocturia, severe pain on bladder filling (typically relieved with voiding), and sterile urine.[19,20] Interstitial cystitis encompasses a major portion of the chronic pelvic pain syndrome,[21,22] which includes many urologic patients with bladder and/or pelvic pain, irritative voiding symptoms, and negative urine culture and cytologic test results.[23] Interstitial cystitis in males is characterized by impairing clinical symptoms typical of chronic prostatitis (pain on voiding and erectile dysfunction) without evidence of leukocytes or bacteria cultured in the prostatic secretions.[24-26] A syndrome remarkably analogous to IC, called feline IC, occurs in domestic cats. Studies[27-29] of cats and humans suggest central nervous system involvement, including subtle abnormalities of the hypothalamic-pituitary-adrenal axis and a significant increase in tyrosine hydroxylase immunoreactivity in the locus coeruleus.

Available treatments for IC are based primarily on observational data and a few clinical trials. Treatments included are cystoscopic hydrodistention of the bladder, amitriptyline hydrochloride, antihistamine (oral hydroxyzine hydrochloride), pentosan polysulfate sodium, and intravesical dimethyl sulfoxide therapy.[30,31] These treatments may improve symptoms, but there is insufficient information to know whether treatment modifies the long-term course.[32] Interstitial cystitis is considered a local manifestation of a systemic disease, possibly an autoimmune disorder, but this is controversial. Systematic studies[33,34] of large samples of patients with IC have found increased rates of autoimmune diseases, migraine headaches, and hypothyroid disease. Recently, the National Institute of Diabetes and Digestive and Kidney Diseases requested research applications in basic cellular, molecular, and genetic studies of IC.

METHODS

PATIENTS

Eligible participants were English-speaking patients aged 18 to 70 years from 2 urology clinics in New York City, headed by Columbia University–affiliated board-certified urologists (D.K. and S.A.K.), based on their urologic diagnosis, independent of the other syndrome disorders.

Cases were women with IC and men with chronic prostatitis (with normal urine sediments and sterile urine and prostatic fluid), considered the male equivalent of IC.[22] Controls were patients with bladder diseases that have well-established, diagnosable, underlying anatomical causes. Controls included men and women with noninvasive bladder cancer or detrusor instability, a condition characterized by involuntary contractions of the smooth muscular coat of the bladder. In women, the condition is usually secondary to cystocele (a condition in which the bladder base descends below the inferior ramus of the symphysis pubis either at rest or with straining, due to a defect in the anatomical support of the bladder), and in men, it is secondary to benign prostatic hypertrophy. Also included among controls were women diagnosed as having cystocele and men with benign prostatic hypertrophy or prostate cancer.

ENROLLMENT OF STUDY PARTICIPANTS

To avoid selection bias, computer-generated lists of all patients diagnosed as having IC were provided to us by assistants (a medical student and a secretary) to the urologists who were unaware of our study hypothesis. For controls, we were given lists of cases that met the control inclusion criteria. No information on psychiatric or other conditions was included, just the urologic diagnosis. As required by the institutional review board, all patients were first sent a letter signed by their urologist inviting them to participate in the study. They were given an opportunity not to participate by calling in and declining. Those who did not call in within 2 weeks were followed up and invited to participate. The patients received no other information about the study from the urologists or the investigators before receiving the letter. When subjects were called back, they were told that we would ask health questions about themselves and their FDRs. All of the calls to the subjects for recruitment and interview were made by an assistant who was blind to the urologic diagnosis and did not have access to the patients' medical records. Sixty-seven (72.8%) of the 92 available cases and 79 (43.4%) of the 182 available controls agreed to participate in the study. All participants gave informed consent and agreed to provide family history information.

ASSESSMENTS

Urologic diagnoses were made by a board-certified experienced urologist (D.K. or S.A.K.), before this study, blinded to the study interview data. Urodynamic tests with cystometry and cystoscopy (with hydrodistention) reports[35] were available for 126 (86.3%) of the patients (27.4% underwent both tests, 36.3% underwent urodynamic tests only, and 22.6% underwent cystoscopy only). Of the 9 patients who underwent neither test, 8 underwent ultrasonography and other tests and 1 underwent ultrasonography only. Medical records were missing for 9 of the 146 patients. Patients were assessed by a trained research assistant, under the supervision of a psychiatrist (R.G.). Both were blinded to the urologic diagnosis and were not affiliated academically or geographically with the urology clinic. Lifetime PD was determined by diagnostic assessment, similar to that used in the genetic linkage study.[2] First, the anxiety section of the Schedule for Affective Disorders and Schizophrenia–Lifetime Version,[36] a structured psychiatric interview, was administered.[37] The interviewer also wrote a narrative case history for patients who reported any psychiatric symptoms. The data were then used by the same 2 senior clinicians who diagnosed PD in the linkage studies (M.M.W. and A.F.), blinded to the urologists' and the interviewer diagnoses, to confirm the psychiatric diagnosis using the best-estimate procedure.[38] Psychiatric symptoms and information on the medical conditions in the FDRs were obtained from the patients using an extended version of the Family History Screen, a brief validated instrument for collecting lifetime psychiatric history on an informant and FDRs.[39] There is a well-documented underreporting of diagnosis using family history methods, because informants may not have sufficient information about all the relatives' symptoms to meet diagnostic criteria. Therefore, we used broader criteria for PD in the FDRs, including panic attacks. Medical examinations were not available on FDRs, but we used the same methods to obtain medical conditions in the relatives as had been used in the linkage study.[1]

DATA ANALYSIS

t Tests and χ^2 tests were used to test for group differences in demographic characteristics. Comparisons were made between the 2 proband groups and between the FDRs of these 2 groups.

Probands

Separate logistic regression analyses were used to evaluate the association of IC with each of the 4 disorders comprising the putative syndrome in probands (PD, MVP, thyroid disorder, and chronic headaches/migraine), with IC as an independent variable (1 indicates present; and 0, absent) and each syndrome disorder as the outcome (1 indicates present; and 0, absent). We also created a binary outcome variable to capture the presence of any of the 4 syndrome disorders. Because probands with IC were younger and had more females than controls, age and sex were entered as covariates in all analyses. Each analysis was performed twice, with age entered as a continuous variable and also as a 5-level categorical variable based on quintiles of the age distribution, because there was no a priori assumption about how age might be acting as a confounder. We tested the interaction between sex and proband IC status in all analyses. Statistical significance was set at the 5% level ($P<.05$, 2-tailed).

First-Degree Relatives

Separate logistic regression analyses were used to evaluate the association of proband IC with each of the 5 disorders comprising the syndrome in FDRs (PD, MVP, thyroid disorder, chronic headaches/migraine, and urologic [bladder or kidney] problems), with proband IC as the independent variable (1 indicates present; and 0, absent) and FDR's status on each syndrome disorder as the outcome (1 indicates present; and 0, absent). We also created 2 binary outcome variables to capture the presence in relatives of any of the 5 syndrome disorders and the presence of MVP, thyroid disorder, chronic headaches/migraine, and/or urologic problems. Panic disorder was omitted from this second definition to rule out the possibility that the presence of PD explained the findings. All parameters were estimated using generalized estimating equations[40] to adjust for the nonindependence of observations among relatives from the same family. We did not use survival or Cox proportional hazards regression models because we did not have the age of onset in relatives. Statistical significance was set at the 5% level ($P<.05$, 2-tailed).

To rule out the effects of PD, which is an independent familial disorder, we performed all of the previously described analyses on a restricted set of FDRs (those with probands who did not have PD). We also controlled for the following variables: FDR age (because FDRs of IC probands were younger than FDRs of non-IC probands), FDR sex (to further reduce potential confounding), sex of the proband informant (be-

Table 1. Panic Disorder and Other Syndrome Conditions in Probands With and Without IC

Disorder	Probands With IC (n = 67)*	Probands Without IC (n = 79)*	OR (95% CI)†	*P* Value
Panic disorder	18 (26.9)	6 (7.6)	4.05 (1.22-13.40)	.02
Mitral valve prolapse	22 (33.8)	17 (22.7)	1.88 (0.74-4.80)	.19
Thyroid disorder	12 (17.9)	6 (7.6)	6.13 (1.50-25.05)	.01
Chronic headaches/ migraines	19 (28.8)	20 (25.3)	0.63 (0.25-1.62)	.34
Syndrome disorder‡	47 (72.3)	37 (48.7)	2.22 (0.89-5.54)	.09

Abbreviations: CI, confidence interval; IC, interstitial cystitis; OR, odds ratio.
*Data are given as number (percentage) of probands. Some percentages are "off" because of missing data (the total number for each disorder outcome varies from 140 to 146).
†These data signify the increased likelihood that probands with IC (vs those without IC) have the disorder listed in the first column, controlling for age and sex.
‡Defined as the lifetime presence of at least 1 of the following: panic disorder, mitral valve prolapse, thyroid disorder, or chronic headaches/migraines.

Table 2. Lifetime Disorders in FDRs of Probands With and Without IC, Excluding Probands With Panic Disorder

Disorder	FDRs of Probands With IC (n = 235)*	FDRs of Probands Without IC (n = 466)*	OR (95% CI)†	*P* Value
Panic disorder‡	4.0	1.5	3.32 (1.19-9.22)	.02
Mitral valve prolapse	8.3	6.2	1.22 (0.55-2.68)	.62
Thyroid disorder	9.0	3.5	2.89 (1.33-6.28)	.007
Chronic headaches/ migraines	8.6	6.7	1.33 (0.57-3.08)	.51
Urologic problems§	15.2	7.4	2.01 (1.04-3.89)	.04
Syndrome disorder‡				
Including panic disorder‖	38.4	24.1	1.95 (1.13-3.38)	.02
Excluding panic disorder¶	34.3	21.2	1.92 (1.14-3.24)	.01

Abbreviations: CI, confidence interval; FDR, first-degree relative; IC, interstitial cystitis; OR, odds ratio.
*Data are given as rate per 100. (There were 49 probands with IC and 73 probands without IC.)
†These data signify the increased likelihood that FDRs of probands with IC (vs probands without IC) have the disorder listed in the first column. Correlation among family members was accounted for by using generalized estimating equations (GEEs) with an exchangeable correlation matrix. The age and sex of FDRs and the sex of the proband were controlled in GEE analyses. For each disorder, 29 (4.1%) of the 701 FDRs were excluded from the analysis because of unknown age and/or sex, and an additional number (range, 3-89 [0.4%-12.7%]) were excluded because their disorder status could not be ascertained.
‡In FDRs, broadly defined and included panic attack.
§A bladder or kidney problem (excluding bladder cancer).
‖Defined as the lifetime presence of at least 1 of the following: mitral valve prolapse, thyroid disorder, chronic headaches/migraines, a urologic problem, a panic attack, or panic disorder.
¶Defined as the lifetime presence of at least 1 of the following: mitral valve prolapse, thyroid disorder, chronic headaches/migraines, or a urologic problem.

cause of differential reporting by sex), and the relationship between FDR and proband (using a 3-level variable coded as parent, child, or sibling). Each analysis was performed twice, with age entered as a continuous variable and also as a 5-level categorical variable based on quintiles of the FDR age distribution, because there was no a priori assumption about how age might be acting as a confounder. We tested the interaction between FDR sex and proband IC status in all analyses. Statistical significance was set at the 5% level ($P<.05$, 2-tailed).

RESULTS

Patients with IC were younger than controls (mean±SD, 44.8±13.3 vs 60.3±9.6 years; $P<.001$), and most were women (83.6% vs 41.8%; $P<.001$). Cases and controls did not differ in race or ethnicity (88.1% vs 77.2% white), number of completed school years (mean±SD, 15.2±2.5 vs 14.8±2.4), or percentage employed (74.6% vs 63.5%). All analyses were adjusted for sex and age. We report the analyses adjusting for age as a continuous variable, because the results were nearly identical when adjusting for age as a categorical variable.

There was more than a 4-fold higher risk of PD and more than a 6-fold higher risk of thyroid disorder among patients with IC compared with controls, and more than a 2-fold increased risk of having any of the disorders composing the syndrome (**Table 1**). Rates of headaches/migraine and MVP did not differ significantly between groups. There was no significant interaction between proband sex and IC status in any of the analyses (*P* range, .13-.83).

Eight hundred fifteen FDRs were identified (315 of IC probands and 500 of controls). There were no sex differences in relatives by proband group. Relatives of probands with IC were younger (mean±SD, 50±22 vs 54±22 years; $t_{784}=2.47$, $P=.01$) and had fewer children. All analyses were adjusted for age. As with the proband analyses, we report the FDR analyses adjusting for age as a continuous variable, because the results were nearly identical when adjusting for FDR age as a categorical variable.

We first examined the prevalence of the syndrome disorders in all the FDRs of all probands, including probands with PD (data not shown). As expected, based on numerous family studies,[41] PD was familial. The odds of the outcome disorder in the FDRs of IC patients were increased more than 2-fold for PD, thyroid disorder, urologic problems (excluding bladder cancer), and the syndrome disorder whether PD was or was not included in the definition. There was no significant interaction between FDR sex and proband IC status in any of the analyses (*P* range, .11-.62).

We next restricted our analysis to FDRs of probands without PD to determine whether the syndrome was being transmitted independent of PD in the proband (**Table 2**). We also controlled for sex of the informant to ensure that bias was not introduced by unequal representation of female informants in the IC groups. The results did not change substantially. The odds of the outcome disorder in the FDRs of IC patients were increased more than 3-fold for PD, more than 2-fold for thyroid and urologic problems, and nearly 2-fold for the syndrome whether PD was or was not included as a syndrome disorder.

COMMENT

These results, in a sample of patients carefully diagnosed as having IC, show an increased risk of PD and of the syndrome in IC patients and their FDRs. These findings, together with findings from the genetic linkage

study,[1] while still tentative, suggest that in a subgroup of patients with PD, IC and other seemingly disparate disorders may be part of the same syndrome.

Previous studies found an increased comorbidity of PD with cardiovascular problems,[42] chronic headaches/migraine,[43] MVP,[44] and thyroid disorders.[45] It is usually assumed that these associations are spurious (ie, a misclassification due to an overlap of symptoms). None of the family studies of PD have determined whether medical disorders that coaggregate with PD have an increased familial risk independent of PD in relatives of probands with IC. Our findings suggest that the associations may be a result of a shared cause, such as genetic susceptibility. Our findings may also explain some of the association observed between MVP and autoimmune thyroid disorders[46,47] and migraine.[48]

A pleiotropic gene might give rise to any of several plausible biological mechanisms shared by IC, PD, and the other syndrome disorders. There are related data, although speculative, that may explain our findings or suggest more specific hypotheses (the study of Weissman et al[1] has details). Autonomic dysregulation is implicated in the cause of PD.[5,6] The bladder's function involves smooth muscle function regulated through innervation from autonomic nuclei,[49,50] so that changes in autonomic tone might lead to voiding difficulties, as seen in patients with IC. Stress, which arouses the noradrenergic system, was shown to be associated with symptom exacerbation in IC patients.[51] Tricyclic antidepressants, mostly amitriptyline, which inhibit central norepinephrine, may be effective in some patients with IC.[52] Animal model data show that cats with IC have increased plasma norepinephrine concentrations.[53] Autonomic mechanisms have also been considered as causative factors in other nonpsychiatric syndrome disorders. Mitral valve prolapse in patients with PD is usually the mild noncalcified type; its cause has been related to a more general dysautonomia.[44] Migraine involves abnormal dilation of cerebral blood vessels, an action that is under autonomic control.[54]

Another way that autonomic reactivity might be involved in IC and PD is via neurogenic inflammation. Human and animal model data indicate a defect in the bladder's cytoprotective glycosaminoglycan lining that could allow penetration of various substances that can activate bladder mast cells. Mast cell–derived proinflammatory and vasoactive molecules may, in turn, contribute to the pathogenesis of IC. Bladder mast cell activation is mediated and augmented by neurotransmitters and neuropeptides, such as serotonin,[55] and serotonergic imbalance is implicated in PD. Mast cells might also play a central role in the pathogenesis of migraine and immune-mediated thyroid disorders.[56]

The common genetic susceptibility possibly shared by the disorders composing the syndrome might be linked to the Barrington nucleus. This pontine nucleus implicated in urination[49] links parasympathetic preganglionic neurons with prosencephalon-projecting nuclei, thus providing an anatomical substrate for coregulation of pelvic visceral symptoms and mental activity in the prosencephalon.[57] The Barrington nucleus contains numerous CRH neurons that project to the spinal parasympathetic nucleus innervating the bladder.[58] Dysregulation of the hypothalamic-pituitary-adrenal axis plays a role in the cause of PD,[59] and causes enhancement of central secretion of CRH. Increased CRH secretion from the Barrington nucleus might, in turn, inhibit urination and cause voiding problems typical of IC.

The strengths of our study include a sizable sample, state-of-the-art urologic diagnoses, reliable assessment of PD, and information on FDRs. A limitation of the family history approach is that a patient with PD may be more likely to report PD in relatives.[60] We took care of this potential bias by also restricting our analysis to relatives of probands who did not have PD. Another limitation is the low response rate among controls. However, this potential selection bias could not distort our findings in the FDRs, even if PD was not equally distributed between responders and nonresponders in the control group, because the strategy we adopted ensured that results in relatives were independent of PD status in probands. Other limitations include the lack of medical assessment of MVP, thyroid disorder, or headaches/migraine. Moreover, we only assessed FDRs, and the genetic linkage study included multiplex families spanning several generations. Thus, disorders in the extended family may have been missed by including only FDRs. Pleiotropy would not require that all elements of the expression of the phenotype be present in an individual. Finally, while our results concerning the increased risk of the syndrome in the IC patients and their FDRs are consistent with the findings of the genetic linkage study, a family history study alone cannot validate a genetic syndrome or confirm pleiotropy.

Potential clinical implications of this finding include identification of new pharmacological interventions for IC, targeting specific neurotransmitter receptors.[61] Selective serotonin reuptake inhibitors, which are effective in PD patients, might inhibit serotonergic activation of mast cells and modulate exaggerated bladder activity through down-regulation of central postsynaptic serotonin receptors.[62,63] In addition, trials of CRH antagonists as anxiolytic agents in PD patients are in process.[64] These novel agents might be effective also in treating IC. Urologists should be aware of the increased prevalence of PD, a treatable disorder, among their IC patients. Future research should include efforts to replicate the family aggregation and genetic findings and clinical trials with selective serotonin reuptake inhibitors for IC.

It is likely that the range of syndrome disorders is larger than we have identified, including disorders shown to be associated with IC, such as fibromyalgia, celiac disease, and irritable bowel syndrome, which in turn have been associated with PD and/or migraine and other disorders of possible autonomic or neuromuscular control, leading to the speculation that many or all of these conditions share underlying pathophysiologic features. Also, PD frequently co-occurs with mood and other anxiety disorders that have also been associated with several other syndrome conditions. The phenotype of PD may be broader than identified in this study. There is increasing recognition that phenotype hunting in family and genetic studies of psychiatric disorders may profit from as-

sessment of a wide range of medical and psychiatric disorders.[65]

Submitted for publication January 13, 2003; accepted September 22, 2003.

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This study was supported by a National Alliance for Schizophrenia and Depression Senior Investigator Award (Dr Weissman); and grants MH2874 (Dr Weissman) and MH35792 (Dr Fyer) and training grant 5T32-MH13043 (Dr Gross) from the National Institute of Mental Health, Rockville, Md.

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