Association of Internalizing Disorders and Allergies in a Child and Adolescent Psychiatry Clinical Sample

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Objective: To investigate the specificity of the association between internalizing disorders (anxiety and depression) and atopic disorders (asthma, allergic rhinitis, urticaria, and atopic dermatitis) in a child and adolescent psychiatric clinical sample.

Method: A sample of 184 youths was evaluated for current DSM-IV psychiatric disorders (clinical interview) and lifetime history of atopic disorders (parent report and chart review) in a child and adolescent psychiatry clinic from September 1, 2001, through December 31, 2002. Logistic regression analyses were used to assess the differential likelihood of having a lifetime history of atopic disorders among psychiatrically ill youths with and without internalizing disorders.

Results: Youths with internalizing disorders were significantly more likely than those with noninternalizing disorders to have a lifetime history of atopic disorders (odds ratio [OR] = 1.95, 95% CI = 1.02 to 3.73, p = .04). Moreover, analyses distinguishing youths with "pure" internalizing disorders from those with comorbid internalizing and externalizing disorders, "pure" externalizing disorders, and other psychiatric disorders showed that the association with atopic disorders was specific for "pure" internalizing disorders only (OR = 2.40, 95% CI = 1.09 to 5.30, p = .03).

Conclusions: Atopic disorders may be associated specifically with "pure" internalizing disorders in psychiatrically ill youths. Additional studies are needed to identify the underlying mechanisms of this specificity for the subsequent development of effective treatment and prevention interventions that target both disorders.

(J Clin Psychiatry 2007;68:1419–1425)

Received July 16, 2006; accepted Jan. 20, 2007. From the Department of Psychiatry, University of Wisconsin School of Medicine and Public Health, Madison.

Support was provided by National Institute of Mental Health grant R03-MH066073 (Dr. Slattery, principal investigator).

The authors thank John E. Huxsahl, M.D., The Mayo Clinic, Rochester, Minn., for his help with study administration. Dr. Huxsahl reports no financial affiliations or other relationships relevant to the subject of this article.

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Previous studies have described associations between psychiatric symptoms and atopic disorders, a familial group of allergic disorders that includes asthma, allergic rhinitis (hay fever), urticaria (hives), and atopic dermatitis (eczema).[1] The majority of existing studies have focused on community and clinical populations of adults, with the overall pattern of results suggestive of a specific association between atopic disorders and the internalizing disorders of anxiety and depression.[2–12]

A smaller number of community and clinical investigations in children and adolescents have shown similar results. Two cross-sectional community studies examined the association of asthma and psychiatric disorders in youths. In one investigation, child asthma was associated with having any type of anxiety disorder.[13] The second study examined psychiatric comorbidity among youths with diagnosed asthma compared to those with asthma attacks. A diagnosis of asthma was found to be associated with having any type of depressive disorder, whereas asthma attacks were associated with having any depressive disorder and any anxiety disorder.[14] A third epidemiological study examined the association of anxiety disorders with allergies in youths.[15] Results revealed a robust association between allergies and panic disorder. Further,

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TAKE-HOME POINTS

- Internalizing disorders are commonly associated with atopic disorders.
- This association may be specific for "pure" internalizing disorders without comorbid psychopathology.
- The clinical evaluation of youths with internalizing disorders should include assessment of comorbid atopic conditions.

prospective epidemiological studies of children and adolescents have shown longitudinal associations of atopic disorders with later internalizing disorders. In one study, it was shown that a diagnosis of hay fever and/or a combined index of hay fever, asthma, and allergies in early childhood predicted the onset of major depressive disorder in adolescence and early adulthood.[16] And, in a second study, which considered child anxious temperament at age 3 and respiratory status at ages 15 and 18 as predictors of later anxiety disorders, it was shown that asthma was a specific predictor of panic disorder/agoraphobia (PDA) among females, and that, among males, asthma combined with anxious temperament was also predictive of PDA.[17] This was not the case for other anxiety disorders.

Studies of clinical samples of children and adolescents have also found associations of internalizing and atopic disorders. The majority of this research has been conducted with clinical asthmatic samples, without a healthy comparison group, in which evidence for the specificity of the atopic-internalizing disorder association has been shown by comparing rates of depression (5% to 15%), and especially anxiety disorders (23% to 33%), with rates of externalizing disorders (5% to 8%).[18,19] One study that included a comparison healthy control group found anxiety disorders present in 42% of asthmatic children compared with 19% in controls, with separation anxiety being the most frequent subtype; the study did not investigate the presence of other types of psychiatric disorders.[20] A study of inner city youths with asthma found that 30% of children had symptoms of depression consistent with a likely diagnosis of major depressive disorder.[21] Other studies using dimensional symptom measures have also found that asthmatic children score higher than healthy controls on child or parent reports of anxiety.[22–24] Group differences for depression and externalizing symptoms have emerged in some,[22,23] but not all,[24] of these studies.

Studies of clinical samples are supplemented by 2 studies of youths at high risk for the development of psychiatric problems due to low family socioeconomic status (SES)[25] or parental psychiatric status.[26] One study assessed psychiatric symptoms using the Beck Depression Inventory (BDI), the Beck Anxiety Inventory (BAI), and the Brief Symptom Inventory to assess psychiatric symptoms in adolescents with asthma and a control group without asthma from a Job Corps program.[25] Those with asthma scored significantly higher on all 3 measures. In addition, more members of the asthma group had scores in the more severe ranges of the BAI and BDI. Thus, even in a sample at high risk for psychiatric problems based on their SES status, those with asthma were at greater risk for experiencing symptoms of anxiety and depression. In a different study of children at risk for anxiety disorders, offspring of parents with either panic disorder (PD), any nonpanic anxiety or mood disorder (NPD), or no psychiatric disorder (NODIS) were assessed. Rates of atopic disorders in children of parents with PD were significantly higher (17%) than in children with either NPD or NODIS (8%). Among the children, separation anxiety disorder (SAD) was associated with atopic disorders at a rate of 22% among children with SAD compared to children with no psychiatric disorder (5%). Children with other disorders were intermediate in atopy risk (12%).[26]

Taken together, these findings support a putative association between atopic and internalizing disorders in youth. However, to our knowledge, previous studies have not systematically addressed the specificity of this association by distinguishing between children with "pure" internalizing disorders and those with comorbid externalizing disorders. The primary aim of this study was to address this issue within the population of youths being treated in specialized child and adolescent psychiatry clinics. A focus on this population has 2 advantages. Because internalizing and externalizing disorders are among the most prevalent types of childhood psychiatric disorders evaluated in the clinical setting, the question of specificity can be addressed with a relatively small sample. Further, assessment of these disorders within the clinical setting permits a unique opportunity to maximize the clinical management of both types of problems. Based on previous findings, we hypothesized that psychiatrically ill youths with current DSM-IV internalizing disorders (anxiety and/or depression) would be more likely to have a lifetime history of atopic disorders compared to youths without DSM-IV internalizing disorders. Importantly, we also examined whether the association was specific to internalizing disorders by comparing the likelihood of having an atopic disorder among youths with internalizing disorders and no associated externalizing comorbidity to the group with comorbid internalizing and externalizing disorders and other diagnostic groups.

METHOD

Subjects

Subjects were 184 (102 female) youths evaluated by a board certified child and adolescent psychiatrist in a child and adolescent psychiatry outpatient clinic. Youths referred consecutively to this clinic for psychiatric evaluation from September 1, 2001, through December 31, 2002, were chosen to reduce sample-selection bias. The sample was predominantly white (93.5%), with 1.6% African American, 2.2% Asian, and 2.7% other. The mean age was 13.2 years (SD = 3.54, range = 4–20 years). The protocol was approved by the Mayo Clinic Institutional Review Board, and parents of subjects provided written informed consent.

Assessment

Each subject and his/her parent(s) participated in a comprehensive clinical psychiatric evaluation by an experienced, board certified child and adolescent psychiatrist (M.J.S.) to determine the presence of current DSM-IV psychiatric disorders.[27] A comprehensive, multisystem medical history was also obtained including information about lifetime diagnosis of any atopic disorder (asthma, allergic rhinitis, atopic dermatitis, and/or urticaria). A second child and adolescent psychiatrist (M.I.), who was blind to the results of the clinical interview, reviewed all the subjects' medical charts to check for medically documented evidence of any lifetime diagnosis of atopic disorders. The lifetime prevalence of atopic disorders (defined as any atopic disorders since birth) for this study was determined by combining the medical information obtained from clinical interview with the child's parent and the chart review.

Diagnostic Groups

All subjects were diagnosed with at least 1 psychiatric disorder by clinical interview. Four groups were defined based on current psychiatric diagnoses. One group included youths with DSM-IV internalizing disorders only (IDO) (major depressive disorder, depressive disorder not otherwise specified [NOS], dysthymic disorder, generalized anxiety disorder, anxiety disorder NOS, separation anxiety disorder, panic disorder, agoraphobia, specific phobia, obsessive-compulsive disorder, social phobia, adjustment disorder with depressed mood, adjustment disorder with anxiety, or adjustment disorder with mixed anxiety and depressed mood). A second group was composed of youths with comorbid internalizing and externalizing disorders (COIE) (internalizing disorder plus attention-deficit/hyperactivity disorder, oppositional defiant disorder, and/or conduct disorder). A third group consisted of youths with externalizing disorders only (EDO). The fourth group was composed of youths without internalizing or externalizing disorders (WIE) but with other psychiatric disorders (learning disorders, substance-related disorders, somatoform disorders, tic disorders, enuresis, reactive attachment disorder, or developmental disorders).

Analyses

Descriptive analyses were conducted to ascertain the percentage of youths in each diagnostic category, and those with and without a lifetime history of atopic disorders. Additional analyses described the breakdown of these subgroups by age and gender.

Two preliminary χ^2 contingency analyses were conducted to aid in decisions defining the major variables. The first analysis assessed whether there were any differences in the likelihood of having a lifetime history of atopic disorders in youths having one or both of the 2 major forms of internalizing disorders (i.e., depression only, N = 53; anxiety only, N = 31; or both depression and anxiety, N = 26). No significant differences were found (N = 110, $\chi^2 = 1.15$, df = 2, p = .56). Thus, for the major analyses, the broad-band category of internalizing disorders was used. The second analysis assessed whether there was a greater likelihood of internalizing disorders with an increasing number of atopic disorders (i.e., a "dose-response relationship"). No significant differences were found between youths with 1 (N = 64) versus 2 or more (N = 41) atopic disorders (N = 105, $\chi^2 = 0.04$, df = 1, p = .83). Thus, a dichotomous measure (none vs. 1 or more) of lifetime history of atopic disorders was used in all analyses.

Logistic regression analyses were used to address the 2 major research questions. Because previous studies have shown both age and gender differences in the distributions of atopic and internalizing disorders,[28,29] they were included as covariates in all analyses. We also checked for interactions of age and gender with internalizing disorders; no significant interactions were found. To test our hypothesis that, among psychiatrically ill youths, those with DSM-IV internalizing disorders would be more likely than youths without DSM-IV internalizing disorders to have a lifetime history of atopic disorders, the first logistic regression analysis combined the subgroups with internalizing disorders (IDO + COIE) and the subgroups without internalizing disorders (EDO + WIE; defined as the reference category) into a dichotomous variable. Next, to examine if the association was specific to internalizing disorders, we used the 4 diagnostic subgroups, with WIE as the reference group.

RESULTS

Sample Characteristics

Approximately two thirds of the youths (67.4%, N = 124) were diagnosed as having an internalizing disorder, either alone (59.8%, N = 110) or in combination with

Table 1. Psychiatric and Atopic Disorders by Gender and Age

Characteristic	Total Sample, N = 184 (100%)	Internalizing Disorders Only,[a] N = 110 (59.8%)	Comorbid Internalizing and Externalizing Disorders, N = 14 (7.6%)	Externalizing Disorders Only,[b] N = 24 (13.0%)	Without Internalizing or Externalizing Disorders, N = 36 (19.6%)	Atopic Disorders,[c] N = 105 (57.1%)	Without Atopic Disorders, N = 79 (42.9%)
Sex, N (%)							
Female	102 (55.4)	70 (63.6)	6 (42.9)	7 (29.2)	19 (52.8)	60 (57.1)	42 (53.2)
Male	82 (44.6)	40 (36.4)	8 (57.1)	17 (70.8)	17 (47.2)	45 (42.9)	37 (46.8)
Age, y							
Mean	13.2	13.7	11.9	12	12.6	13.6	12.6
Range	4–20	5–20	8–18	7–18	4–20	5–19	4–20

[a]Internalizing disorders only: separation anxiety disorder, panic disorder, agoraphobia, specific phobia, obsessive-compulsive disorder, generalized anxiety disorder, social phobia, anxiety disorder not otherwise specified, major depressive disorder, dysthymic disorder, depressive disorder not otherwise specified, adjustment disorder with anxiety, adjustment disorder with depressed mood, and adjustment disorder with anxiety and depressed mood.
[b]Externalizing disorders only: attention-deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder.
[c]Atopic disorders: asthma, allergic rhinitis, urticaria, and atopic dermatitis.

Figure 1. Atopic Disorders and Internalizing vs. NonInternalizing Disorders

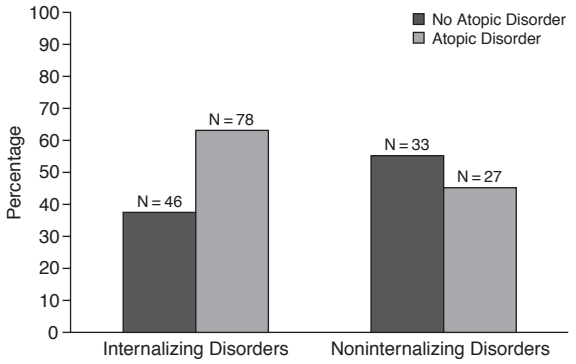
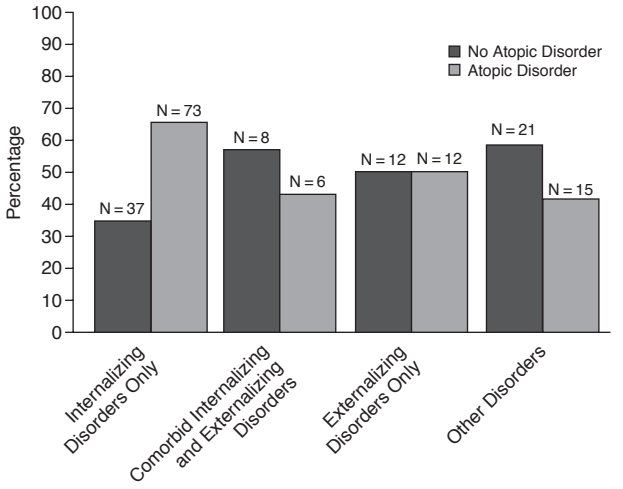


Figure 2. Atopic Disorders and "Pure" Internalizing vs. Other Psychiatric Disorders



an externalizing disorder (7.6%, N = 14). Of the 110 with "pure" internalizing disorders, 42 (38.2%) had depressive disorders, 27 (24.5%) had anxiety disorders, 20 (18.2%) had both depressive and anxiety disorders, 11 (10.0%) had adjustment disorders with depressed mood, 4 (3.6%) had adjustment disorders with anxiety, and 6 (5.5%) had adjustment disorders with anxiety and depressed mood.

Over half of the youths (57.1%, N = 105) had a lifetime history of atopic disorders. Of these, 20 subjects had chart review evidence of an atopic disorder that was not reported at the time of the clinical interview (10.9% of the total sample and 19.1% of the atopic cases). Forty-one subjects (22.3% of the total sample) had 2 or more atopic disorders. Table 1 summarizes the gender and age distributions of the diagnostic and atopic disorders subgroups.

Atopic Disorders Among Youths With and Without Internalizing Disorders

The results of the first logistic regression analysis showed that, among psychiatrically ill youths, those with internalizing disorders were almost twice as likely as those with noninternalizing disorders to have a lifetime history of atopic disorders (odds ratio [OR] = 1.95, p = .04, 95% CI = 1.02 to 3.73). The actual percentages of youths with and without atopic disorders in each group are shown in Figure 1.

Importantly, when the 4 diagnostic subgroups were considered, the results showed that the association of internalizing disorders with atopic disorders was specific to the "pure" internalizing group. As shown in Figure 2, the percentage of youths with comorbid internalizing and externalizing disorders (COIE) who had a lifetime history of atopic disorders was very similar to the percentage for the 2 noninternalizing subgroups (EDO and WIE) and different from the percentage for the "pure" internalizing subgroup (IDO). The results of the logistic regression analysis show that, compared with the WIE subgroup (defined

as the reference group), youths with "pure" internalizing disorders were more than twice as likely to have a lifetime history of atopic disorders (OR = 2.40, p = .03, 95% CI = 1.09 to 5.30); however, neither of the 2 subgroups with externalizing disorders, with (COIE) or without (EDO) internalizing disorders, were significantly more likely to have a lifetime history of atopic disorders (OR = 0.95, p = .93, 95% CI = 0.26 to 3.45; and OR = 1.24, p = .70, 95% CI = 0.42 to 3.67, respectively).

DISCUSSION

The aim of this study was to investigate the specificity of the association between internalizing disorders and atopic disorders in a child and adolescent psychiatric clinical sample. Results indicated that, among psychiatrically ill youths, those with internalizing disorders were significantly more likely to have a lifetime history of atopic disorders compared to those with noninternalizing disorders. Moreover, the association was found to be specific for "pure" internalizing disorders; the likelihood of having a lifetime history of atopic disorders did not differ significantly among youths with comorbid internalizing and externalizing disorders, youths with externalizing disorders only, or those with other disorders.

These findings add to the growing body of evidence supporting an association between anxiety, depressive, and allergic disorders. It is the first investigation, to our knowledge, to examine the impact of comorbid psychiatric disorders on the specificity of the association between internalizing and atopic disorders and, in particular, the effect of comorbid externalizing disorders. Importantly, the results extend previous findings by suggesting that the association between internalizing and atopic disorders may be specific for pure forms of anxiety and depressive disorders.

The association between pure internalizing disorders and atopic disorders suggests that these psychiatric and medical disorders may share risk factors and underlying pathways that contribute to the etiopathogenesis of both types of disorders. Although the basis of the relationship between these disorders is very likely multifactorial, including both biological and psychosocial components, increasing interest has focused on potentially shared genetic, inflammatory, and stress-response mechanisms. Evidence of genetic vulnerability is suggested by "top-down" and "bottom-up" family studies that report an association between internalizing and atopic disorders among first-degree relatives.[26,30,31] Twin studies support these findings but also indicate that the association is only partially accounted for by shared genetic vulnerability,[32,33] that is, other biological and environmental influences are also very likely present. Inflammation is one such mechanism believed to contribute to the etiology of both types of disorders. Proinflammatory cytokines (e.g., IL-6, tumor necrosis factor alfa) and acute phase proteins (e.g., C-reactive protein) have been implicated in the pathophysiology of internalizing disorders, especially depression, and inflammatory medical disorders such as atopic allergies.[34] Related investigations have begun to explore possible "triggers" of the inflammatory response and subsequent expression of comorbid medical and psychiatric clinical symptoms. A confluence of studies suggests that psychosocial stress may activate inflammatory mediators, directly and indirectly, through complex interactions of the autonomic nervous system and neuroendocrine systems including the hypothalamic pituitary adrenal axis.[34,35] Findings may, in part, explain the association of psychosocial stress with the onset and exacerbation of both atopic and psychiatric illnesses.[36–38]

The identification of common etiologic pathways is clinically important to the development of novel treatments that result in meaningful improvement in both internalizing and allergic symptoms. Recent studies have begun to explore the clinical impact of primary psychiatric or medical interventions for the treatment of comorbid internalizing and atopic disorders. For example, an improvement in both depressive symptoms and asthma severity was reported in a recent study of citalopram for the treatment of asthma and major depressive symptoms in adults.[39] Results may reflect, in part, an anti-inflammatory effect of citalopram. Studies suggest that antidepressant medications may inhibit the release or production of proinflammatory cytokines while stimulating the production of antiinflammatory cytokines.[40] Cytokine-focused treatments hold similar promise, as suggested in a recent investigation that reported improvement in depressive symptoms by blocking the action of the proinflammatory cytokine tumor necrosis factor alfa.[41] Additional studies are needed to examine the physiologic impact of psychosocial interventions, e.g., relaxation, stress management, and psychotherapy, for the treatment of comorbid internalizing and atopic disorders. Although limited, past studies suggest that these interventions may have a positive impact on both allergic and internalizing symptoms.[42–45]

There are several limitations to the current study. Although psychiatric interviews were conducted by an experienced child and adolescent psychiatrist, diagnoses were based on clinical interview due to assessment time constraints within a traditional clinical setting. The use of a semistructured diagnostic interview would permit a more objective assessment of current and lifetime disorders. A history of atopic disorders was based upon report or clinical chart documentation and did not include rigorous confirmation of atopic diagnostic criteria or biological measures of atopy such as a skin-prick test. Analyses did not control for other potential confounding variables such as medication use (psychiatric or allergic), other nonallergy medical disorders, or family psychiatric or medical disorders. In addition, study subgroups were limited in size.

Further, because this was a study of a clinical sample, results may not generalize to the community setting. Despite these limitations, findings importantly highlight the need to examine the impact of psychiatric comorbidity on the association between internalizing and atopic disorders. Results of this study suggest that the association is specific for pure internalizing disorders.

Additional studies are needed to replicate these findings, including further assessment of the association of atopic disorders, specifically with pure anxiety and depressive disorders. Future studies should also consider including both dichotomous (i.e., diagnosis) and continuous (i.e., symptom) parent and child psychiatric measures in assessing the association between these psychiatric and allergic conditions. Finally, additional studies are needed to more rigorously investigate associated risk factors and shared etiologic mechanisms to explain the specificity of the putative association of atopic and pure internalizing disorders for the subsequent development of effective prevention and treatment interventions.

Drug name: citalopram (Celexa and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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