Association between allergy and anxiety disorders in youth

Pavel A. Kovalenko, Christina W. Hoven, Ping Wu, Judith Wicks, Donald J. Mandell, Quyen Tiet

Objective: Studies have documented associations between anxiety disorders and allergy in adults, but these associations have not been studied extensively in children. The objective of this study is to examine the associations between allergy and six anxiety disorders (AD) in youth.

Method: This is a data analysis of two epidemiologic-services studies: (i) alternative service use patterns of youth with serious emotional disturbance (n = 936), and (ii) methods for the epidemiology of child and adolescent mental disorders (n = 1285). Child psychiatric diagnoses were measured by the diagnostic interview schedule for children. Allergy was assessed by the service utilization and risk factors interview.

Results: Among ADs, the strongest association found was between allergy and panic disorder (adjusted odds ratio 5.0; $p \leq 0.001$). Associations of allergy and the other ADs do not seem to be clinically significant.

Conclusions: Findings suggest that in some patients panic disorder may be associated with hypersensitivity of immune system. Panic disorder should be considered in anxious children reporting allergy when no organic cause of allergy is found, and likewise allergy should considered in children with panic disorder.

Key words: allergy, anxiety, conditioning, panic disorder.

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Studies have documented associations between anxiety disorders and allergy in adults [1–4], but these associations have not been studied extensively in children. Study of the association of allergy and anxiety disorders (ADs) in children is important due to the high prevalence rates of both allergic diseases and ADs in youth.

Several studies have demonstrated a significant association between allergy and both state and trait anxiety [3–8]. Additionally, shy patients have been found to experience a poorer course and outcome of treatment for allergies [9]. A strong association of allergy and panic disorder (PD) has been found in clinical psychiatric and medical samples [1,10]. Considerable research has demonstrated an association between asthma and symptoms of AD, and a strong association between asthma and PD, as summarized in a review article [11]. Although asthma in some cases can be caused by allergy [12], asthmatic patients often do not have an allergy and allergic patients often do not have asthma. Therefore, the association between allergy and ADs may be different from the association between asthma and ADs, and thus requiring special examination. Because the association of asthma and ADs is relatively well studied [11], it is only briefly addressed here.

Anxiety can be manifested by a number of somatic symptoms, such as dizziness, dyspnoea, nausea, sweating, and increased heart rate. The same symptoms also frequently occur during an allergic reaction. A few

Pavel Kovalenko, Research Associate (Correspondence)

Virginia Institute for Psychiatric and Behavioural Genetics, Virginia Commonwealth University, 800 East Leigh Street, PO Box 980126, Richmond, VA, 23298–0126, USA. Email: kovalenp@yahoo.com

Christina W. Hoven, Research Scientist; Ping Wu, Research Scientist; Judith Wicks, Research Specialist; Donald J. Mandell, Research Scientist; Quyen Tiet, Research Scientist

Department of Child Psychiatry, Columbia University and New York State Psychiatric Institute, New York, USA

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studies have demonstrated that physicians sometimes fail to find evidence for allergic or immunological mechanisms underlying symptoms attributed to allergy [13,14], pointing to the possibility of misdiagnosis. For example, anxiety may masquerade as food allergy [15]. It was even proposed that a psychiatric diagnosis ought to be considered for patients who claim to have symptoms of allergy for which no organic cause can be found [14]. When a biological reaction associated with anxiety mimics an allergic reaction, it may cause the release of histamine, an amino acid that is released during conditions of inflammation, stress, and allergy [16]. Histamine plays an important role in the body's protective response to injury or invasion by foreign substances. It is responsible for some visible symptoms of an allergic attack, such as redness of the skin, wheezing, sneezing, and tissue swelling. A secretion of histamine may be mediated by antibodies, acetylcholine, opioids, and adrenocorticotropic hormone [16]. Although fear may cause the release of histamine, thus imitating allergy, the association between allergy and PD is reported to be very strong in adults in both clinical and epidemiological samples and cannot be explained by misdiagnosis alone [1].

The relationship between allergy and ADs is complicated, may be bidirectional, and may differ in patients [6,8,17]. Because allergy may cause strong somatic symptoms and may even be life threatening, an allergic reaction might be viewed as a psychologically traumatic event. Hence, allergy may increase symptom counts in more than one AD. An extensive search of the literature did not reveal any systematic research which compares the associations of allergy and ADs in children. This study addresses the question whether the associations between allergy and ADs in children are similar. Because a strong association between PD and allergy has been found in adults, the primary hypothesis is that allergy is most strongly associated with symptoms of PD in children. Because the role of panic attacks in the onset of agoraphobia is unclear [18], attention is also paid to the association between allergy and agoraphobia.

Method

Samples

1. Methods for the Epidemiology of Child and Adolescent Mental Disorders (MECA Study) [19]. This four-site community sample (New York (n = 360), Connecticut (n = 314), Puerto Rico (n = 312), Georgia (n = 299)) consists of 1285 youth, including 604 girls and 681 boys aged 9–17 years. The community sample in the MECA study constitutes a randomly selected representative sample [19–21]. The New York MECA sample was drawn from Westchester County.

2. Alternative Service Use Patterns of Youth with Serious Emotional Disturbance (Westchester County Study, Principal Investigator: Christina Hoven) [22–24]. This is an epidemiological-services study (n = 936) of psychopathology of children and adolescents in five service systems (juvenile justice, special education, child welfare, mental health, substance use; n = 763), and in the community (n = 173) from Westchester County, New York. In this study, 391 girls and 545 boys aged 9–17 years and their parent/guardian were interviewed.

To collect data on the service samples, 62 representative service agencies were selected from all five child service systems, according to the number and proportion of youth served by that agency. Youth were then randomly selected from each of the representative agencies/schools. Representative public schools with special education programmes were selected according to school district size and geographical location. Random samples were recruited from the entire juvenile justice and child welfare systems. Mental health and substance use agencies were selected to obtain representation by size, level of service intensity, and geographical location.

Data for the 1458 children from the combined community samples (1285 children from the MECA study and 173 children from the Westchester County Study) and the 763 children from service systems are included in this study (n = 2221).

Measures

Both the MECA and Westchester County Studies used essentially the same instruments [19,20,22]. Child psychiatric diagnoses were measured by DISC 2.3 [25], which is based on DSM-III-R criteria for psychiatric disorders. The following ADs were assessed: agoraphobia, overanxious disorder (OAD), obsessive-compulsive disorder (OCD), panic disorder (PD), separation anxiety disorder (SAD), and social phobia (SOPH). Criteria for agoraphobia did not include criteria for PD and criteria for PD did not include criteria for agoraphobia. By definition, cases with PD were not excluded from cases with agoraphobia and cases with agoraphobia were not excluded from cases with PD. Therefore, comorbidity between agoraphobia and PD is possible. In this study, diagnoses were considered without disorder-specific impairment [25]. Responses to both stem and secondary (follow up) questions were included in the symptom scales. Symptoms of ADs include somatic symptoms. These are only symptoms for which 'no physical basis can be established' (DSM-III-R). Among agoraphobia items 5% concerned somatic symptoms, 15% in OAD, 0% in OCD, 48% in PD, 13% in SAD, and 15% in SOPH.

In the MECA and Westchester County Studies Child medical conditions were measured by the Service Utilization and Risk Factors (SURF) Interview [19]. SURF Interview included parent reports on the life history of the child's allergy and asthma. Methods used to establish the presence of ADs were completely independent of the criteria used to establish history of allergy and asthma. Ten children had a missing report of allergy history and were excluded from the analysis.

Unfortunately, only the Westchester County Study interview was supplemented by DSM-IV criteria for mental disorders. Therefore, we had to use DSM-III-R assessment. Generalized anxiety disorder (GAD) of DSM-IV now subsumes DSM-III-R OAD of childhood. Overanxious disorder and GAD represent essentially the same disorder (adjusted odds ratio is 53.0).

Procedures

A computer-assisted version of the DISC-2.3 [25] was administered in both studies.

To collect data on service system samples, representative agencies and schools were selected from the five child service systems in Westchester County, New York, according to the number and proportion of children and adolescents served [22–24]. Youth were randomly selected from each of the representative agencies or schools.

Procedures for the community sample in the Westchester County Study replicated procedures for the MECA study in terms of sampling methodology, instruments, and field procedures. The same team collected data on the Westchester Couny sample and New York MECA sample. In this study the MECA and Westchester County Samples are combined to increase power of statistical tests. There were no dropouts in the study because only one interview session was conducted. The compliance rate of the MECA Study is 86%. The compliance rate of the Westchester County Study is 89.6%.

Statistical analysis

Descriptive analyses were conducted first. The prevalence of allergy and ADs was compared across different socio-demographic groups.

Non-parametric methods – logistic regression and Spearman correlation analyses – were used to assess the associations between allergy and ADs. Logistic regression was also used to estimate adjusted odds ratios between allergy and specific DISC items for every AD. Associations between ADs were also evaluated to better understand the associations between allergy and ADs.

The Spearman correlation analysis was applied to symptom counts because when AD is analysed at the diagnostic level, important subclinical information that is present in symptom counts is lost. For example, subclinical panic attacks may be robust predictors of PD later in life [26]. When prevalence rates of disorders are low and there is a number of covariates, estimates from logistic regression may be unstable, but Spearman correlation analysis applied to symptom counts provide more reliable results.

The Spearman correlation analysis was also applied to symptom counts, which did not include somatic symptoms. This was done to determine whether somatic items explain the significant association between allergy and ADs.

A number of covariates were tested, including age, gender, service system, geographical location of the interview, IQ, and externalizing disorders. On the basis of descriptive, logistic regression, and Spearman correlation analyses, age, gender, service system, and geographical location of the interview were chosen as covariates to take into account that the sample was not balanced across different demographic groups. Adding IQ score, externalizing disorders, or substance use disorders to the covariates does not change the results.

Due to comorbidity in symptoms among different ADs, a significant association between allergy and the symptom count of a particular AD may in fact be secondary to such associations and the symptom counts of other ADs. Therefore, the association between allergy and the symptom count of each AD was tested, using symptom counts of the other ADs as covariates. Significant Spearman correlation between allergy and, for example, a symptom count of PD when symptom counts of the other ADs are used as covariates, may indicate that an association between allergy and particular symptoms of PD is specific. Results of similar tests obtained from logistic regression are not provided here, because some estimates were unstable due to the excessive amount of covariates and the low prevalence of PD in children.

Results

The percentages of children with anxiety diagnoses and an allergy are presented in Table 1.

In the combined sample, 24.3% of children have a history of allergy without asthma, 7.1% have a history of asthma without allergy, and 9.8% have a history of both allergy and asthma. Because the association of asthma and PD is relatively well studied, it is only briefly addressed here.

Adjusted odds ratios (AOR) between diagnoses for the combined community and service system sample were estimated. Demographic variables were used as covariates. This analysis serves the purpose of facilitating a better understanding of the associations between allergy and ADs. Thus, if allergy is strongly associated with one AD, and is not associated with another one, a low odds ratio between these two ADs would help to explain the difference in associations, suggesting that not only allergy, but the other risk factors, may affect these two ADs differently.

The lowest AOR was observed between PD and SOPH (AOR = 1.6). The second lowest AOR is between PD and agoraphobia (AOR = 2.2). For all other paires of ADs AOR ranged from 3.5 (PD and SAD) to 14.4 (OAD and OCD). All AORs were significant, except between PD and agoraphobia and between PD and SOPH.

Table 2 presents adjusted and unadjusted odds ratios and Spearman correlation coefficients of allergy and AD diagnoses for the combined community and service system samples. Each odds ratio and Spearman correlation coefficient is estimated with and without demographic variables as covariates. Odds ratios between allergy and anxiety diagnosis, adjusted on diagnosis of all other ADs, are not presented because some estimates of AOR were unstable due to the low prevalence of AD. Allergy is strongly associated with a diagnosis of PD (Table 2, odds ratios).

Symptom counts, which include somatic items, show an association of allergy and ADs similar to that for diagnosis, when symptom counts of the remaining ADs are used as covariates. Removing somatic items from the symptom counts of agoraphobia, OAD, SAD, and SOPH barely changes either the adjusted or unadjusted Spearman correlation coefficients between symptom counts for these disorders and allergy. Removing somatic items from the symptom counts of PD substantially reduces Spearman correlation coefficients between allergy and symptom count of PD, rendering three of the four correlation coefficients in Table 3 not significant. When OAD was replaced with generalized anxiety disorder it did not change the basic results.

The association of asthma and PD was not as strong as the association of allergy and PD (AOR = 2.3, $p = 0.0764$). When children with a history of asthma were excluded, the unadjusted odds ratio (OR) between allergy and PD was still significant (OR = 5.4, $p = 0.0018$). Here, the unadjusted OR between allergy and PD is reported because, although covariates produced almost no change in the OR and p-value, they caused optimization problems in the logistic regression.

The AOR between specific DISC items and allergy was estimated, which helped to explain the associations between allergy and ADs. Table 3 presents two items with the highest AOR for every disorder.

Table 1. Prevalence rates of anxiety disorder, allergy, and asthma (%): youth 9–17 years of age in the community and service systems (n = 2221)

Anxiety disorders, allergy, asthma, and demographics	Prevalence in service sample (n = 763)	Prevalence in community samples, (n = 1458)	Prevalence in combined sample, (n = 2221)
Agoraphobia	10.7	6.8*	8.1
Overanxious disorder	17.2	10.9*	13.1
Obsessive-compulsive disorder	4.5	2.7*	3.3
Panic disorder	1.7	0.7*	1.1
Separation anxiety disorder	16.2	6.8*	10.0
Social phobia	20.5	14.7*	16.7
Any anxiety disorder	40.2	27.1*	31.6
Any allergy	30.4	36.0	34.1
Sinus allergy	18.4	20.7	19.9
Hospitalization for allergies	1.3	3.0	2.4
Asthma	20.1	15.2*	16.9
Age	14.0	13.4*	13.6

*Logistic regression model shows significant differences in the prevalence of anxiety disorder in the service systems and community samples with demographic variables as covariates.

Table 2. Association of allergy with anxiety diagnoses and symptom counts (n = 2211)

Anxiety disorder	Odds Ratio		Spearman correlation coefficient		Spearman correlation coefficient[a]	
	Unadjusted[b]	Adjusted[c]	Unadjusted[b]	Adjusted[c]	Unadjusted[b]	Adjusted[c]
Agoraphobia	1.0	1.1	0.025	0.039	–0.010	–0.003
			0.025[d]	0.038[d]	– 0.005[d]	0.002[d]
Overanxious disorder	1.5[e]	1.6[f]	0.082[g]	0.091[g]	0.052[h]	0.046[h]
			0.0079[fd]	0.087[gd]	0.058[ed]	0.051[hd]
Obsessive-compulsive disorder	1.3	1.3	0.030	0.039	–0.029	–0.029
			0.030[d]	0.039[d]	–0.029[d]	–0.029[d]
Panic disorder	4.5[f]	5.0[f]	0.085[g]	0.092[g]	0.059[e]	0.059[e]
			0.038[d]	0.044[hd]	0.012[d]	0.012[d]
Separation anxiety disorder	1.2[h]	1.3[h]	0.057[e]	0.081[f]	0.008	0.027
			0.052[hd]	0.075[fd]	0.013[d]	0.031[d]
Social phobia	1.1	1.1	0.043[h]	0.049[h]	–0.001	–0.001
			0.040[d]	0.047[hd]	0.002[d]	0.002[d]

[a]Spearman partial correlation coefficients between a symptom count of an AD and allergy, with symptom counts of the other ADs used as partial variables; [b]Unadjusted on demographic variables; [c]Adjusted on demographic variables; [d]Correlation coefficients for symptom counts without somatic items.
[h]$p \le 0.05$; [e]$p \le 0.01$; [f]$p \le 0.001$; [g]$p \le 0.0001$.

In general, allergy was strongly associated with somatic items and items indicating frequency, duration, or severity of symptoms. Allergy was less associated with general questions about symptoms, which do not specify frequency, duration, or severity of the pathology. Among the somatic symptoms of PD, the AOR was the highest between allergy and dyspnea (AOR = 2.2, p = 0.0024).

Analysis revealed similar odds ratios using DSM-III-R and DSM-IV diagnoses when association between diagnoses and allergy was assessed, but there was not enough power to conduct the statistical tests due to small sample of DSM-IV diagnoses.

Discussion

The important association identified in the analyses was between allergy and PD, compared to the AOR between allergy and the other ADs. This finding is consistent with the results of adult studies [1] and confirms the primary hypothesis of this study.

Logistic regression analysis revealed a high AOR between allergy and PD (Table 2), but Spearman correlation

Table 3. Two items of each anxiety disorder interview which are associated with allergy with the highest odds ratios (n = 2211)

Anxiety Disorder	Item	Adjusted odds ratio[a]
Agoraphobia	When you are afraid of leaving the house/being in car/being in large crowded place/being in a large open space do you feel cold?	1.6
	In the past 6 months, have you been afraid to go out by yourself?	1.3[b]
Overanxious disorder	Are you generally healthy? [This question was asked if child very worried about health or about getting sick at least once a week.]	3.1[c]
	In the past six months, have you had a lot of other aches and pains that are not headaches or stomach aches?	2.0[d]
Obsessive-compulsive disorder	Do you have thoughts or ideas that bother you going in your mind almost every day?	2.0[c]
	Do you think something bad might happen if you don't put your clothes in certain order or get dressed in a certain way?	1.9[b]
Panic disorder	Has feeling scared or panicked kept you from doing things you would like to do or should do?	4.6[e]
	Has there been time when you were frightened or panicked at least 4 times within 4 weeks?	3.7[e]
Separation anxiety disorder	When you were supposed to go out on your own, did you complain a lot about stomach aches or headaches for 2 weeks or longer?	2.6[c]
	In the past 6 months, has worrying like this [referred to a list of 18 separation anxiety items] caused problems at home?	1.8[d]
Social Phobia	Does being nervous or anxious when going to a place with a lot of people/meeting new people bother you a lot?	1.5[b]
	Does being always afraid of going to a place with a lot of people/meeting new people keep you from doing things you would like to do or should do?	1.5[b]

[a]Adjusted on demographic variables. [b]$p \leq 0.05$; [e]$p \leq 0.01$; [c]$p \leq 0.001$; [d]$p \leq 0.0001$.

coefficients between allergy and symptom count of PD were not particularly high. This was because the association between allergy and symptom counts in children who do not have a diagnosis of PD was weak. Allergy is strongly related to PD, but not to each symptom of PD. To be diagnosed with PD it is necessary to have at least 3 somatic symptoms. The presence of all 3 symptoms may affect the association between allergy and PD synergistically.

Removing somatic items from symptom counts of PD substantially reduces Spearman correlation coefficients between allergy and the symptom count of PD, possibly because somatic symptoms are the basis of PD. Without somatic items, it is no longer PD.

Because the onset age of allergy is normally earlier than the onset age of PD, it is possible that among patients with both allergy and PD, PD is secondary to allergy. Developmental mechanisms of PD secondary to allergy may be different. First, an allergic reaction can cause somatic symptoms, which may provoke anxiety and cause a panic attack. Second, panic attacks may be a result of classical conditioning to stimuli, which can cause allergy [1]. Third, because a response of the immune system can be conditioned [17], a panic attack may follow an allergic reaction when the allergic reaction is not caused by environmental factors, but is a conditioned response to a particular situation usually associated with the presence of an allergen. Fourth, certain types of antibodies may affect the CNS, thus leading to PD [27].

Allergy or allergic-like reactions may also be secondary to PD. First, panic may induce an imbalance of neuroimmunomodulation [28]. Second, patients with PD may be more likely to develop conditioning of the immune system compared to normal controls due to acquired hypersensitivity of the CNS to harmful stimuli. Third, fear may mimic an allergic reaction [16].

It is possible that both allergy and PD may be caused by other factors. A sodium lactate infusion was used to study patients with multiple chemical sensitivity syndrome [10], which is considered to be a type of allergy. Sodium lactate infusion is a technique used to study ADs, particularly PD. The fact that multiple chemical sensitivity syndrome (MCS) patients exhibited a positive symptomatic response to sodium lactate and that most of them had been diagnosed with PD, may indicate that allergy has a neurobiologic basis similar to that of PD [10], suggesting that in some subgroups of patients, ADs and allergy may result from the same dysfunction of the

central nervous system (CNS). Control of the immune system by the CNS is a very complex process [29]. The CNS modulates immune system functions through releasing neurotransmitters and neuropeptides [29]. A number of abnormalities in the CNS may cause both ADs and allergy. First, there is evidence of the immunoregulatory role of dopamine, and serotonine [29–31], which are also involved in the regulation of anxiety. Therefore, abnormalities in serotonergic and/or dopaminergic neurones may cause both ADs and allergy. Second, central and peripheral benzodiazepine receptors may contribute to the effect of anxiety on the immune system, because benzodiazepine decreases anxiety symptoms and suppresses the immune system [32]. Third, the limbic system has been suggested to be central to anxiety [33]. Because increased limbic system symptomatology and sensitizability was also found in young adults with MCS [34], limbic system hypersensitivity may be related to both allergy and ADs. Fourth, the locus ceruleus has been implicated in both panic attacks [35] and immune responsiveness [36]. Therefore, pathologic activity of the locus ceruleus may be associated with both panic attacks and immune overreaction in some patients. It is not clear whether abnormalities in locus ceruleus activity are directly related to allergy and panic attacks or whether these abnormalities are caused by abnormalities in other brain regions.

Although the association between combined OAD diagnosis and allergy is statistically significant, the AOR is low and an association does not seem to be clinically significant. Allergy may cause anxiety about food and environment and therefore contribute to symptoms of overall anxiety. Symptoms of OAD may be associated with many medical conditions, which may also affect symptoms of other ADs. Results do not reveal that somatic items substantially contribute to the appearance of an association between allergy and OAD (Table 2).

A weak association between allergy and SAD was observed. Some medical conditions require increased parental involvement and children may habituate to such parental monitoring and attention, and consequently develop symptoms of separation anxiety [37]. Allergy may be such a medical condition, which may explain the significance of the association between allergy and SAD. The results demonstrate that somatic items may not substantially contribute to the appearance of an association between allergy and SAD.

Allergy is significantly correlated with the symptom counts of four ADs, but when symptom counts of the other ADs are used as covariates only the associations with PD and OAD remain significant (column 3 of Table 2). This might indicate that the association between allergy and some ADs is partially explained by comorbidity of AD symptoms. The associations of allergy with agoraphobia, SOPH, and OCD seem particularly weak. In fact, the association between allergy and the diagnosis of agoraphobia is the weakest among all ADs. Comorbidity of PD and agoraphobia was also not significant. Although PD in adults is highly comorbid with agoraphobia, such association may be weak in adolescents [18]. This helps to explain our finding of high comorbidity between PD and allergy and low comorbidity between agoraphobia and allergy.

Longitudinal research is required to test hypotheses about causal relationships between ADs or between allergy and ADs because cross-sectional data do not allow us to study causality. Allergy was present in 69.6% of PD cases only. Therefore, the association between PD and allergy cannot be considered as a universal finding.

Because some symptoms of allergy and PD are the same, the results suggest that PD should be considered in anxious children reporting allergy when no organic cause of allergy is found, and allergy considered in children with PD.

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