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Allergen Specific IgE, Number and Timing of Past Suicide Attempts, and Instability in Patients with Recurrent Mood Disorders

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Abstract

Suicide and decompensation of mental illness peak in spring and, to a lesser extent, in fall. Several recent studies reported that suicide and decompensation peaks coincided with spring and fall aeroallergen peaks. Allergic symptoms occur as the result of a complex biochemical cascade initiated by IgE antibodies (sensitization) and allergens (triggers). Animal models have shown molecular/neurochemical changes in the brain, as well as relevant behavioral changes associated with this IgE-mediated biochemical cascade. These factors suggest that seasonal allergy could precipitate suicidality and mood instability. In the current study, we compared the prior suicide attempt and history of decompensation of mood disorders in allergen sensitive vs nonsensitive patients. Further, we compared the ratio of events (attempts and decompensations) during the allergy season to events occurring during the rest of the year. Patients with Major Depressive Disorder or Bipolar I or II Disorder (n=80) were studied. There were no statistical differences in any measurement performed between the allergen sensitive and nonsensitive patients. These negative results are not consistent with recent epidemiological studies supporting a predictive association between allergy and categorical measures of suicidality (ideation, attempts, and completion). Clinical samples are likely not adequate to study less than strong predictive associations with suicide and suicide risk factors.

Keywords

Environment; allergy; mood disorders; suicide; psychiatry

Introduction

Suicide attempts and completed suicides are common results of decompensation among persons with bipolar disorder (BPD) and major depressive disorder (MDD). Spring is the most common season for depression exacerbation, hospital admissions for depression, and electroconvulsive therapy (ECT) use (1-7). In addition, hospital admissions for

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bipolar depression also peak in April (8,9). Studies conducted in several countries located in both hemispheres have revealed a strong relationship between spring decompensation and increases in suicide (6,10,11). There is also a less robust and less replicated fall peak in suicides that is worthy of investigation.

To date, no studies have adequately explained the spring and fall peaks in either decompensation or suicide. The most commonly considered cause of this relationship is a suspected association between suicide and photoperiod, changes in photoperiod, and light intensity (12,13). Closer examination, however, reveals that spring suicide occurrence peaks in April and May which precedes peak photoperiod and is considerably later than the interval of greatest change in photoperiod (14-17). A gender effect of the seasonal peak in suicide has been reported (16,18,19). However, photoperiod is longest around the Summer Solstice in late June and photoperiodic changes peak around the spring equinox in March and the fall equinox in September (13,20-24).

Seasonal aeroallergens, such as pollen from deciduous trees (e.g., maple, elm, oak) and weeds (e.g. ragweed), peak in early spring and late summer/early fall, respectively. The highest incidence of allergic rhinoconjunctivitis occurs during spring peaks of atmospheric tree-pollen (25-27). Tree pollen allergies affect 10-30% of adults (25), while ragweed-induced hay fever affects more than 25% of adults (28). The prevalence of sensitization to these allergens far exceeds the prevalence of either BPD or MDD (12). Timonen et al. (29,30) reported that atopy is more prevalent in patients with depression and in those persons who have a family history of depression.

Allergic disease results from a hypersensitivity to otherwise harmless environmental substances. Allergen sensitization can be assessed by measuring specific IgE antibodies directed against allergens in serum. In sensitized individuals, allergen exposure causes the immune system to release cytokines. Similar cytokines given during treatment and research studies have induced depression and, occasionally, suicidal thoughts (31,32). Recent epidemiologic and clinical studies have shown a relationship between the timing of seasonal peaks in mood decompensation and suicide and peaks in aeroallergens. Timonen et al. (29,30,33) and Marshall et al. (34) recently reported a strong association between allergic disease and depression. In a recent study (35), we found a significant relationship between worsening mood and pollen exposure in pollen sensitive, but otherwise healthy, college students. We also reported an increased incidence of suicide during and after peak pollen periods (19). An increased suicide rate could be associated not only with exposure to allergens, but also with a previous diagnosis of allergic disease (36).

Additional support for the relationship between decompensation of mood disorders, suicide, and aeroallergen-induced inflammation comes from postmortem studies of the human brain, where increased markers of allergic inflammation have been found in suicide victims. Upper respiratory immune responses to intranasally-instilled bacterial lipopolysaccharides (which increase TNF-alpha transcription in the brain) may act as a mediator for depressive-like symptoms in rats (37). The brains of Brown Norway rats that were sensitized and exposed to tree pollen expressed higher levels of inflammatory markers (e.g. interleukin-5, interleukin-6, and interleukin-13) than did brains from saline-exposed control rats (38).

In consideration of the relationship between allergen-induced upper respiratory inflammation, depression, and suicide, we hypothesized that sensitization to seasonal allergens might be associated with a higher level of mood instability and with a higher number of lifetime suicide attempts in persons with MDD or BPD. Therefore, in the

current study, we have tested whether there is a temporal relationship between seasonal allergen exposure, the presence of IgE antibodies specific to those seasonal allergens, and seasonal mood instability in persons with MDD and BPD. We expected that seasonal allergen sensitive individuals with MDD and BPD would exhibit a higher Instability Index and Suicide Attempt Index during the atmospheric tree pollen period (in spring) or ragweed pollen period (in late summer-early fall), depending on the individual's sensitivities, than would similarly diagnosed non-allergic controls.

Methods

We recruited a convenience sample (n=80) of patients with MDD and BPD who had a history of suicide attempts, from a variety of sources including inpatient psychiatric facilities, private psychiatrists' offices, hospital-based clinics, and stand-alone clinics. Inclusion and exclusion criteria are summarized in Table 1. Charts were prescreened as approved by the Institutional Review Board of the University of Maryland School of Medicine. A staff member approached patients who met the entrance criteria to request permission for us to interview them. Patients were then given informed consent and the Mini-Mental State Exam (MMSE) (39), on which they had to score >27 for inclusion.

Designation into the sensitized test group or non-sensitized control group was made based on the results of the allergen-specific IgE analysis (described in Instruments section), with both the participant and rater being masked to the IgE antibody results. Demographics of participants in both groups are presented in Table 2.

Periods of High Pollen

The pollen periods were selected after initially reviewing the airborne pollen concentrations from local pollen counting stations enrolled in the Aeroallergen Monitoring Network of the American Academy of Allergy Asthma and Immunology. Due to our location in the Southern mid-Atlantic region, the tree and ragweed pollen windows followed those expected based on historical data: April through May for tree pollen and September through October for ragweed pollen.

Data Collection and Instruments

Raters who were trained in psychiatric testing techniques guided the subjects through a rigorous 90-minute interview, which consisted of a series of semi-structured and structured interview instruments. These instruments included the Structured Clinical Interview for the DSM-IV for Axis I Disorders (SCID) (40) to verify a diagnosis. Since the primary purpose of the SCID was as a gold standard screening tool, we selected only those modules that related to mood, psychotic, and substance use disorders. An additional benefit of the SCID is its excellent history module that provided a useful timeline and comparison for verification of information collected with subsequent tools. Only patients who "passed" the SCID continued on to the remaining modules.

The first evaluation instrument in the interview was the Columbia Suicide History Form (CSH) (41). This instrument is a semistructured interview that is used to document prior lifetime suicide attempts, including indicators of lethality. The resulting data identifies ambiguous from actual suicide attempts. Raters then employed the retrospective self-version of the NIMH Life Chart Methodology (LCM) (42). This instrument documents mood episodes, the number of suicide attempts, and the number of ER admissions during the past two years. This instrument, combined with the lifetime history given during the SCID, permitted researchers to estimate the participants' seasonal patterns of decompensation and suicidality.

This outcome of these instruments produced an Instability Index (INIX) and a Suicide Attempt Index (SAI). The INIX was calculated from the LCM and the SCID timeline by the following equation:

$$[(\text{admissions} \geq 5 \text{ days} \times 5) + (\text{admissions} < 5 \text{ days} \times 3) + (\text{ER w/o admission} \times 2)] / \text{participant's age}$$

The SAI was calculated from the CSH and the SCID timeline, as:

$$\# \text{ of actual suicide attempts} / \text{participant's age}$$

After the interview, a Registered Nurse collected serum for IgE antibody analysis. The Multi-allergen screen (Phadiatop, Kalamazoo, MI) was selected for the primary multi-allergen screening assay for IgE antibody since it detects IgE antibodies specific for a panel of 15 aeroallergens that elicit the majority of aeroallergen related allergic disease. Results of this analysis are highly predictive of an individual's predisposition to manifest rhinitis and other aeroallergen induced allergic symptoms. The Phadiatop results were reported as positive or negative. Its diagnostic sensitivity ranges from 75-95% and its diagnostic specificity ranges from 85-95% (43). The Phadiatop screen positive sera underwent a subsequent specific IgE antibody analysis for individual specificities including oak, beech, maple, elm, birch, ash, sycamore, poplar, and ragweed pollen using the Pharmacia ImmunoCAP 250 (Kalamazoo, MI). Analyses were performed in the Johns Hopkins Dermatology Allergy and Clinical Immunology (DACI) Reference laboratory using a positive/negative cut-off threshold of 0.35 kIU/L (44).

Statistical Analysis

Categorical variables for patient characteristics were summarized by proportions and percents, and Phadiatop positive and negative groups were compared by Pearson chi-square tests. Phadiatop positive and negative groups were compared on prior suicide history (number of suicide attempts / age) and prior stability (considering attempts, admissions, and ER visits) using t-tests. Similarly, the positive and negative groups were compared on the ratio of suicides in spring to those in the entire year, and the same ratio for hospital and ER admissions with t-tests.

Results

No statistical differences were observed between the two sensitized and non-sensitized groups involving either the overall or the spring ratios. Differences between the groups were not close to statistical significance, with all p-values > 0.38 (see Table 3).

These data failed to support the working hypothesis that either the number or timing of past suicide attempts or the instability measures were associated with aeroallergen sensitization as identified by a positive serological IgE antibody status.

Discussion

The conclusions of the present study contrast with those of recent studies suggesting a relationship between either the seasonality of suicide and allergen exposure (19) or the seasonality of suicide and a prior history of allergic disease (36,45). The current study data do not support a relationship between the presence of allergen sensitization and number and timing of prior suicide attempts. Our negative findings may be a result of several factors. First, the study design may have had limited power with a relatively small sample size of 80 subjects. While a larger sample size may have provided more power for

examining differences in the prevalence rates between allergic and non-allergic subjects, the required size to potentially see a significant difference, based on the differences observed in this study, could exceed 5,000 subjects, which, practically, is not achievable in clinical samples.

Second, the study included patients on psychotropic medications, and those with comorbid substance abuse and personality disorders. These factors may have counteracted the measurable effect of the allergic response on suicidality. Subjects taking psychotropic medications, however, were not excluded from the study for several reasons. It would have resulted in the study recruitment falling short of the study's goals. Moreover, patients who are medication free but have a history of major affective disorders and suicide attempts do not represent the typical patient population. Additionally, it would have been ethically questionable to request that participants discontinue prescribed medications for any period in order to participate in a study of this nature, particularly considering a large proportion of individuals were recruited from an inpatient hospital setting.

With this in mind, patients with personality disorders and substance abuse are more likely to have histories of ambiguous suicide attempts. Furthermore, patients from these groups might use the hospital and ER more frequently than would patients with BPD or MDD who do not have those comorbidities (46,47). However, because personality disorders and substance use disorders are frequently comorbid with MDD and BPD (48-50), including these diagnoses in the study increased our overall ability to generalize the findings.

Suicide attempts are the strongest predictor of completed suicide (51). However, a recent study by Lindqvist and colleagues (52) supports the conclusion of previous studies suggesting that persons who attempt suicide are significantly different in suicidal intent from those who complete suicide. To address the temporality of suicide attempts, we asked participants to provide a timeline of their lifetime suicide attempts, hospitalizations, and ER visits. Because corroboration with medical records could not be accomplished, the history may not be temporally accurate.

Another potential limitation was our reliance on a self-reporting instrument to ascertain information on attempted suicides, as accurate identification of "attempted" suicide is particularly difficult to determine from a personal history, in part because of the associated stigma and tendency to avoid a hospital admission when possible. A very recent report (Welch et al 2008) supports an association between allergy and presence or absence of history of suicidal attempts (53). Moreover, the authors reported a relationship between history of suicidal ideation and allergy. The authors used data from the National Comorbidity Survey (NCS-R), a US representative sample of 9882 people aged 18 years or older. Logistic regression models were used with adjustment for age, sex, and race. A positive relationship between a history of allergy and suicidal ideation, with an adjusted odds ratio of 1.37 (95% CI, 1.13 – 1.65), was found; after controlling for depression, the odds ratio was 1.27 (95% CI, 1.04 – 1.54). Correlation of allergy and a history of suicide attempts was also significant (1.07 – 1.84), and remained significant after controlling for depression, with somewhat lower odds ratios 1.32 (1.003 – 1.74). In contrast to our model using the number or prior suicide attempts in attempters only as dependant variables, Welch et al. (2008) compared those with vs. without suicidal ideation or attempt in an epidemiological sample. It is likely that the relationship between allergy and suicidality is not strong enough to be uncovered in clinical samples, and may have little impact in predicting suicide and suicide attempts in a cross-sectional situation, such as an emergency room. However, this becomes relevant for long term follow-up in patients who

share allergy (a highly prevalent condition) and other risk factors for suicide. As changes in allergy symptoms correlate to changes in depression symptoms (54), it is likely that the relationship between allergy and suicide risk factors is a state level relationship, rather than only a trait (vulnerability) level relationship. As such, there is more potential for interventions and responsibility to invest in uncovering and addressing pathophysiological mechanisms.

It will be critical to find out if allergic rhinitis is distinct from other forms of intranasal inflammation (37) in worsening suicide risk factors. The nose has a privileged communication with the brain: for instance, cytokines (which may result from inflammatory processes in the nose) produced or delivered to the nasal mucosa may reach the brain from bypassing the blood-brain barrier (55,56).

We have recently reported increased mRNA levels for cytokines involved in allergic inflammation in the orbitofrontal cortex of victims of suicide (57). Future research on the mechanisms underlying predictive associations between allergy, suicide, and suicide risk factors is paramount to uncovering novel preventative and therapeutic targets and interventions.

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Table 1

Study inclusion/exclusion criteria

Inclusion criteria		Exclusion criteria	
1	Aged 18-65	1	Clinical diagnosis of schizophrenia or schizophreniform disorder
2	Clinical diagnosis of MDD, BPD I, or BPD II made at least two years before enrollment (NOTE: Diagnosis verified by Structured Clinical Interview for the DSM-IV (40))	2	Cognitive disorder (or MMSE<27)
3	Lifetime history of at least one non-ambiguous suicide attempt	3	Diagnosis and treatment of asthma within two years of enrollment
		4	Current treatment with medications that could interfere with IgE levels (e.g., corticosteroids)
		5	History of parasite infections
		6	History of bronchopulmonary aspergillosis

Table 2
Characteristics of participants in total and by Phadiatop status

Variable	Total	Phadiatop status		p value
		Positive	Negative	
	n=81	n=33	n=48	
Gender (%)				
Male	43.2	51.5	37.5	0.21
Female	56.8	48.5	62.5	
Race (%)				
White	59.3	39.4	72.9	0.02
Black	34.6	54.6	20.8	
Hispanic	2.5	3.0	2.1	
Other	3.7	3.0	4.2	
Diagnosis (%)				
MDD	38.3	39.4	37.5	0.46
Bipolar I	60.5	57.6	62.5	
Bipolar other	1.2	3.0	0.0	
History of Psychotic symptoms during mood episodes (%)	75.3	78.8	72.9	0.55
Tree pollen positive (%)	12.4	30.3	0.0	0.0001
Ragweed positive (%)	8.6	21.2	0.0	0.0008
Phadiatop positive (%)	40.7	--	--	

Table 3
Comparisons of aeroallergen sensitive and non-sensitive groups on suicide attempts and instability index

Variable	Total	Phadiatop status		p value *
		Positive	Negative	
	n=81	n=33	n=48	
Suicide attempt index mean (SD)	0.113 (0.102)	0.105 (0.091)	0.119 (0.109)	0.56
Ratio spring suicide attempts mean (SD)	0.226 (0.340)	0.186 (0.292)	0.254 (0.370)	0.38
Instability index mean (SD)	0.072 (0.062)	0.072 (0.064)	0.073 (0.061)	0.96
Ratio spring instability mean (SD)	0.379 (0.408)	0.359 (0.429)	0.394 (0.398)	0.72

*
 p values from t-test comparisons.