Effects of Seasonal Allergic Rhinitis on Fatigue Levels and Mood

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**Objective:** Many allergy patients complain of fatigue, moodiness, and dysphoria during their allergy seasons. This study evaluated the effect of symptomatic allergic rhinitis on both fatigue level and mood. **Method:** Symptomatic ragweed allergic rhinitis patients on no medications and healthy control subjects completed the Multi-Dimensional Fatigue Inventory and the Positive Affect-Negative Affect mood rating scales in an in-out-in ragweed season research design. **Results:** During ragweed seasons, allergic patients reported higher levels of general fatigue and mental fatigue, but not physical fatigue, as well as reduced motivation. Patients described experiencing feelings of greater sadness and reduced pleasurable engagement. Increased anxiety or emotional distress was not reported. **Conclusions:** These findings suggest that having allergic reactions to ragweed pollen causes significant fatigue and mood changes in at least a subgroup of patients. Psychoneuroimmunology and medical genetics research suggests that allergic reactions engender biochemical changes that directly affect the central nervous system. **Key words:** allergic rhinitis, fatigue, depression, mood.

**INTRODUCTION**

Some allergists have reported that allergic reactions can cause CNS symptoms in some individuals such as confusion, irritability, anxiety, sleepiness, apathy, and depression (1, 2). These claims are unproven and controversial.

Several older clinical studies have found a surprisingly high co-occurrence of allergy in patients with depression as opposed to other psychiatric patients and control subjects, raising the possibility of a causal relationship (3–5). In a study of 397 college students, Bell et al. found that students with a history of clinically diagnosed depression had much higher rates of both self-reported (71% vs. 43%) and professionally diagnosed (64% vs. 35%) allergic disorders than students without a reported history of clinical depression (6). More recently, Addolorato and colleagues reported higher rates of depression as measured by the Zung self-rating depression scale in females with allergic rhinitis (20.8%) and vasomotor rhinitis (23.8%) than control subjects (10.9%). However, these group differences were not statistically significant (7).

A causal relationship between having allergic rhinitis (hay fever) in particular and major depression is also suggested by two large epidemiological studies. Cohen et al. studied a cohort of over 700 randomly selected children from ages 1 to 10 years to young adulthood. Cross sectional and longitudinal analyses revealed that children with hay fever at ages 5 to 6 were more than twice as likely (odds ratio = 2.68) to develop a major depressive episode over the next 17 years than those without this illness (8). Hurwitz and Morgenstern (9) did another cross-sectional analysis of survey data from 6836 adults between the ages of 20 and 39. They found that respondents with hay fever were, once again, twice as likely (odds ratio = 2.03) to have been diagnosed with major depression in the past 12 months. Respondents were even more likely to have been diagnosed with major depression if they had a history of having received allergy shots or a positive skin-test reaction (odds ratio = 3.82). Major depressive disorder was diagnosed using the Diagnostic Interview Schedule in both of these epidemiological studies.

Marshall and Colon (10) gave allergy and control subjects mood ratings in, out of, and in allergy seasons. Results suggested that having allergic reactions lowered positive affect but not negative affect. Both theoretical and empirical evidence suggests that low positive affect, the loss of pleasurable engagement, is a characteristic of biochemically mediated depression (11). However, allergic subjects in the study had been recruited precisely because they reported having significant depression symptoms with their classic rhinitis symptoms. Consequently, though none reported having major depression, the subjects may very well represent an unusual subgroup of allergic subjects.

The objective of the present study was to extend the research initiated by the Marshall and Colon study in two ways. First, the study examined the effect of symptomatic allergic reactions on not only positive and negative affect but also on fatigue levels. Second, the study was conducted using a larger group of unselected patients with classic ragweed allergic rhinitis. Specifically, it was hypothesized that seasonal allergic

CNS = central nervous system, FSL = Flinders sensitive line, IL = interleukin, MFI-20 = Multidimensional Fatigue Inventory, NA = negative affect, PA = positive affect, TNF = tumor necrosis factor.
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rhinitis patients experience fatigue and subtle changes in mood in season when having allergic reactions.

METHODS

Subjects

The study included both allergic patients and control subjects. Investigators did not preselect patients for mood, fatigue, or cognitive function complaints. Subjects ranged in age from 23 to 50. The initial study design envisioned testing subjects three times: ragweed season 1996, winter of 1997, and ragweed season of 1997. However, the ragweed season of 1997 was unusually mild and many allergic subjects were significantly less symptomatic than in previous years. Consequently, the study was extended and subjects returned for testing in the ragweed season of 1998. Thirty-two patients and 25 control subjects completed administration of the test battery in ragweed season 1996. Twenty-nine patients and 24 controls completed testing in winter 1997. 21 patients and 20 controls in ragweed season 1997, and 16 patients and 20 controls in ragweed season 1998.

Allergic and control subjects were similar with respect to age, estimated Wechsler Adult Intelligence Scale-Revised Full Scale Intelligence Quotient score, sex, and years of education (Table 1). A history of allergic symptoms and positive skin-prick tests to ragweed established a diagnosis of ragweed rhinitis as previously reported (12). Patients were not tested for perennial sensitivities, eg, mite and mold sensitivities. All subjects were in good health other than having allergic rhinitis. A medical history questionnaire and interview insured that they had no history of drug abuse or major physical or psychiatric illness that may have affected mood or fatigue levels. No subject was taking any CNS-active medication (including antihistamines) that may have affected mood or fatigue levels.

Procedure

Symptom severity scoring. Allergic subjects rated their rhinitis symptoms in the morning and before dinner beginning the first week of August for a maximum of 30 days. Nasal drainage, nasal stuffiness, sneezing, and nasal itching were rated according to the following scale: 0 = none; 1 = trivial or doubtful; 2 = mild, causing little or no discomfort; 3 = annoying, causing noticeable discomfort; 4 = moderate, causing loss of sleep but not interfering with routine activities; 5 = severe, interfering with routine activities; 6 = incapacitating. A total symptom discomfort score was the sum of the morning and evening scores. Patients came to the hospital and completed the cognitive test battery the same day they had recorded a total symptom discomfort score of 30 or greater for the previous 3 days. Thus, the patients clearly had been experiencing major allergic rhinitis symptoms for at least 3 full days before undergoing cognitive testing. They began taking their allergy medications immediately after completing this testing.

Assessment of mood. Allergy subjects completed the Positive Affect Negative Affect Scales (PANAS) each evening on the same days they were rating their allergic rhinitis symptoms in ragweed season 1996 and 1997. Control subjects, and the allergy subjects during winter 1997 only, completed the PANAS each evening for the 7 days before their undergoing cognitive testing. Two scores are derived from this scale: positive affect (PA) and negative affect (NA). Positive affect is the mood dimension reflecting feelings of enthusiasm, activity, attentiveness, and alertness. A high PA score reflects a state of high energy, pleasurable engagement, and full concentration, while a low PA score is indicative of sadness and lethargy. Negative affect reflects the degree to which a person feels distressed and/or not pleasurably engaged. A high NA score indicates a state of anger, contempt, disgust, guilt, and fear, while a low NA score suggests a state of calmness and serenity (13).

Assessment of fatigue. All subjects were given the fatigue rating scales (Multidimensional Fatigue Inventory or MFI-20) after they had completed their cognitive testing sessions in ragweed seasons 1996, 1997, and 1998 as well as in winter of 1997. This was at the same time of the day across the seasons to control for potential effects of diurnal variables (eg, arousal level) on fatigue. The MFI-20 is a 20-item self-report instrument designed to measure several dimensions of fatigue: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity (14). There are four items on each scale measuring the five dimensions. Subjects indicate on a five-point scale to what extent a particular statement applies to them, with a higher rating indicative of greater fatigue. Scores on each scale can range from 4 to 20.

Statistical Analysis

A series of repeated measures, two-way, univariate analysis of variance (ANOVA) was run to assess the differences between groups and seasons on each dependent variable. These repeated measures ANOVAs compared subjects’ MFI-20 fatigue ratings in ragweed season 1996, winter 1997, and ragweed season 1998. They compared subjects’ PANAS ratings in ragweed season 1996, winter 1997, and ragweed season 1997. Specifically, they compared the sum of the PANAS rating-scale scores for the 3 days immediately preceding the day of cognitive testing. This is the time period in which allergy patients were certain to be experiencing significant allergic reactions during ragweed seasons. If repeated measures ANOVAs were significant, t tests were also run to determine the significance of changes within groups across seasons. Nested ANOVAs using a fixed effect model were employed. Overall experimentwise alpha was not controlled because of the anticipated small effect size and small sample sizes. Pearson product moment correlations were used to examine the association between allergy symptom rating scores for the 3 days before testing and both PANAS mood scale ratings for the same 3 days and MDFI scale scores on the day of testing. All statistics were run using the Statistical Package for the Social Sciences (15).

RESULTS

Mood and fatigue rating results of allergy patients who completed and dropped out of the study were compared. One-way ANOVA revealed no significant differences between these two groups on any rating made during ragweed season 1996 or winter of 1997.

Allergy patients reported experiencing more motivational fatigue ($t = 3.62, p = .01$), activity-related

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**TABLE 1. Subject Characteristics Winter 1997 Mean (Standard Deviation)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Allergic</th>
<th>Control</th>
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</thead>
<tbody>
<tr>
<td>Education (years)</td>
<td>16.13 (2.7)</td>
<td>16.61 (2.6)</td>
</tr>
<tr>
<td>Age</td>
<td>35.9 (8.5)</td>
<td>37.5 (7.9)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>66%</td>
<td>63%</td>
</tr>
<tr>
<td>Estimated WAIS-R full scale IQ</td>
<td>109 (11)</td>
<td>114 (11)</td>
</tr>
<tr>
<td>Number of subjects</td>
<td>29</td>
<td>24</td>
</tr>
</tbody>
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fatigue \( (t = 3.04, p = .01) \), general fatigue \( (t = 3.30, p = .01) \), and mental fatigue \( (t = 3.68, p = .01) \) but not more physical fatigue \( (t = 1.02, p = .32) \) in ragweed season 1996 than in winter 1997. They also reported having more motivational fatigue \( (t = -4.76, p = .01) \), general fatigue \( (t = -2.92, p = .01) \), and mental fatigue \( (t = -2.87, p = .01) \) but not more physical fatigue \( (t = -0.92, p = .37) \) or activity-related fatigue \( (t = -1.41, p = .18) \) in ragweed season 1998 than in winter 1997. On the other hand, control subjects did not report feeling more motivational fatigue \( (t = -0.80, p = .43) \), activity-related fatigue \( (t = -0.92, p = .37) \), general fatigue \( (t = -1.40, p = .17) \), mental fatigue \( (t = -0.88, p = .39) \), or physical fatigue \( (t = -0.34, p = .74) \) in ragweed season 1996 than in winter 1997. Control subjects also did not report experiencing more motivational fatigue \( (t = 1.91, p = .07) \), general fatigue \( (t = 1.17, p = .26) \), mental fatigue \( (t = 1.58, p = .13) \), physical fatigue \( (t = 0.74, p = .47) \), or activity-related fatigue \( (t = -0.31, p = .76) \) in ragweed season 1998 than in winter 1997 (Figures 1 and 2).

The hypothesis that experiencing allergic reactions causes central nervous system fatigue was supported by statistically significant group-by-season interactions for the changes in general fatigue \( (F = 5.40, p = .01) \), mental fatigue \( (F = 6.98, p = .01) \), and motivational fatigue \( (F = 6.21, p = .01) \) from ragweed season 1996 to winter 1997 to ragweed season 1998. Interestingly, group-by-season interactions suggest that experiencing allergic reactions does not adversely affect physical fatigue \( (F = 0.80, p = .46) \) or the more closely related activity fatigue \( (F = 1.25, p = .29) \).

Positive affect (PA) scale scores of allergy patients rose from ragweed season 1996 to winter 1997 \( (t = -3.26, p = .01) \), while PA scores of control subjects \( (t = 0.44, p = .66) \) remained unchanged (Figure 3). PA scale scores decreased from winter 1997 to ragweed season 1997 for the allergy group \( (t = 3.79, p = .01) \) but did not change significantly for the control group \( (t = -1.03, p = .32) \). The finding of a statistically significant group-by-season interaction for the changes in PA from ragweed season 1996 to winter 1997 to ragweed season 1997 \( (F = 6.40, p = .01) \) supports the hypothesis that experiencing allergic reactions lowers positive affect.

In contrast, negative affect (NA) scores did not change significantly from ragweed season 1996 to winter 1997 \( (t = -0.70, p = .49) \) or from winter 1997 to ragweed season 1997 \( (t = -0.39, p = .70) \) for the allergy subjects or the control subjects \( (t = 1.01, p = .32 \text{ and } t = 0.07, p = .94, \text{ respectively}) \) (Figure 3). The group-by-season interaction was not statistically significant for changes in NA between ragweed season 1996, winter 1997, and ragweed season 1997. These results suggest that having allergic reactions is unrelated to experiencing negative affect. There were no
Fig. 2. Multidimensional Fatigue Inventory Scale ratings for general, mental, and physical fatigue by group and seasons. The mean ± 1 SD for allergic rhinitis patients and control subjects is shown. There were 32 allergic rhinitis patients in fall 1996, 29 in winter 1997, and 16 in fall 1998. Control subjects numbered 25 in fall 1996, 24 in winter 1997, and 20 in fall 1998. ** < .05 comparing fall ragweed season vs. winter scale ratings.

Fig. 3. Positive affect (PA) and negative affect (NA) scores in ragweed seasons (1996, 1997) and winter (1997) by group. ** < .05 comparing fall ragweed season vs. winter scores.
significant correlations between the patients’ allergy symptom rating scores and PANAS positive affect, PANAS negative affect, or any MDFI scale scores.

DISCUSSION

Many patients in this study voiced complaints during their allergy seasons similar to those reported by some allergists, ie, problems with fatigue, anxiety, irritability, depressed mood, and apathy (1, 2). At the very beginning of the study, patients were asked if they had any of the following problems when having allergic reactions: 69% reported increased irritability, 63% more fatigue, 41% difficulty staying awake, and 31% feeling sad. These complaints were generally supported by the behavioral ratings in this study.

Allergic patients exhibited a change in mood in their ragweed seasons. They showed a decline in positive affect (PA), a change away from a state of high energy and pleasurable engagement in winter toward a state of lethargy and sadness in ragweed seasons. This shift is contrary to studies in the general population that indicate that PA tends to be highest in the spring and lowest in the winter (16). On the other hand, having allergic reactions did not result in patients reporting experiencing more negative affect (NA), ie, more feelings of anxiety, irritability, guilt, or disgust. These changes in PA and NA across seasons replicate the findings of the earlier Marshall and Colon study (10).

Responses on the Multidimensional Fatigue Inventory clearly indicate that allergic patients felt they were experiencing greater fatigue when having allergic reactions. Interestingly, this fatigue seems to be mental rather than physical, suggesting it is the result of allergic reaction effects on the CNS. Patients reported that they have greater general fatigue during ragweed season, ie, they feel more tired and tire more easily. They also reported more motivational fatigue: they do not feel like doing as much. Patients also described having greater mental fatigue, ie, trouble concentrating, in season. In contrast, patients did not report greater fatigue in the sense that they can do less physically or are less active when experiencing allergic reactions.

Thus, allergic patients reported both a decline in alertness and attentiveness (aspects of positive affect) and more mental fatigue during their ragweed seasons. Therefore, it is not surprising that these changes in allergic patients’ emotional and mental status were accompanied by a decline in performance on tests of speed of cognitive processing and working memory, as previously reported (12).

Several explanations have been proposed regarding how experiencing allergy symptoms might engender fatigue and depressive feelings. There are very few studies that directly address this issue, and all of these explanations are speculative in nature. The traditional view is that emotional and behavioral changes associated with having allergy symptoms are the result of the physical effects of the illness and not a result of a biochemically mediated direct effect of allergy on CNS function. That is, side effects of allergy medications, nasal congestion interfering with sleep, and oxygen deficiencies (secondary to asthma) cause the reported emotional and behavioral effects, including depression, sometimes attributed to allergy (17, 18). Depression symptomatology experienced by allergic patients is considered a psychological reaction to the physical discomfort and practical inconveniences caused by allergy symptoms (19). However, two general theories have been put forward arguing that experiencing allergic reactions results in biochemical changes that directly affect CNS function.

Recent research suggests that allergic reactions might engender feelings of fatigue and depression by causing the release of proinflammatory cytokines that directly affect the CNS. The release of IL-1 beta in particular in the brain induces sickness behavior, ie, weakness, malaise, inability to concentrate, decreased appetite, depressed activity, hypersomnia, and loss of interest in usual activities (20).

There are several psychoneuroimmunologic animal studies providing substantial evidence that IL-1 beta and, to a lesser extent, TNF-alpha released by activated monocytes and macrophages in the periphery signal the brain through multiple routes. A primary route appears to be these cytokines acting in a paracrine manner at the site of their synthesis and release to activate peripheral afferent sensory neural fibers. Activation of these peripheral afferent nerves ultimately results in release of IL-1 beta within the brain (21).

One likely peripheral pathway is macrophages releasing IL-1 beta in the lung, which is heavily innervated by the vagus nerve (21). In that respect, it is very interesting that challenge with ragweed has resulted in increased IL-1 beta release from bronchial epithelial cells and bronchial lavage cells as well as nasal epithelial cells during both the immediate and late-phase allergic responses (22, 23). A correlation between IL-1 beta levels in nasal secretions and allergy symptoms in late-phase reactions has been reported (24). Research also indicates that mast cells produce TNF-alpha in response to IgE-mediated hypersensitivity reactions (25).

Research suggests that allergic inflammation can affect neural activity in a variety of ways in the CNS and autonomic nervous system (26). Studies indicate that, after antigen exposure, mediators released at the site of the allergic inflammation increase the excitabil-
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ity of vagal afferent nerves near the lung. By increasing neuronal excitability, allergic reactions make the vagus nerves much more sensitive to stimuli, increase the frequency of vagal action-potential discharge, and overall increase vagus nerve neuronal output to the CNS. This phenomenon may explain how the quite small levels of IL-beta released at the site of inflammation after experiencing allergic reactions could signal the CNS effectively and mediate the onset of sickness behaviors in the late-phase allergic response. There are human studies supporting the hypothesis that release of proinflammatory cytokines directly affects the central nervous system and engenders feelings of depression. Subjects injected with an endotoxin have exhibited increased circulating levels of TNF-alpha and IL-1 receptor antagonist as well as feelings of depressed mood (27). Several studies by Maes et al. have found increased monocyte production of IL-1 beta and IL-6 in acute episodes of major depression (28). Severely depressed patients have been found to have higher concentrations of IL-1 beta in their cerebrospinal fluid (29).

Marshall has hypothesized that allergy and depression have a common underlying neurochemistry: cholinergic hypersensitivity and beta-adrenergic hyposensitivity in both the autonomic and central nervous systems (30). It was argued that experiencing allergic reactions increases trait CNS cholinergic sensitivity, making it much more likely that the acute increase in acetylcholine release caused by stressors results in symptoms associated with excessive CNS cholinergic activity. These symptoms are very similar to the so-called vegetative symptoms of depression: lethargy, feelings of being drained, slowed thinking, and social and emotional withdrawal.

This hypothesis that genetically transmitted trait cholinergic-system hypersensitivity underlies both allergy and depression has received some preliminary support in studies involving Flinders sensitive line (FSL) rats. These rats are selectively bred for CNS cholinergic hypersensitivity and represent a major genetic model of depression (31). After being sensitized to and challenged with ovalbumin, FSL rats were more susceptible than controls in a small intestinal tissue allergic anaphylaxis model (32). After being sensitized to ovalbumin and challenged with nebulized antigen, FSL rats exhibited increased susceptibility to allergen-induced bronchoconstriction and inflammation of the airways (33).

Animal research also suggests that transient activation of the immune system results in sensitization of the hypothalamic pituitary axis similar to that seen in depression, thereby increasing an individual’s vulnerability to depression resulting from psychological stressors. In particular, exposure to IL-1 beta increases hypothalamic pituitary axis responsivity (specifically responsivity of hypothalamic corticotrophin-releasing hormone neurons) to psychological stress (34).

Thus, there is research suggesting that allergic reactions might contribute to the onset of depression by two different biochemical mechanisms: causing the release of proinflammatory cytokines and increasing CNS cholinergic-system hypersensitivity. In that respect, allergic reactions may have the same effect as psychological stressors. Animal studies suggest that psychological stressors cause release of cytokines (eg, IL-1 beta) in the CNS (35–38) as well as increase CNS cholinergic-system hypersensitivity (39–41).

Importantly, two twin studies (42, 43) suggest there is a common genetic etiology rather than a common environmental etiology for allergy and depression. Wamboldt et al. found a much greater association between allergy status and anxious/depressed behaviors for monozygotic twins (correlation = .27) than dizygotic twins (correlation = .07) (42). These results are not consistent with the viewpoint that medication side effects, oxygen deficiencies, physical discomfort, poor sleep due to congestion, or practical inconveniences caused by allergy symptoms are the cause of depression attributed to allergic reactions by many patients. Rather, the results of this twin study suggest that patients with allergy and depression/anxiety affective disorder—or a subgroup of these patients—have both these disorders because they are the result of a shared biological/developmental process that is genetically determined (42).

In conclusion, this study provides further evidence that experiencing allergic reactions engenders fatigue and depressive feelings. Research in psychoneuroimmunology and medical genetics provides support for the argument that experiencing allergic reactions induces biochemical changes that affect the central nervous system directly and produce the vegetative symptoms of depression: emotional and social withdrawal, mental fatigue, malaise, decreased activity, and loss of interest in usual activities. These allergic reactions are usually not producing all the symptoms present in major depression. For the great majority of individuals with allergic rhinitis do not report having been treated for major depression (8, 9). Rather, it appears that, when present with other factors such as chronic stress, allergic reactions might very well contribute biochemically to onset of depression in some individuals. Epidemiological and other studies suggest that having allergies does contribute in some manner to the development of depression (5–11). Therefore, research to clarify the relationship between these illnesses is clearly warranted.
REFERENCES


