

Factors that affect the allergic rhinitis response to ragweed allergen exposure

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Background: People with seasonal allergic rhinitis (SAR) respond to allergen exposure differently.

Objective: To determine the factors that affect the rate and degree of symptom development upon controlled allergen exposure.

Methods: Study participants underwent skin prick testing (SPT) to selected aeroallergens, completed the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) and the 36-Item Short Form Health Survey, and provided a detailed allergy and exposure history. Nasal eosinophil counts and late-phase responses to SPT were measured. Eligible participants underwent a 3-hour ragweed pollen exposure in the Environmental Exposure Unit, rating rhinoconjunctivitis symptoms every 30 minutes. Data were analyzed using a mixed-effects model for repeated measures.

Results: One hundred twenty-three participants completed the study. Skin test reactivity to ragweed was not correlated with the rate of symptom development or with severity. Participants with positive SPT reactions to dust mite, dog, or grass and those with self-reported symptoms to dog or cat exposure tended to develop symptoms earlier and to a greater degree by 90 minutes. Self-report of SAR symptoms during the ragweed or grass season and RQLQ scores were positively associated with the rate and degree of symptom development. No other significant associations were detected.

Conclusions: The rate of symptom development upon ragweed exposure was related to concomitant hypersensitivity to perennial allergens and grass pollen as determined by SPT and clinical history. The RQLQ was a powerful predictor of the priming response to ragweed, showing a dose-response-type association. These data suggest that a “prepriming” phenomenon is present in patients with SAR. No correlation was shown between symptomatic responses and degree of SPT reactivity.

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INTRODUCTION

Seasonal allergic rhinitis (SAR) is a common allergen-induced upper airway inflammatory disease characterized by hyperactive airway mucosae; nasal symptoms, such as rhinorrhea, sneezing, nasal congestion, and pruritus; nonnasal symptoms, such as itching of the throat, palate, or both; and conjunctival symptoms upon exposure to relevant allergens.¹ Some people with SAR develop symptoms very early in the season, on the first evidence that the reacting pollen is present in the environment, whereas others do not develop symptoms until much later. Likewise, there are differences in the severity of responses during the pollen season. This naturally occurring variability and dynamic clinical response to pollen exposure has also been observed in allergic individuals participating in clinical trials using the Environmental Exposure

Unit (EEU). Participants in EEU trials are exposed to controlled levels of ragweed pollen at concentrations known to generate the full spectrum of AR symptoms.²

The EEU is a unique, internationally recognized research facility that allows for the exposure of groups of 5 to 160 volunteers to ambient levels of airborne allergens, such as ragweed pollen. In this specially designed room located at Kingston General Hospital, allergen levels can be precisely maintained at predetermined levels, and environmental variables, including air quality, temperature, humidity, and carbon dioxide levels, are tightly regulated.² With the ability to control these variables, study conditions can be reproduced on different days and at any time of the year, something that cannot be achieved with any other research model for AR.³ The EEU has gained international acceptance as a model for AR research and is accepted by the Food and Drug Administration as an appropriate study setting for determination of the onset of action or prophylaxis of antiallergic therapies.⁴

Based on the observation that an allergic individual's reactivity to a seasonal allergen increases at variable rates during the season due to the priming effect of repeated allergen exposure,⁵⁻⁷ all the studies conducted in the EEU include a “priming phase.” Volunteers that take part in EEU clinical trials vary in their requirements for priming visits, with a range from 1 to 6 sessions depending on individual responsiveness. The observed variability in the onset and severity of allergic symptoms during controlled exposure is typical of that occurring in SAR in the real world,

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thus making controlled allergen exposure via the EEU an excellent setting in which to evaluate possible factors that affect symptom development.

Elucidating the factors that affect the differing responses of persons with SAR during pollen seasons has broad implications on the allergic state. This study, using the EEU model, aimed to answer some of the questions about concomitant sensitivities to indoor antigens or other outdoor allergens and their importance in the induction of reactivity to specific seasonal allergens. We also evaluated the size of the epicutaneous response to the seasonal allergen as a predictor of symptom development, the relevance of late-phase responses to skin prick testing, and the effect of attendant exposure to respiratory irritants on SAR symptom generation. Gathering such information should not only shed light on factors that affect or enhance symptom development but also should provide insight into the relationships of different antigens in the production of seasonal symptoms. The primary objective of the present study was to identify which factors, if any, were associated with more rapid development of symptoms upon exposure to ragweed allergen in the EEU and, by extension, during the ragweed pollen season.

METHODS

Study Design

This study was conducted at Kingston General Hospital in affiliation with Queen's University. All the participants (or guardians for those aged <18 years) provided written informed consent before study entry. The trial protocol, amendments, and informed consent documents were approved by the Queen's University Health Sciences and Affiliated Teaching Hospitals research ethics board, and the study was conducted according to Good Clinical Practice standards and International Conference on Harmonization guidelines.

Participants

Participants were 16 years or older with a minimum 2-year history of SAR and a positive skin prick test reaction in the past 12 months confirming hypersensitivity to short ragweed pollen. The inclusion and exclusion criteria were reviewed to ensure that participants were in good health and free of any clinically significant disease that would have interfered with the study schedule or procedures or compromised the individual's safety.

Potential participants were excluded if they had a respiratory tract infection in the 2 weeks before their priming visit, rhinitis medicamentosa, nasal structural abnormalities that substantially impaired airflow, or other clinically significant medical conditions that might interfere with the study or the required treatment. Participants who were dependent on nasal, oral, or ocular decongestants; nasal topical antihistamines; or nasal corticosteroids were also excluded. Medications used to treat inflammatory respiratory conditions and nasal and ocular allergy symptoms, including antihistamines, decongestants, cromolyn sodium, all corticosteroids (except for low-potency topical corticosteroids), montelukast, nasal

and ocular saline, and oral anticholinergics required specific washout periods before the priming visit ranging from 12 hours to 2 months. Maintenance immunotherapy was permitted. Participants who did not observe the prescribed washout periods for prohibited medications were ineligible.

Screening Visit

At the screening visit, a medical history was taken, including SAR history and medication use. Skin prick testing was performed to the following allergens: short ragweed, mixed ragweed, mixed grasses, mixed trees, dust mite (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), dog hair, cat pelt, and molds endemic to the Kingston region, including *Aspergillus*, *Alternaria*, *Penicillium*, and *Cladosporium* (*Hormodendrum*). Participants completed a questionnaire package that documented demographic data, self-report of "hay fever" season symptoms, other allergic history (food and drugs), and exposure history to other allergens and irritants; the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ);^{8,9} and the Medical Outcomes Study 36-Item Short Form Health Survey, a nonspecific quality of life instrument.^{10,11} In addition, participants underwent nasal smears to determine the presence of eosinophilia, and they were asked to measure the presence and size of late-phase reactivity 8 to 12 hours after the screening visit.

Pollen Exposure (Priming Visit)

At the pollen exposure visit, participant eligibility and medication use were reviewed to ensure that all the participants still met the eligibility requirements. Participants were exposed to short ragweed pollen (*Ambrosia artemisiifolia*) (Greer Laboratories, Lenoir, North Carolina) for 3 hours in the EEU at a concentration of 3500 ± 500 grains/m³. Seven Rotorod samplers (Sampling Technologies Inc, Minnetonka, Minnesota) positioned throughout the participant seating area were used to monitor pollen levels every 30 minutes and to adjust the pollen levels as required. During pollen exposure, participants were asked to record symptom scores on diary cards every 30 minutes.

Outcomes

Participants rated the following symptoms: runny nose, nasal congestion, sneezing, itchy/red/watery eyes, and itchy nose/palate/throat using a severity scale from 0 to 3 corresponding to none (symptom is completely absent), mild (symptom is present but not bothersome), moderate (symptom is bothersome but tolerable), and severe (symptom is hard to tolerate, desiring treatment). A total symptom score (TSS) was calculated by adding the scores for all individual symptoms (maximum possible score, 15). The primary outcome was the longitudinal TSS response during the 3-hour exposure to ragweed allergen and at 90 minutes in particular.

Statistical Analyses

The TSS curves were modeled by a second-order polynomial. A mixed-effects regression model with unstructured within-subject correlation was used to account for the dependence

induced by the repeated measures design. Likelihood ratio tests with 3 *df* were used to compare the overall shape (intercept, slope, and curvature) of the curves between groups. In addition, the model was used to compare the expected difference between groups at 90 minutes. Estimates were calculated by maximum likelihood as implemented in the SAS V8.2 MIXED procedure. Time was centered at 90 minutes so that the model intercept provided an estimate of the mean TSS at 90 minutes. Likelihood ratio tests, Akaike information criterion, and Schwarz Bayesian criterion were used to confirm that the second-order polynomial model (3 *df* including the intercept) adequately fit the overall time trend, but the unstructured covariance (28 *df*) was necessary to account for the complex within-subject covariance structure across the 7 time points.¹² All *P* values are 2-sided, without adjustment for multiple comparisons.

RESULTS

One hundred forty volunteers were screened for potential participation, of which 123 were eligible and completed the study. Complete data capture was obtained for all 123 eligible individuals. The mean age of study participants was 37 years (range, 16-69 years), and 76 (61.8%) were female.

The symptoms experienced by the study group were variable and represented a range of mild to moderately severe symptom scores by completion of the 3-hour pollen exposure. Figure 1 illustrates the mean and upper and lower quartiles of TSSs across time.

Skin test reactivity to ragweed did not correlate with the rate or degree of symptom generation upon exposure to ragweed pollen in the EEU. Figure 2 depicts the quartiles of

ragweed skin test wheal responses vs TSS curve generation. The results were similarly nonsignificant when the smallest quartile was compared directly with the largest quartile (data not shown).

The quartiles of RQLQ scores exhibited a “dose-response” curve, with each quartile of lower RQLQ (ie, worse rhinitis-specific quality of life) generating a significantly more reactive curve ($P < .001$) (Fig 3). The curves of each quartile were approximately parallel across time, suggesting that the magnitude of differences in TSS were present at time 0 and persisted throughout the 3-hour exposure period. Positive responses to various skin tests were consistently associated with higher TSS scores, although statistical significance was not achieved for all tests. Specifically, individuals with positive test reactions to *D pteronyssinus* ($P = .10$ for overall curve [OC]; $P = .03$ at 90 minutes), *D farinae* ($P = .07$ OC; $P = .03$ at 90 minutes), dog hair ($P = .09$ OC; $P = .01$ at 90 minutes), cat pelt ($P = .07$ OC, $P = .07$ at 90 minutes), and grass pollen ($P = .06$ OC; $P = .009$ at 90 minutes) were more responsive at 90 minutes than were those without these sensitivities. In addition, participant self-report of symptoms upon exposure to various animals was associated with greater TSS scores, that is, dog ($P = .005$ OC; $P = .02$ at 90 minutes), cat ($P = .04$ OC; $P = .07$ at 90 minutes), and other animals ($P = .27$ OC; $P = .06$ at 90 minutes).

Visual analog scale ratings of AR symptoms by participants during the ragweed ($P = .03$ OC) and grass ($P = .04$ OC) seasons were associated with more reactive TSS curves across the entire 3-hour exposure. No other statistically significant associations were detected. Specifically, skin test positivity to the mold species and mixed trees, the presence or absence or degree of late-phase responses to the allergens

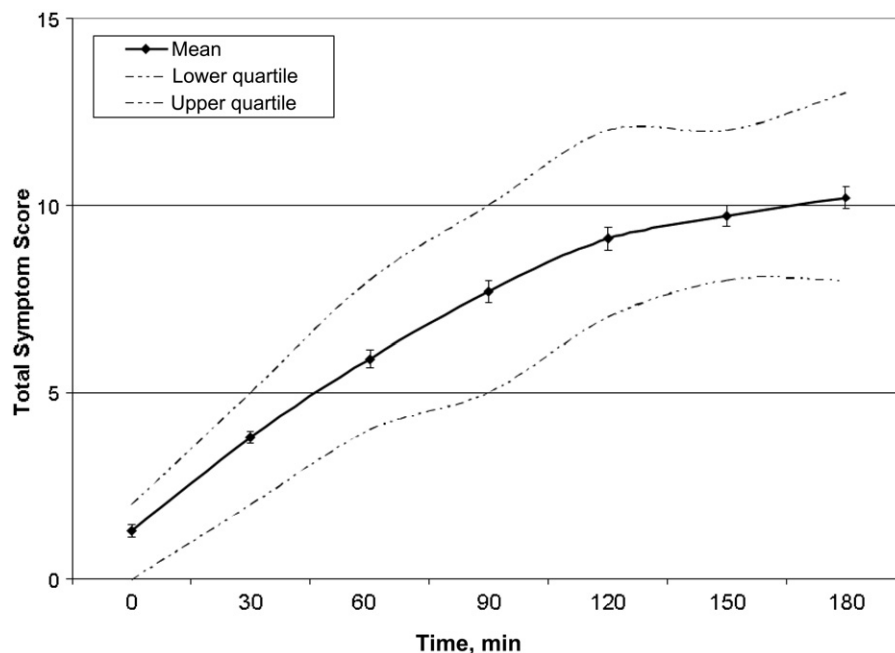


Figure 1. Total symptom scores for the 123 study participants across time. Error bars represent SEM.

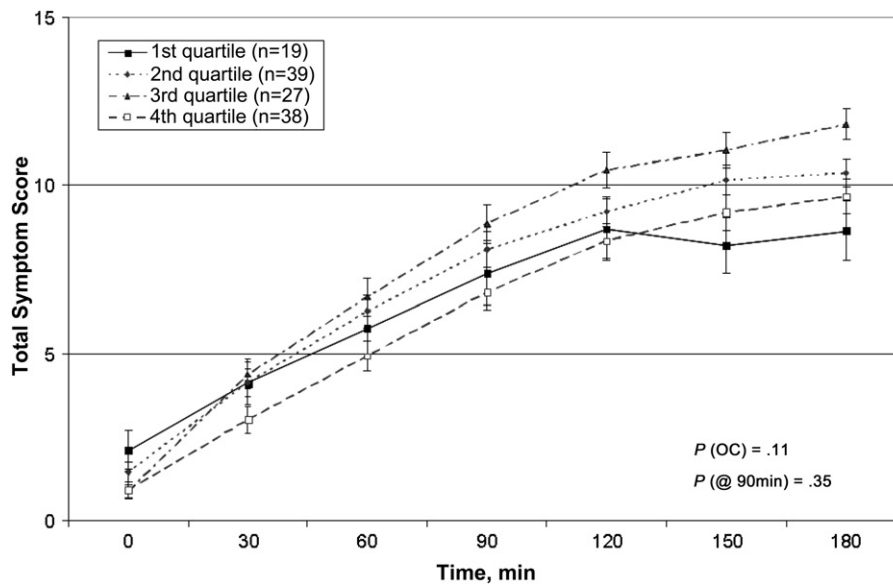


Figure 2. Mean total symptom scores across time by quartiles of skin prick test reactivity to short ragweed. The P values are derived from the likelihood ratio test of the overall curve (OC) and the expected mean difference at 90 minutes (@ 90 min). Error bars represent SEM.

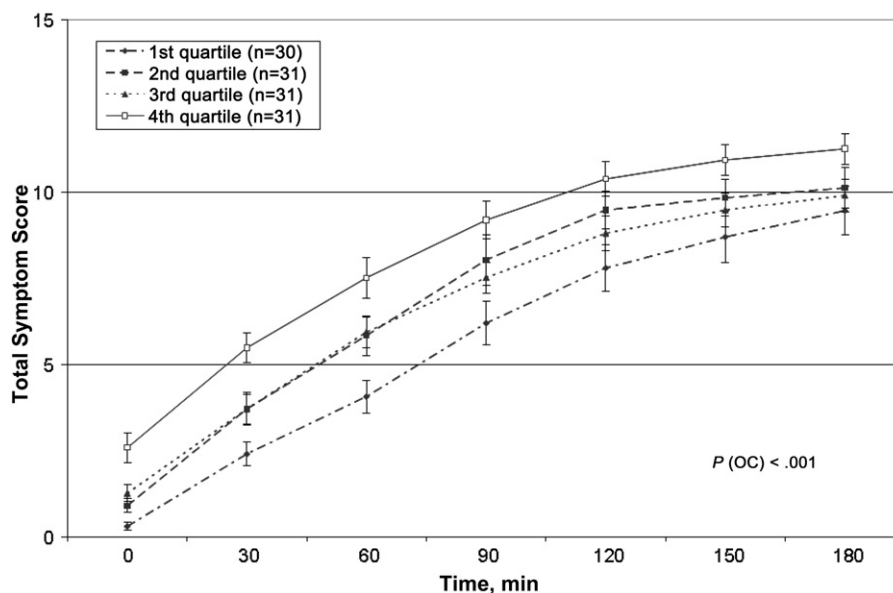


Figure 3. Mean total symptom scores across time by quartiles of Rhinoconjunctivitis Quality of Life Questionnaire scores. The P value is derived from the likelihood ratio test of the overall curve (OC). Error bars represent SEM.

tested (except for *D pteronyssinus*: $P=.006$ OC, $P=.092$ at 90 minutes), and 36-Item Short Form Health Survey scores were not related to symptom generation upon ragweed exposure. Neither were current smoking, exposure to environmental tobacco smoke, other respiratory irritant exposure, or concomitant food or drug allergy associated with symptomatic responses. The presence of nasal eosinophilia was also not statistically significant, but this may have been due to the small number of participants who had demonstrable nasal

eosinophils. A post hoc analysis to evaluate the role of polysensitization revealed no significant differences comparing the TSS curves for participants with 5 or more and 9 or more positive skin prick test results with the TSS curves for participants with fewer positive reactions.

DISCUSSION

Patients with AR are usually skin tested to determine which allergens are relevant for their symptoms. Although one

might infer that larger skin test responses would confer greater clinical significance, it has been shown that the size of the wheal and flare reaction generated via skin prick testing does not generally correlate with the degree of clinical reactivity to that allergen.¹³ This observation is further supported by studies that demonstrate a lack of correlation between reduction in wheal and flare response after treatment with H₁ antagonists and clinical SAR responses.¹⁴ What, then, determines the degree of clinical symptoms and the rapidity of symptom onset with exposure to a specific allergen in someone with a positive skin test reaction to the same allergen? The present study aimed to determine identifiable factors that were predictive of clinical responses upon exposure to ragweed pollen using a controlled allergen challenge chamber model of AR (the EEU).

This evaluation confirmed that the rate of symptom development or maximal symptom level achieved by participants exposed to ragweed pollen was unrelated to the size of their ragweed skin test response, consistent with the observations of other investigators^{5,13,15} evaluating clinical responses to various allergens. Instead, ongoing background allergic reactivity seemed to be the main influence on symptoms experienced by study participants, as evidenced by the rapidity of symptom development related to their baseline RQLQ scores. Based on the individual skin test analyses, the apparent contributing concomitant factors causing increased RQLQ scores were current sensitivities to *D pteronyssinus* and *D farinae*, dog, and cat but not indoor molds or concomitant exposure to respiratory irritants. This suggests that some participants may have retained a nonspecific “preprimed state” so that at the time of their study-related pollen exposure visit, symptoms occurred more rapidly upon ragweed exposure in the EEU, with important application to seasonal symptom development. That grass allergy seems to affect symptomatic responses to ragweed exposure (based on the skin test data and the visual analog scale scores during the grass pollen season) whereas concomitant tree pollen and mold sensitization does not was surprising. This observation may indicate a general increase in allergic burden by enhancement of the priming process, resulting in early development of seasonal symptoms. The most robust finding, however, was the current RQLQ association with increased priming reactivity, and it is evidently the best basis on which to formulate conclusions.

Contributors to the priming effect to date have not been well studied. Andersson et al¹⁵ evaluated the incidence of allergen-induced nasal hyperresponsiveness and aimed to determine whether the presence or strength of induced nasal hyperreactivity could be predicted by the size of skin prick test responses to the relevant allergen. No such relationship was established, and neither was there a connection with late-phase reactivity. Other possible predictors were not evaluated. Bacon et al⁵ were unsuccessful in inducing a priming response with a respiratory irritant, that is, ammonia. We similarly found no relationship between current irritant exposure and the priming response.

The noted variability in the priming response that prompted this study was based on the important observation that although some individuals require only 90 to 120 minutes of out-of-season pollen exposure to achieve the minimum level of symptoms for study entry, others require two, three, or, rarely, up to six 3-hour pollen exposure sessions to obtain the same level of symptoms. This study examined the symptomatic responses of individuals with and without concomitant allergies after a single 3-hour pollen exposure outside of the local ragweed pollen season. This design simulated and allowed us to study the observed variability in patient responses to allergen not only in the EEU but also at the start of the outdoor pollen season. Although the rationale behind the inclusion of a priming phase in EEU studies is to awaken allergic responsiveness in the study participants, it also has the effect of equalizing the responsiveness of the participants who meet the minimum symptom scores before randomization into a clinical trial. This “equalization” effect of priming leads to equivalent baseline symptom scores between treatment arms and consistent, reproducible study results in the EEU.^{3,16–20} For example, 2 studies^{21,22} undertaken in the EEU that had identical protocols but that were conducted with different individuals, at different times of the year, and separated in time by 4 years had equivalent baseline symptom levels among all cohorts and yielded identical results. This underscores that although individuals may prime differently, responses during study visits are balanced through priming and randomization and do not affect study outcomes.

The EEU offers a real-life experience in a controlled setting in relation to the development of AR symptoms by bringing the outdoors indoors. The findings from this study are readily applicable to real-world conditions and have confirmed the absence of skin test reaction size relevance to symptom development and indicate a minimal contribution of irritant factors. Differences in the development of SAR symptoms in the EEU setting seem to be related to a process of prepriming mediated through concomitant sensitivity to perennial allergens and the overall allergic burden. Persons with preexisting nonspecific allergic reactivity have earlier onset of symptoms upon exposure to a different allergen, but their participation in controlled allergen challenge studies has been found to be unaffected.

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