
Tobacco hypersensitivity and environmental tobacco smoke exposure in a pediatric population

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Background: Skin testing and RAST have verified the existence of tobacco-specific IgE. However, published studies report conflicting results concerning the clinical significance of tobacco IgE. Previous studies have not focused on the role of environmental tobacco smoke (ETS) as it relates to tobacco hypersensitivity (TH) in nonsmoking children.

Objective: We used nonsmoking pediatric patients to investigate the relationship between ETS and TH.

Methods: Children, ages 4 to 10 years, were prospectively enrolled. ETS exposure and smoke-triggered symptoms were recorded by questionnaire and physician history. Patients were given a skin test (ST) with a panel of aeroallergens plus tobacco extract. A ST reaction to at least one aeroallergen classified a patient as atopic; a ST reaction to tobacco classified a patient as TH.

Results: We enrolled 170 patients, mean age 7.2 years. We found 58 (34%) patients reported routine exposure to ETS and 78 (46%) patients reported ETS-induced symptoms. We found 121 (71%) atopic patients and 61 (36%) TH patients. TH was more common in atopic patients ($P < .0001$) and those routinely exposed to ETS ($P < .05$). However, TH failed to predict ETS-induced symptoms in either atopic or non-atopic patients (PPV = 0.40, NPV = 0.69).

Conclusions: We evaluated the clinical significance of TH in a nonsmoking patient population related to ETS exposure. We concluded that although TH is statistically related to atopy and ETS exposure, the low predictive values of skin testing for TH limit its clinical usefulness.

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INTRODUCTION

Environmental tobacco smoke (ETS) is an identified risk factor for multiple medical conditions, including cardiopulmonary diseases. In children, ETS is implicated as a risk factor for the

development of asthma,^{1,2} as well as a trigger for asthma exacerbations.³ Some investigators have speculated that many of the upper and lower airway symptoms associated with ETS are IgE-mediated. An allergenic glycoprotein has been purified from tobacco leaf extract, and an immunochemically similar glycoprotein has been purified from cigarette smoke condensate.⁴ Using tobacco leaf and tobacco smoke extracts, tobacco-specific IgE has been demonstrated by intracutaneous skin testing and RAST in adults^{3,4} and children.⁵ The scientific literature contains reports that support the clinical significance of tobacco hypersensitivity, including the successful use of tobacco immunotherapy.⁶ However, more recently, studies using a standardized

ETS challenge have refuted the clinical utility of skin testing with tobacco.⁷

Upon review of the literature using MEDLINE 1966 to 1999, we found no studies investigating ETS exposure as it relates to tobacco hypersensitivity in a nonsmoking pediatric population. We chose to study a pediatric population whose exposure to tobacco antigens is limited to ETS in an attempt to clarify the clinical significance of tobacco hypersensitivity.

METHODS

Patients

The Institutional Review Board of Wilford Hall Medical Center reviewed and approved all procedures involving patients. The investigators obtained informed consent from the legal guardian of minor patients before study enrollment. Nonsmoking pediatric patients, aged 4 to 10 years, referred to the Wilford Hall Medical Center Allergy Clinic for the evaluation of allergic rhinitis and/or asthma were invited to enroll. Exclusion criteria were: 1) significant concurrent medical illness, 2) active smoking, and 3) failure to complete the questionnaire or skin testing.

Questionnaire

Each patient (or patient's guardian) completed a questionnaire upon enrollment. The questionnaire defined the patient's exposure to ETS and ETS-triggered symptoms. Patients were classified as "ETS-exposed" if they were exposed to ETS more than 12 hours per week over the preceding 6 months. Patients who did not meet this definition were classified as non-exposed. In addition, concurrent illnesses, medications, food allergies and consumption of foods from the So-

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lanaceae family (green pepper, eggplant, tomato, and potato) were recorded. A physician confirmed the questionnaire responses.

Skin Testing

Aeroallergens. All patients underwent diagnostic skin testing using the modified prick method with either a panel of 45 aeroallergens or a pediatric panel of 10 aeroallergen extracts (Bayer Pharmaceutical Division, Elkhart, IN). The pediatric panel was limited to the following glycerinated (1:20 wt/vol) extracts: oak/mountain cedar mix; pigweed/ragweed GSW mix; *Aspergillus fumigatus* /*Alternaria tenuis* mix; and dog hair, cat hair, and cockroach mix. The non-glycerinated extracts included timothy/Bermuda grass mix (10,000 BAU/ml) and *Dermatophagoides farinae/pteronysinus* (10,000 allergenic units [AU]/ml) mix. A wheal of > 3mm with flare was considered a positive result.

Tobacco Leaf. All patients underwent skin testing with tobacco leaf extract (1:20 wt/vol; Miles Pharmaceutical Division, Elkhart, IN) using the modified prick method and if the result was negative, an intradermal test was applied (0.02 mL; 1:1000, wt/vol). A wheal of >5 mm with flare was considered positive for intradermal testing.

Cotinine

Cotinine, a nicotine metabolite, was used as a marker for ETS exposure. To verify the accuracy of the reported ETS exposure, we tested urine from the first 100 enrolled patients for cotinine level and compared the result with the patient's questionnaire responses.

Statistics

Statistical analysis was performed using SPSS 9.0 software (SPSS, Chicago, IL). The Student's *t* test and Pearson χ^2 tests were used where appropriate. Statistics with *P* values $\leq .05$ were considered significant.

RESULTS

One hundred seventy patients completed the study. Table 1 lists the patient characteristics. We found that 34% of our patients reported routine

Table 1. Patient Characteristics

Age data are shown as mean $\pm$ standard deviation. Unless otherwise specified, data represented absolute number and (%) of the number for each column.

	ETS-exposed	ETS-non-exposed	Total
Number (% of total)	58 (34%)	112 (66%)	170
Age (years)	7.6 $\pm$ 1.9*	7.04 $\pm$ 1.7	7.2 $\pm$ 1.8
Gender	25F, 33M	44F, 68M	69F, 101M
Asthmatic	32 (55%)	57 (51%)	89 (52%)
Atopic	43 (74%)	78 (70%)	121 (71%)
Tobacco skin test (+)	27 (47%)†	33 (29%)	60 (35%)
Atopic and tobacco skin test (+)	23	31	54‡
Non-atopic and tobacco skin test (+)	4	2	6‡
ETS-triggered symptoms	27 (47%)	51 (46%)	78 (46%)

* ETS-routine-exposed versus non-exposed; *P* = .041, Student *t* test.

† ETS-routine-exposed versus non-exposed; *P* = .027, Pearson χ^2 .

‡ Tobacco skin test (+), atopic versus non-atopic patients; *P* < .0001, Pearson χ^2 .

exposure to ETS (defined as ETS-exposed). Interestingly, the ETS-exposed group was significantly older than the non-exposed group (Student's *t* test, *P* = .041). The sex distribution and the prevalence of both asthma and atopy were similar between ETS-exposed and non-exposed patients. Overall, atopic patients demonstrated significantly more positive skin test responses to tobacco than did non-atopic patients (45% vs 12%, χ^2 ; *P* < .0001). Independent of atopy, ETS-exposed patients demonstrated significantly more positive ST results to tobacco than did non-exposed patients (47% vs 29%, χ^2 , *P* = .027). Both ETS-exposed and non-exposed groups reported a similar prevalence of ETS-triggered symptoms. The most commonly reported ETS-triggered symptoms were cough (70%), tearing (52%), ocular pruritus (41%) and sneezing (40%). The predictive values for skin testing with tobacco were calculated and found to be low: PPV = 0.40, NPV = 0.69. We found no correlation between a positive ST to tobacco and any of the aeroallergens in our panel (data not shown). Predictably, all of our patients consumed foods from the *Solanaceae* family, and no history of *Solanaceae* family food allergies was noted. Finally, we detected urinary cotinine only in ETS-exposed patients, suggesting that the questionnaire responses were accurate.

DISCUSSION

Our findings refute the hypothesis that subjective ETS-triggered symptoms in children are the result of hypersensitivity to allergenic tobacco glycoproteins. We found that tobacco hypersensitivity, defined as a positive skin test to tobacco extract, correlated with atopy and ETS exposure, but failed to correlate with self-reported ETS-triggered symptoms. Although similar findings have been reported previously in adults,^{3,7} to our knowledge, this is the first reported investigation of the clinical relationship between ETS and tobacco hypersensitivity using a pediatric population.

Environmental tobacco smoke is both chemically irritating and potentially allergenic. Multiple studies have shown that tobacco contains allergenic glycoproteins,^{4,8} and there is strong evidence that actively smoking tobacco influences the immune system. Tobacco smokers have decreased levels of IgG and IgM and elevated levels of IgE compared with nonsmokers.⁹⁻¹² Tobacco-induced IgE elevation has been associated with a concurrent rise in the eosinophil count.¹³ Interestingly, in smokers, the IgE elevation fails to decline with aging as observed in nonsmokers.^{10,12} It has been shown, and we have verified in our lab (data not presented), that tobacco allergenic glycoproteins survive combustion and remain immunologically active in

ETS.^{4,8} Clinically relevant to our study population is the finding that similar to results in active smokers, elevated IgE and eosinophil counts have been reported in children whose parents smoke.¹⁴

The elevated IgE observed in smokers and nonsmokers regularly exposed to ETS may be qualitatively different from the elevated IgE observed in atopic disease. Despite elevated IgE, smokers have decreased ST reactivity to aeroallergens.¹⁵ Exposure to tobacco smoke likely alters the cytokine milieu to favor IgE production. This hypothesis is supported by in vitro studies that demonstrated that peripheral blood mononuclear cells from smokers produce significantly more IL-4 than do peripheral blood mononuclear cells from nonsmokers.¹⁶ Increased levels of IL-4 would favor a generalized increased production of IgE that is unrelated to atopy.

In the absence of ETS exposure, a ST result positive for tobacco may have multiple explanations. Foods from the *Solanaceae* family (green pepper, eggplant, tomato, and potato) have been shown to contain glycoproteins that are immunochemically similar to the glycoprotein isolated in tobacco.^{4,17} To the best of our knowledge, significant biologic cross-reactivity in vivo remains unconfirmed. All of our patients reported routinely consuming *Solanaceae* food without adverse reactions. It has been hypothesized that the consumption of foods from the *Solanaceae* family can induce tobacco-cross-reactive IgE, which may arise in the absence of clinical symptoms. This is consistent with reported ST reactivity to foods in the absence of an overt clinical syndrome. Unfortunately, skin testing to the *Solanaceae* foods was beyond the scope of our study and this hypothesis requires further investigation. An alternative hypothesis is that exposure to an aeroallergen other than ETS induces tobacco-cross-reactive IgE. This hypothesis is supported by a recent report of tobacco leaf extract and *Artemisia vulgaris* (mugwort) pollen cross-reactivity.¹⁷ Too few of our patients were skin tested with *A. vulgaris* for us to

comment on tobacco-mugwort cross-reactivity in our population. We found no correlation between a positive ST to tobacco and any of the aeroallergens or aeroallergen mixes we used for testing.

In conclusion, our findings in this pediatric population refute the clinical significance of tobacco hypersensitivity as related to allergic symptoms. We believe that there is no role for routinely testing patients with tobacco extract and we feel that strict avoidance remains the best clinical advice for all patients.

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