Correlation Between Aeroallergen Levels and New Diagnosis of Eosinophilic Esophagitis in New York City

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See ''Aeroallergens in Eosinophilic Esophagitis: Significant Triggers or Noise in the System?'' by Atkins on page 1 and See ''Seasonal Variation in the Diagnosis of Eosinophilic Esophagitis: There and Back Again'' by Lucendo et al on page e25.

ABSTRACT

Objective: The relation between food allergies and eosinophilic esophagitis (EoE) is well established. Aeroallergens may also contribute to the development of EoE; however, there are limited data to support or refute this hypothesis. The objectives of this pilot study were to determine whether there is a seasonal variation in the onset of symptoms and/or diagnosis of EoE and whether these variations correlate with a specific pollen concentration within New York City.

Methods: We performed a retrospective chart review to identify all pediatric patients at New York Presbyterian Weill Cornell Medical Center diagnosed with EoE between 2002 and 2012. Sixty-six patients were identified and 28 were excluded. Cases were classified by both date of initial symptoms and date of histologic diagnosis. Pollen counts from a certified New York City counting station and the percentage of EoE cases were collated monthly and seasonally and compared.

Results: There was a seasonal variation in onset of symptoms and diagnosis of EoE, with the highest number of patients reporting onset of symptoms of EoE in July to September, and those being diagnosed with EoE in October to December. There was a seasonal correlation between peak levels of grass pollen and peak onset of EoE symptoms, which were both highest in July to September. The diagnosis of EoE peaked one season later.

Conclusions: The study findings suggest that there is a correlation between specific aeroallergens and both the onset of symptoms and time of diagnosis of patients with EoE.

Key Words: aeroallergen, allergy, eosinophilic esophagitis, pollen, seasonality

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What Is Known

- Eosinophilic esophagitis is often associated with atopic/allergic disorders.
- Food allergens are felt to trigger eosinophilic esophagitis.
- Seasonality has been established in the diagnosis of eosinophilic esophagitis, but the specific aeroallergens are unknown.

What Is New

- There is a seasonal variation in onset of symptoms in patients with EoE and time of diagnosis.
- Peak levels of grass pollen have a seasonal correlation with peak onset of EoE symptoms.
- Environmental factors should be investigated as rigorously as food triggers.

Eosinophilic esophagitis (EoE) is a newly recognized chronic clinical histopathologic disease characterized by significant upper gastrointestinal symptoms including dysphagia, heartburn, food impaction, and failure to thrive. These symptoms affect the daily lives of many patients including children. Eosinophils are commonly present in allergic and parasitic diseases and not typically found in the normal esophagus. Eosinophilic predominance in the esophagus is abnormal and suggestive of EoE once gastroesophageal reflux and proton pump inhibitor (PPI) responsive esophageal eosinophilia have been excluded (1,2). Current guidelines define a diagnosis of EoE as persistent esophageal eosinophilia of >15 eosinophils per $\times 40$ high power field despite >6 weeks of PPI therapy (3).

The relation between EoE and allergic disorders such as food allergies, allergic rhinitis, asthma, and atopic dermatitis in children is well established (4,5). Several investigators have published data supporting the association between food allergies and EoE (6). Aeroallergens may be a contributing factor in the development of EoE; however, to date there are very limited data to support or refute this hypothesis. The bulk of support has mainly been through articles documenting seasonality to EoE diagnosis (7,8). One previous study by Moawad et al (9) specifically investigated whether there is an association between adult EoE and aeroallergens in Maryland. This retrospective review of adult patient data showed a seasonal variation in the diagnosis of EoE and a correlation with grass pollen counts. In addition, there have been no studies to date that investigate this hypothesis in pediatric patients or in the New York City area.

The objective of this pilot study was to determine whether there is a seasonal variation in the onset of symptoms and/or diagnosis of EoE in pediatric patients and whether this variation correlates with a specific pollen concentration within the New York City region.

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METHODS

Identification of Pediatric Eosinophilic Esophagitis Patients

We performed a retrospective chart review to identify all pediatric patients ages 0 to 21 years old at New York Presbyterian Weill Cornell Medical Center diagnosed with EoE by histologic diagnosis between 1/1/2002 and 12/31/2012. Histologic diagnosis of EoE was defined as >15 eosinophils per high-powered field on esophageal biopsies. Patients with eosinophils present in other areas of the gastrointestinal tract were excluded from the present study. We excluded patients who did not meet the strict criteria of taking a PPI for 6 to 8 weeks before endoscopy or if they were older than 21 years. If patients were not on a PPI at time of the initial endoscopy, but were then placed on a PPI for 6 to 8 weeks and underwent a second endoscopy that was diagnostic for EoE, the second date was considered the date of diagnosis. We collected both date of initial symptoms as identified by the pediatric patient and parental recall and date of histologic diagnosis. Demographic data including sex, ethnicity, concomitant atopic disorders, and residential county were obtained from the electronic medical record during the chart review. The institutional review board at New York Presbyterian-Weill Cornell Medical Center approved the present study.

Pollen Sampling and Analysis

Atmospheric pollen was collected using a Burkard volumetric spore trap (Burkard Manufacturing Co., Rickmansworth, UK), a Hirst-type sampler deployed 47 ft above street level on a rooftop of the Fordham University Law School on the west side of 9th Avenue at 61st Street (10). For each 24-hour period, the Burkard trap generates a strip of clear melamine tape that is then adhered to a microscope slide, treated with phenosafranine stain and glycerine jelly mounting medium. Fordham University's Department of Natural Sciences then archives a permanent record of pollen microscope slides. The airflow of the Burkard trap is calibrated at 3-month intervals to maintain its operating rate at a constant 10 L/min.

A National Allergy Bureau/American Academy of Allergy, Asthma, and Immunology certified pollen counter analyzed pollen slides using a light microscope at ×400 magnification. Resulting daily pollen counts were converted into concentrations, measured as pollen grains per cubic meter of air for the years 2009 to 2012.

We note that the Burkard trap has been at the current location since April 2009, and is normally in operation continuously throughout the year. No significant amounts of pollen have been observed during the months November to February.

We chose to examine the following 11 taxa at each pollen center: *Acer* (maple), *Betula* (birch), *Populus* (poplar), *Ulmus* (elm), *Quercus* (oak), *Carya* (hickory), *Fraxinus* (ash), *Platanus* (sycamore, London planetree), *Fagus* (beech), Poaceae (grass pollen family), and *Ambrosia* (ragweed).

Statistical Analysis

Categorical variables are expressed as n (%) and continuous variables are expressed as mean ± standard deviation. The Kruskal-Wallis test was used to compare differences in mean allergen levels across seasons. To assess seasonal deviations in the distribution of observed EoE patients diagnosed, the binomial test was used comparing observed results to a theoretically expected distribution, assuming equal probability of 0.25 in each season. Mean allergen count was plotted against onset of EoE across all seasons. A Spearman rank correlation coefficient was used to assess the correlation between peak allergen count and onset of EoE. All P values are 2-sided with statistical significance evaluated at the 0.05 alpha level. All analyses were performed in SAS version 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

There were 66 patients identified during this period, and 28 were excluded because the patients were not on PPI therapy at the time of initial endoscopy. Initial symptoms included abdominal pain, emesis, poor weight gain, dysphagia, failure to thrive, gastroesophageal reflux, gagging, and food/foreign body impaction. Table 1 shows the demographic data for the patient population, and Table 2 shows the distribution of the initial symptoms. Several

TABLE 1. Demographics

Sex, n (%)	
Male	29 (81)
Female	7 (19)
Ethnicity, n (%)	
Non-Hispanic	23 (64)
Hispanic	2 (6)
Unknown	11 (31)
Age at onset of symptoms, y	
Mean ± SD	4 ± 5
Concomitant atopic disorders, n (%)	
Allergic Rhinitis	13 (36)
Trees (Maple, Birch, Oak)* (all confirmed by skin testing)	5 (14)
Grass, ragweed, weed* (all confirmed by skin testing)	6 (17)
Other Pollens	2 (6)
Seasonal/environmental (obtained by history only)	3 (8)
Dust mite	6 (17)
Mold	0 (0)
Cockroach	2 (6)
Cat dander, dog dander, mouse	6 (17)
Feather	2 (6)
Food allergies by RAST testing, n (%)†	16 (44)
Food allergies by skin testing, n (%)†	22 (61)
Food allergies by history, n (%)	26 (74)
Grains (wheat, barley, oat, rye)	12 (33)
Nuts	18 (50)
Vegetables	8 (22)
Fruit	6 (17)
Meat (beef, chicken, turkey)	4 (11)
Seafood (shelled and not shelled)	5 (14)
Egg	14 (39)
Milk	11 (31)
Soy	10 (28)
Residential county, n (%)	
Manhattan	12 (33)
Queens	8 (22)
Bronx	1 (3)
Brooklyn	3 (8)
Nassau	8 (22)
Westchester	3 (8)
Suffolk	1 (3)

RAST = radioallergosorbent test.

*Twenty-nine patients were not skin tested for tree or grass pollens.

†Sixteen patients did not have RAST testing for food allergies and 10 patients did not have skin testing for food allergies.

TABLE 2. Presenting symptoms

	n
Abdominal pain	11
Emesis	11
Poor weight gain	6
Dysphagia	6
Failure to thrive	4
Gastroesophageal reflux	4
Gagging	3
Asymptomatic	3
Food/foreign body impaction	5

patients reported concurrent onset of more than 1 initial symptom, and each were included in Table 2.

There was a seasonal variation in onset of symptoms of EoE (Fig. 1), depicted as the blue line graph of figure Y, with the highest number of patients reporting onset of symptoms of EoE in July to September. This held true when evaluating the entire pediatric EoE data set from 2002 to 2012, and when assessing only the patients from 2009 to 2012. There was also a seasonal variation in the diagnosis of EoE, with the highest number of patients being diagnosed in the October to December season (Fig. 2). If patients could not definitively identify the month or season of onset of symptoms, they were excluded from the analysis comparing season of onset to the seasonal variation of aeroallergens. All patients were included in the analysis of the seasonal variation of diagnosis of EoE, with diagnosis defined as date of endoscopic diagnosis.

When evaluating the 2009 to 2012 pollen data from the Manhattan Pollen Center, researchers noted that Poaceae, or grass pollen, peaked in the July to September season. Therefore, there was a seasonal correlation between peak levels of grass pollen and peak onset of EoE symptoms for patients with onset of symptoms between 2009 and 2012, as both were highest in July to September period. The diagnosis of EoE was noted to peak one season later.

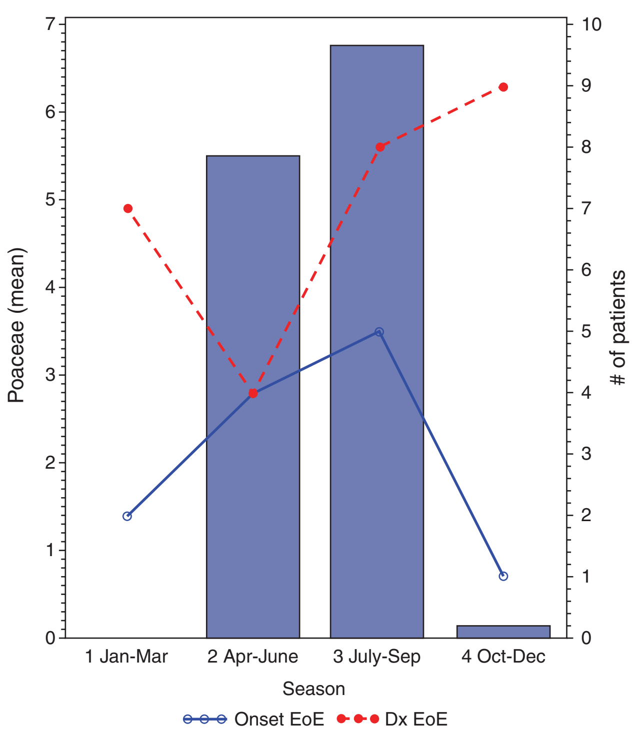

FIGURE 1. Seasonal correlation between Poaceae and symptom onset in newly diagnosed EoE. EoE indicates eosinophilic esophagitis.

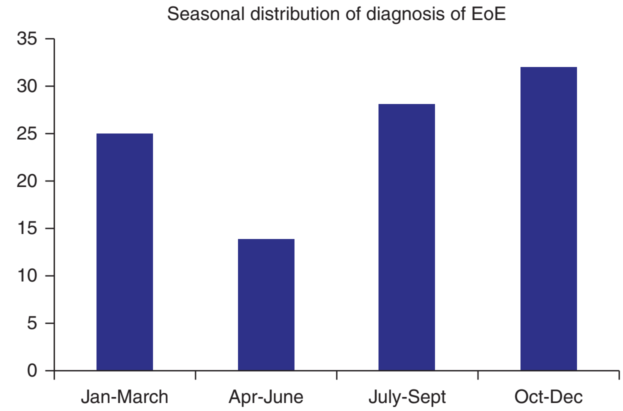

FIGURE 2. Distribution of diagnosis of EoE by season. EoE indicates eosinophilic esophagitis.

There was no seasonal correlation between levels of the other aeroallergens counted at the Manhattan Pollen Center and either onset of symptoms or diagnosis of EoE.

In a further subanalysis, all pediatric EoE patients who met inclusion criteria with onset of symptoms between 2002 and 2012 were collated and these data were compared to aeroallergen data collected at the next-nearest pollen counting station, in Westchester, New York, between 2002 and 2012. These data revealed that ambrosia, or ragweed, had the highest incidence in the July to September period, rather than grass pollen. These results suggest a trend toward correlation between ragweed and peak onset of symptoms of EoE, which were both highest in the July to September period.

DISCUSSION

Food allergy has been well established as potentially contributing to the pathology of EoE. In 1995, Kelly et al (11) showed that placing patients on elemental diets resulted in resolution of EoE symptoms and reintroduction of the previously eliminated foods lead to symptom recurrence. Although in theory aeroallergens may contribute to the development of EoE as well, this has not yet been well studied. The first group to provide evidence for this theory was Mishra et al (12) whose work with a murine model showed that intranasal exposure to Aspergillus or dust mites resulted in localized esophageal eosinophilia. Fogg et al (13) described a case of a patient with EoE with no food allergies, whose symptoms and esophageal eosinophilia count were worse during pollen season and improved once pollen season was over. Moawad et al then went on to investigate whether an association exists between adult EoE and aeroallergens. Consistent with research by Moawad et al, we also found that diagnosis of EoE varies with seasons. In contrast, our study suggests that high pollen levels of grass and ragweed pollen correlate with onset of symptoms of EoE, whereas the former study suggests that high pollen levels correlate with diagnosis of EoE.

Daily pollen concentrations follow a distinct seasonal pattern in the New York City metropolitan region, with tree pollen typically present during the spring (March to May) and grass and weed pollen present during the summer and fall (May to October for grass, July to October for weed). During the winter months, pollen concentrations fall to zero. This seasonal pattern was observed at both of the counting stations in the present study, and is similar to those observed in other cities in the northeastern United States (14).

While upwards of 70 pollen taxa are observed over the course of the year at pollen monitoring stations in Manhattan, NY and Westchester, NY, we chose to examine only the following 11 taxa: *Acer* (maple), *Betula* (birch), *Populus* (poplar), *Ulmus* (elm), *Quercus* (oak), *Carya* (hickory), *Fraxinus* (ash), *Platanus* (sycamore, London planetree), *Fagus* (beech), Poaceae (grass pollen family), and *Ambrosia* (ragweed). We chose these 11 taxa because they are clinically significant allergens with well-established sensitization patterns in populations from the northeastern United States (15,16).

Our study findings suggest a seasonal variation of both the onset of symptoms of pediatric patients with EoE, and with the diagnosis of this disease. Previously published retrospective data showed an increase in EoE diagnosis in the spring, summer, and fall seasons with a decrease in the winter months (2). Surprisingly, the lowest distribution in our data set was in April to June rather than January to March. Furthermore, our data have a trend toward correlation between specific aeroallergens and onset of symptoms in patients with EoE, rather than the time of diagnosis. The Manhattan pollen data from 2009 to 2012 suggest a seasonal correlation between grass pollen and onset of symptoms of EoE, and the Westchester pollen data from 2002 to 2012 suggest that ragweed pollen is correlated with EoE onset of symptoms. An adult study by Elias et al (17) retrospectively examined 372 patients and found a reaction to any aeroallergen in 69% and to >4 aeroallergens in 47% patients without a seasonal relation. These patients were identified by testing profiles, and not by examining actual pollen counts in the environment. Similar to the knowledge about food triggers in EoE, individual testing may not be a reliable measure but future investigation is needed to verify this. In a retrospective study, the Vanderbilt group found that older patients with EoE had greater aeroallergen sensitivity than younger ones, specifically dust and weed, grass and tree pollens, when tested by skin prick testing, and atopy patch testing (APT) (18). Published data indicated that APT is a more accurate way of identifying allergens responsible for EoE given the delayed, non-IgE–mediated pathway (19,20). APT was first described with aeroallergens by Rostenberg in 1937 and later by Mitchell and Platts-Smith (21). Although the sensitivity, specificity, and predictive values have varied in the literature, it might be an area of future investigation as an adjunct in identifying potential environmental triggers. In addition, although there was no distinct seasonal correlation among the other aeroallergens evaluated in the present study, this may be secondary to the small sample size. The present study suggests that larger populations of pediatric EoE patients should be evaluated to determine whether there is a statistically significant seasonal correlation between individual aeroallergen levels and the onset of symptoms of EoE in pediatric patients.

There was significant variability in the length of time between initial onset of symptoms of EoE and date of diagnosis of EoE. We believe that the diagnosis may have peaked in the season following the initial pollen peak because of delays between onset of symptoms and a patient's ability to get a timely appointment with a pediatric gastrointestinal specialist. In addition there may have been a delay between the initial visit and endoscopic procedure when their symptoms worsened or were no longer tolerable.

Limitations of this retrospective study include limited data that met the strict diagnostic criteria for EoE, the fact that this was a retrospective analysis, and the possibility of inaccurate patient recall of month or season of symptom onset. The Manhattan pollen data could only be collected over a 4-year period starting in 2009, the year that this pollen center was established. Because the aeroallergen levels in the atmosphere may change from one region of the country to another, we can only comment on the seasonal correlation between grass and ragweed pollens and onset of symptoms of EoE in the New York City area.

In addition to tree, grass, and weed pollens, future studies may investigate other sources of aeroallergens such as fungi. Future studies may also look at whether there is a seasonality of the recurrent symptoms that patients with EoE experience, and whether these symptoms peak during a particular pollen season.

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