

Original Article

Eosinophilic esophagitis: comorbidities and atopic disease in Nevada

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SUMMARY. Eosinophilic esophagitis (EoE) is a rare, immune-mediated illness. We aimed to examine the comorbidities and sensitization patterns associated with an EoE diagnosis in Nevada. The study goal was two-fold: to determine the most common EoE comorbidities and sequela in the state of Nevada using healthcare utilization records across all settings and to determine the most common food and aeroallergens in histologically positive EoE pediatric patients using clinical sensitization data. Esophageal obstruction/stricture was the most frequently reported diagnosis in adults with EoE (29.5%). Among pediatrics, the highest ranking comorbidities included asthma (13.4%); diseases of the stomach, duodenum, and intestine (7.26%); allergies (7.01%); and gastroesophageal reflux disease (GERD) (3.69%). Additionally, the top sensitizations reported in histologically positive EoE patients were largely pollen related (82.9%). Atopic disease and specifically food allergens are commonly reported as comorbid conditions with EoE in the literature. However, our clinical pediatric data set from this study revealed that aeroallergen sensitizations far exceeded that of food allergens (82.9% aero-positive vs. 17.1% food positive). The high presence of esophageal stricture/obstruction in adults could be indicative of late diagnosis; in addition, the aeroallergen sensitization in children could suggest different clinical management techniques necessary may be needed for this disease. Education among healthcare providers regarding the presence of aeroallergen sensitization in this population may result in earlier diagnoses and help reduce morbidity and the cost from this disease.

KEY WORDS: allergy, eosinophilic esophagitis, epidemiology, esophageal strictures.

INTRODUCTION

The prevalence of eosinophilic esophagitis (EoE) continues to increase in parallel with atopic disease.¹ In adults, symptoms arise in the form of persistent heartburn, difficulty swallowing, and food impaction; among the pediatric population, symptoms often include vomiting, abdominal pain, and failure to thrive.^{2,3} Guidelines indicate proton pump inhibitor (PPI) and pH monitoring for 8 weeks via expert consensus to rule out GERD, with follow-up on endoscopic biopsy with the presence of >15 eosinophils per high-power field (HPF) regardless of age.^{4,5}

Hurrell et al. reports that the odds of developing EoE is 39.0% higher (OR = 1.39; 95% CI: 1.34, 1.47) in cold zones, 27.0% higher in arid zones (OR = 1.27; 95% CI: 1.19, 1.36), and lowest in tropical zones (OR = 0.87; 95% CI: 0.71, 1.08) when compared to temperate regions.⁶ The Northern region of Nevada experiences cooler than average temperatures in the winter (January 25°F/−3.9°C) and summer (July 58°F/14°C) when compared to the Southern

region (January 39°F/−3.8°C and July 81°F/27°C, respectively).⁷ The warmer weather in the southern region allows for a longer pollination season when compared to the north. Due to the increased temperature and lack of rain, atopic illness remains high among the Nevadan population.

Comorbidities and sequela of EoE have been reported in the literature worldwide. Australia reports EoE in conjunction with allergic rhinitis (93.3% of patients), followed by asthma, eczema, and anaphylaxis.⁴ Investigators in Brazil identified allergic rhinitis as the most common comorbidity (74.2% of cases) along with asthma and atopic dermatitis.⁸ In the United States, Massachusetts (70%), Ohio (61.9%), New York (36%), and Illinois (58.9%) all reported allergic rhinitis as the most common comorbidity, followed by food allergies, asthma, and atopic dermatitis.^{9–12}

Sensitizations are relatively common in patients diagnosed with EoE, and food allergens are most often reported. Australia and Brazil both reported cow's milk allergy in EoE patients (27 and 22.8% of

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cases, respectively).^{1,4,5} In the US, Illinois reported the most common food allergen as soy (38.9% of all cases), whereas Ohio, Wisconsin, and New York had higher rates of nut allergies (40.9, 51, and 50% of cases, respectively).^{11–13} Few prior investigations report high pollen sensitization; in Wisconsin, native trees were identified as the dominant aeroallergen (70%), Spain reported sensitization to rye (36.4% of patients) and Bermuda grasses (27.1% of cases), and New York reported less than 20% of records documented sensitization to grasses, dust mites, or animal dander.^{11,14,15}

The goal of this retrospective cross-sectional study was two-fold. First, atopic comorbidities and sequela of EoE in Nevada were examined using a large hospital database. The most common comorbidities and sequela were identified across demographic subgroups of interest. Second, this study aimed to investigate unique allergen sensitization patterns due to the extreme climate in Nevada. This was performed by utilizing a clinical data set from histologically positive EoE pediatric patients. It was hypothesized that statewide Nevada EoE records would exhibit differences in comorbidities and sensitizations when compared to other US geographic locations.

METHODS

Study population—state of Nevada

Data for this manuscript were provided by the Center for Health Information Analysis (CHIA) located at the University of Nevada in Las Vegas. This center collects hospital utilization data from all hospital settings in Nevada: ambulatory surgery centers, emergency departments, inpatient, and other outpatient or outpatient clinics including therapy centers, family physicians, and specialty doctors with outpatient clinics. Records were extracted and filtered to include only Nevada residents. Inclusion criteria for this study included healthcare patient records with primary (1) through quaternary (4) EoE diagnosis codes (ICD-9 = 530.13 or ICD-10 = K20.0) from all hospital settings, resulting in a total of 2,296 records. Primary through quaternary diagnosis codes were used for this disease as a way to reduce comorbid illness overlap. The CHIA database contains diagnosis codes 01–33, and in an effort to reduce repeat visits, only 01–04 were utilized. Due to de-identification of the hospital record data, the individual level for analyses is the patient record and not the individual. A retrospective cross-sectional study design was chosen based on data availability in this rare disease population.

Study population—pediatric subset

The second part of the study included sample results derived from pediatric gastroenterology referrals to the University of Nevada Reno School of Medicine

(UNR SOM). These records included patients ≤ 18 years of age who had PPI resistant EoE with biopsy confirmed >15 eos/hpf identified referred to the UNR SOM allergy clinic by pediatric gastroenterology subspecialist to undergo allergy testing. Selection of panel of aeroallergen for skin testing was identical to Wong et al., reflecting commercially available common indoor and outdoor aeroallergens for the microclimate of Nevada and consistent with care of the general allergy patient of the region.⁷ Skin testing methods derived from Wong et al. were performed with glycerinated extracts purchased from ALK-Abello (Denmark, EU).⁷ Percutaneous skin test utilizing a DermaPik was performed, and a positive control of histamine and negative saline control was placed.¹⁶ A histamine result of 3 mm or larger was considered an adequate positive control, and all patients were interpreted by the same pediatric allergist.⁷ Sensitization was noted with either an aeroallergen or food extract if the reaction was at least half the size of the measured histamine and was also larger than then negative control.⁷ The clinical subset included 59 cases of histologically confirmed pediatric EoE patients from Nevada with sensitization results for over 100 potential food and aeroallergens.

Statistical analysis

Descriptive statistics were performed to identify the demographic factors associated with EoE records across various characteristics. The results are presented by demographic of interest. All variables were categorical (race, gender, age [pediatric 0–17 and adult 18+] and all-cause diagnosis levels 1 through 4). Using diagnosis variables, comorbidities were extracted and ranked by frequency from the highest to lowest by age and gender, which allowed for identification of comorbidities for stratification. Similar clinical conditions and codes were grouped together for ease of ranking the comorbidities. Chi-square testing for independent proportions was performed to identify significant differences between comorbidities among demographic subgroup. P-values of ≤ 0.05 were considered significant. Frequencies were calculated for the clinical sensitization data provided by the UNR SOM.

Ethical considerations

The data provided by CHIA is Health Insurance Portability and Accountability Act compliant. Prior to the start of the study, a Limited Data Set Use Agreement was approved and signed by all parties participating in the project. Furthermore, permission was Institutional Review Board granted by the University of Nevada Reno School of Medicine (UNR SOM) and subsequently an Intent to Rely Document was received by the University of Nevada Las Vegas (signed and dated 04/30/13) to use the

Table 1 Demographic analysis of positive EoE records in Nevada by age, gender, and comorbidity

	Pediatric (0–17) <i>n</i> = 785		Adult (18+) <i>n</i> = 1,411		Female <i>n</i> = 798	Male <i>n</i> = 1,398
Age (mean/SE [†])	10 (0.18)		46.2 (0.42)		39.2 (0.75)	29.8 (0.57)
Race						
(White/Caucasian)	526 (67.0%)		834 (59.1%)		504 (63.2%)	856 (61.2%)
Asian/Pacific Islander	22 (2.80%)		28 (1.98%)		14 (1.75%)	36 (2.58%)
Black/African American	66 (8.41%)		33 (2.34%)		24 (3.00%)	75 (5.36%)
Hispanic	66 (8.41%)		58 (4.11%)		40 (5.01%)	84 (6.00%)
Native American/Alaskan	1 (0.13%)		2 (0.14%)		1 (0.12%)	2 (0.14%)
Other	43 (5.48%)		21 (1.49%)		13 (1.63%)	51 (3.65%)
Unknown/missing	61 (7.78%)		435 (30.8%)		202 (25.3%)	294 (21.4%)
Gender						
Female	191 (23.9%)		607 (76.1%)			
Male	594 (42.5%)		804 (57.5%)			
	<i>P</i> -value				<i>P</i> -value	
Comorbidity						
Obstruction, stricture/stenosis of the esophagus	18 (2.29%)	<0.001	430 (30.5%)	159 (19.9%)	0.717	289 (20.7%)
Diseases of the stomach, duodenum, and intestine	92 (11.7%)	0.554	179 (12.7%)	89 (11.2%)	0.225	182 (13.0%)
Gastroesophageal reflux disease (or related)	63 (8.03%)	<0.001	197 (13.9%)	103 (12.9%)	0.271	157 (11.2%)
Hiatal hernia	13 (1.66%)	<0.001	150 (10.6%)	74 (9.27%)	0.0157	89 (6.37%)
Atrophic gastritis	171 (21.8%)	0.006	239 (16.9%)	162 (20.3%)	0.154	248 (17.7%)
Asthma	105 (13.4%)	<0.001	38 (2.69%)	33 (4.14%)	<0.001	110 (7.87%)
Listed allergies	83 (10.6%)	<0.001	8 (0.567%)	18 (2.25%)	0.001	73 (5.22%)

**P*-value utilized Chi-square test for two independent proportions in a 2 × 2 comparison

[†]Standard error (SE)

Italics indicate statistical significance of *P* < 0.001.

pediatric allergy/immunology clinical skin test data set.

RESULTS

Demographic analysis—state of Nevada

The median age of the pediatric population was 11 (median = 11, SE = 0.18); and the adult population was 45 (median = 45, SE = 0.42) (Table 1). Median age among female EoE records was 40.5 (median = 40.5, SE = 0.75) and 27 in males (median = 27, SE = 0.57) (Table 1). Caucasian was the predominant race among all EoE records and Native American/Alaskan was the least represented (<1.0% of the data set) (Table 1). Pediatric records had a higher male representation (*n* = 594) (Table 1).

Comorbidities identified from EoE records in Nevada

Records selected by diagnosis code were extracted to describe the comorbidities presented by age and gender. Gastritis codes were reduced to include only specified, post-biopsy ICD codes to prevent over-representation of a common “catch-all” code. Esophageal obstructions, strictures/stenoses ranked highest among the adult, male, and female demographic groups in Nevada (30.5, 20.7, and 19.9%, respectively) (Table 1). Hiatal hernias were present in 10.6% of adult, 9.3% of female, and 6.4% of male subgroups (Table 1). A common atopic comorbidity in males included asthma (7.9%). Other comorbidities

were similar among the female and male demographic subgroups and included diseases of the stomach, duodenum, and intestine (11.2 and 13.0%, respectively), atrophic gastritis (20.3 and 17.7%, respectively), and GERD (12.9 and 11.2%, respectively) (Table 1). The top comorbidity among pediatric records was asthma (13.4%), followed closely by diseases of the stomach, duodenum, and intestine (11.7%) (Table 1). Food allergies (10.6%) were the third most common comorbidity listed. Pediatric patients also exhibited atrophic gastritis (21.8%) and GERD (8.03%) (Table 1).

Chi-square testing for independent proportions revealed that several significant comorbid differences existed between demographic subgroups with a listed positive EoE diagnosis code. Among pediatric and adult records, adults had significantly higher frequencies of obstruction, stricture/stenosis of the esophagus (*P* < 0.001), GERD (*P* < 0.001), and hiatal hernia (*P* < 0.001), whereas pediatric records showed significantly higher frequencies of atrophic gastritis (*P* = 0.006), asthma (*P* < 0.001), and listed allergies (*P* < 0.001) (Table 1). Among males and females, male records showed significantly higher frequencies of asthma (*P* < 0.001) and listed allergies (*P* = 0.001) than females, whereas females had higher frequencies of hiatal hernias (*P* = 0.015) (Table 1).

Sensitization data—pediatric clinical subset

Overall, 49 foods and 51 aeroallergens were tested across 59 pediatric patients. Among EoE patients with food allergy sensitization, the food group with

Table 2 Sensitization profile from histologically positive EoE pediatric patient skin prick tests

Food allergens (n, %)			Aeroallergens (n, %)		
Nuts/seeds	34	57.6%	Weed	50	84.8%
Dairy	23	38.9%	Tree	49	83.1%
Seafood	23	38.9%	Grass	45	76.3%
Vegetables	18	30.5%	Dander	43	72.9%
Grains	13	22.0%	Mold	15	25.4%
Meat	12	20.3%			
Seasonings	11	18.6%			
Fruit	7	11.9%			
All allergens (n = 1,495 total + reactions)					
Food positive	255			17.1%	
Aero-positive	1,240			82.9%	

Nuts/seeds—peanut/cashew/almond/walnut/pecan/hazelnut/pistachio/Brazil/coconut/sunflower seed/sesame seed

Dairy—egg/milk/soy

Seafood—cod/oyster/shrimp/crab/flounder/tuna/lobster/clam/salmon/scallops

Vegetables—celery/garlic/onion/pea/tomato/carrot/corn/white potato/sweet potato

Grains—wheat/barley/oat/rice

Meat—beef/chicken/lamb/pork/turkey

Seasonings—vanilla/cinnamon/mustard/cocoa

Fruit—avocado/orange/apple/strawberry/blueberry/banana/pear/peach/apricot/pineapple/cantaloupe

Weed—pigweed/sagebrush/plantain/dock/ragweed/ragweed-mix/marsh elder/Russian thistle/rabbit bush/saltbush

Tree (other)—pecan/juniper/cedar/alder/oak/elm/willow/locust/cottonwood/birch/maple/privet/aspens/olive/sycamore/pine/walnut/sweet gum/mulberry/ash/ailanthus

Grass (other)—timothy/brome/Bermuda/saltgrass/Johnson/alfalfa

Dander—horse/hamster/feather/cat/dog/cattle/mouse/cockroach

Mold—*Alternaria*/*Aspergillum*/*Penicillium*/*Cladosporium*/*Drechslera*/*Curvularia*/moldmix2/Smuts

(Reported as percentage of total cases with at least one positive result; n = 59).

the highest sensitization frequency was nut and seed (57.6%); followed by dairy (38.9%), seafood (38.9%), vegetables (30.5%), and grains (22.0%) (Table 2). Nearly 95% of all patients demonstrated at least one aeroallergen sensitization. In total, over 80% of the positive EoE pediatric patients were sensitized to weed pollen (84.8%) and tree pollen (83.1%) and over 70% to grass pollen (76.3%) and animal dander (72.9%) (Table 2). Overall, aeroallergen sensitization from weed and tree was >20% higher in pediatric patients than the most prevalent food allergen (57.6%) (Table 2).

Skin prick results (n = 59) are presented in Table 2. Overall, among the 59 pediatric patients tested there were 1,495 total positive reactions between food allergens and aeroallergens. Only 17.1% of the positive reactions were from food allergens and 82.9% of the positive reactions were from aeroallergens.

DISCUSSION

The results for this study are novel as the reported comorbidities, and allergens are different than those most often reported in the literature. Pediatric allergy sensitization data suggest that those with atopic comorbidities may have more disease from airborne allergens as compared to versus food allergy associated disease than previously reported. Additionally, the lack of physicians in the state may play a vital role in the under or misdiagnosis of this rare disease. According to a UNR SOM report, Nevada ranks 47

out of 50 in the nation for physicians per 100,000 people.¹⁷ The official 2018 report estimates that there are 63 primary care physicians per 100,000 individuals, and the rates for specialty physicians are even lower.

Comorbidities identified from EoE records in Nevada

Over 30% of the adult EoE population were diagnosed with esophageal obstruction/stenosis, or stricture of the esophagus, with adults receiving this diagnosis far more than pediatrics ($P < 0.001$). These results indicate that EoE patients in Nevada are seen in the later stages of the illness where the cost is highest and when damage is potentially irreparable. A 2016 study examined a cohort of EoE positive patients and identified that delay in EoE diagnosis was associated with stricture formation.¹⁸ The study reported a significant difference in mean time of diagnosis was observed in positive EoE patients with less than 10 mm esophageal diameter when compared to patients with a diameter greater than 10 mm.¹⁸

The high frequency of gastric comorbidities compared to the more common atopic comorbid illness is worthy of note. Significant differences were observed between adult and pediatric patients across most of the gastric comorbidities identified. Over 10% of all adult EoE records in Nevada listed hiatal hernia as comorbid. Both Barrett's esophagus, a serious complication of GERD (13.9% of adults with EoE), and hiatal hernias have been loosely associated with EoE in several studies.^{19–23} One study from Minnesota

highlighted that hiatal hernias likely contribute to the development of Barrett's esophagus.¹⁹ Based on published literature, an association between EoE, hiatal hernia, and Barrett's esophagus may exist, particularly in the Nevadan population where Barrett's esophagus codes were observed among 2.09% of all positive EoE records. If EoE can be identified during earlier disease stages, prevention of significant gastric comorbid illness as an adult may be preventable.

Several studies report high asthma or other atopic comorbid rates among EoE patients.^{8,10,20} Atopic comorbidities present in the CHIA data set only appeared among the male and pediatric subgroups, both of which exhibited significant differences when compared to demographic counterparts ($P < 0.001$). When the diagnosis code search was expanded to include all diagnosis codes (01-33), allergic rhinitis was observed in <1% of the EoE population in Nevada. Compared with the published literature worldwide, the atopic comorbidities identified in Nevada EoE records were much lower than expected. The lack of allergy physician presence in Nevada and the lack of knowledge of EoE and associated co-morbid diseases in the state could explain this phenomenon. This disease is difficult to identify, and given its rare nature, it is unlikely that a non-specialty physician would immediately refer a patient based on initial symptomology. This delay in diagnosis could be leading to more severe gastrointestinal comorbidities observed among patients within the state.

Sensitization data—pediatric clinical subset

The clinical subset highlighted several notable distinct allergens not found in other regions. In three of the largest EoE population studies, the authors claim that food allergies were the causative agent of the disease in over 90% of patients.^{3,19,24} However, in the clinical subset of Nevada patients, weed, tree, and grass sensitization dominated. Overall, positive skin prick tests for food allergens accounted for 17.1% of the total positive skin test results, whereas positive aeroallergen results were found in over 80% of the cases.

Within the food sensitized patient population, the percent having specific food group, positive skin test results were similar to or lower, than other published studies. The highest food allergen group identified in Nevada among positive EoE patients was nuts/seeds. Other studies report nut allergens in EoE patients between 4 (Australia) and 51% (Wisconsin, USA).^{25,26} Dairy and seafood were among the other food allergens identified in Nevada. In other studies, dairy ranges from 4.00 (Australia) to 39.0% (New York, USA) and seafood ranges from 0.00 (Australia) to 14.0% (New York, USA) in EoE patients.^{11,25}

Weed sensitization in Nevada was reported in nearly 85% of EoE patients. The highest identified

weed allergens in the literature were reported from Wisconsin and Ohio, where allergens were identified in 40 and 60% of cases, respectively.^{13,26} Grass sensitization in Nevada was identified in over 75% of the pediatric patients tested; sensitization elsewhere is reported at 17.0% in New York, but close to 70% in Australia.^{11,25} Animal dander was reported in 72.9% of the EoE Nevadan population but lower in Wisconsin, Ohio, and New York (66.0, 39.4, and 23.0%, respectively).^{11,13,26} This suggests that a geographic etiology may play a role in our findings as most comparable studies are based on other regions.

In a study examining a cohort of children, Wong et al. identified that over 50% of children aged between 6 and 7 were sensitized to at least one aeroallergen in the state of Nevada.⁷ The pediatric data set found the same aeroallergen pattern as previously demonstrated for the allergic rhinitis population of Nevada.⁷ This suggests that the unique microclimate of Nevada may contribute to the findings of this current study. Nevada receives the least amount of rain in the US. Pollen grains remain in the region past plant production of the aeroallergen due to decreased rain, resulting in the presence of pollen despite the end of the season. This makes pollen a perennial exposure rather than seasonal in this microclimate.⁷ Another study found significant variations in pollen concentrations and compositions across Nevada.²⁷ Tree was the greatest contributor to the average pollen concentrations, followed by weed and grass.²⁷ Increased pollen counts and longer exposure may impact pediatric EoE patients more than food allergens making aeroallergen sensitization a major issue for EoE patients in Nevada. This could suggest that other regions with individualized microclimates may need performing investigations to determine if aeroallergen or food allergy should be the predominate focus for a clinician.

Strengths and limitations

A major strength of this study is the large population size of EoE records gathered from the database across multiple years, as well as the large number of conditions identified with diagnosis codes. As these are healthcare utilization data with diagnosis codes, these data are typically more accurate than the self-reported data. The pediatric clinical subset provided by UNR SOM was highly specialized. These results were referred between subspecialties, from gastroenterologist to allergist, making this a unique and clinically precise data set. The availability of these data allowed for clinical and parallel assessment among a unique population.

One limitation for this study includes the retrospective study design and the inability to calculate true disease prevalence rates and patient level comorbidities.

ties, as the individual level for analyses is the patient record and not the individual. Repeat visits cannot be accounted for in the data, making it difficult to determine how many individual patients are truly represented. Another limitation includes the lack of subspecialty allergists in Nevada, making EoE difficult to capture within the population. Due to the lack of allergy subspecialists, inconsistencies in treatment likely exist by provider and region.

CONCLUSIONS

While the knowledge of EoE continues to grow, more adequately powered studies are required across larger geographic regions. In Nevada obstructions/stenosis was significant among adult patients, indicating a significant delay in diagnosis. This result was not observed, however, in the pediatric subset. This shows that adequate care of pediatrics among gastroenterologists and allergists may help prevent disease progression. Children with obstructions are rarely seen in the literature and may reflect the lack of accessible care which then in turn contributes to a late diagnosis with severe GI symptomatology and sequela.

The clinical allergy sensitization data set indicated that sensitization to aeroallergens in EoE patients far exceeded the presence of food sensitization. These patterns are in contrast with most other studies, making this novel information for providers of EoE patients, especially in climates similar to Nevada. Additionally, given the large number of patients with aeroallergen sensitizations from the referral clinical database, we suspect that this comorbidity is being under diagnosed statewide.

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