Lack of seasonal variation in the incidence of eosinophilic oesophagitis in adolescent and adult non-PPI-responsive oesophageal eosinophilia midwestern US populations

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Abstract

Background: Eosinophilic oesophagitis (EoO) has been associated with allergic disorders as well as aeroallergens. The current literature has shown a possible association between seasonal variation, mainly in the spring, and the incidence of EoO. However, this data was based on small population studies that did not exclude proton-pump inhibitor (PPI)-responsive oesophageal eosinophilia (PPI-ROE) in their cohort.

Aim: The aim of this study was to determine if there is a seasonal variation associated with the diagnosis of EoO in patients that had been treated with high-dose PPI prior to diagnosis.

Methods: Oesophageal biopsies were obtained from a cohort of patients who presented with symptoms of dysphagia, odynophagia, and heartburn during a 10-year period. Symptomatic patients who had biopsies from the mid and distal oesophagus with ≥ 20 eosinophils per high-power field (hpf) while on high-dose PPI treatment for at least 5 weeks were diagnosed as having EoO. The monthly and seasonal incidences were determined (winter, January–March; spring, April–June; summer, July–September; Autumn, October–December).

Results: A total of 20,718 patients were identified and their records evaluated. From this cohort, 193 (0.93%) symptomatic patients had biopsy-proven oesophageal eosinophilia (≥ 20 eosinophils/hpf) and no seasonal variation was seen in this group. However, only 57 (0.28%) had been adequately treated with PPI prior to diagnosis (i.e. non-PPI-ROE biopsy-proven EoO; ≥ 20 eosinophils/hpf: 39 males, 18 females; age 29.5 years). The most common medical history components included asthma (12.3%) and food allergies (3.5%), and the most common presenting symptoms included dysphagia (50.9%) and heartburn (26.3%). The monthly and seasonal incidences in our cohort were with no apparent trend ($p = 0.713$ and 0.703 , respectively).

Conclusions: The incidence of EoO was consistent across all 12 months as well as during the four seasons. Our data does not support a seasonal variation in relation to the incidence of EoO in the US midwestern non-PPI-ROE population.

Keywords

Annual, incidence, PPI-responsive oesophageal eosinophilia, seasonal variation

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Introduction

Eosinophilic oesophagitis (EoO) is a chronic, immune/antigen-mediated disease characterized clinically by symptoms related to oesophageal dysfunction and histologically by eosinophil-predominant inflammation. EoO was first reported approximately 30 years ago^{1,2} with probable cases suggested even more than four decades ago.³ Historical studies lack a histological consensus of defining EoO, and the presence of ≥ 20

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eosinophils per high-power field (hpf) at any level of the oesophagus was commonly adopted.⁴ However, in recent years the definition has been specified and currently the diagnostic criteria are symptoms of oesophageal dysfunction with an eosinophil count of ≥ 15 eosinophils/hpf and eosinophilia limited to the oesophagus, with exclusion of other possible causes of oesophageal eosinophilia.^{5–7}

The incidence and prevalence of EoO have increased significantly over the past decade in both children and adults.⁸ Opposing views remain as to whether this represents a true increase in disease or increased recognition of the disease. Vanderheyden et al.⁹ concluded that the apparent increase in the incidence of EoO is largely a result of increased recognition as opposed to an increase resulting from an environmental factor. Straumann et al.¹⁰ concluded that increasing incidence led to increasing prevalence, a trend that reflects a real increase in EoO and not just enhanced awareness. Regardless, EoO is clinically encountered more often than before, hence leading to a need for an enhanced understanding of the disease process.

The exact aetiology of the antigen/immune-mediated process in EoO still remains unclear. Current theories postulate the role of both food allergens and aeroallergens as potential initiating factors for the cellular response in genetically predisposed individuals.^{11–14} In recent years, there have been studies that demonstrated the effectiveness of proton-pump inhibition (PPI) in reducing symptoms and improving histopathology in a subset of patients with oesophageal eosinophilia and suspected EoO, leading to the terminology ‘PPI-responsive oesophageal eosinophilia’ (PPI-ROE).^{15,16} Several studies have reported increased incidence in the late summer/early autumn while others have reported an increased incidence in the spring/summer with a lower incidence in the winter. However, all cohorts studied for seasonal variation had <50% rate of PPI treatment during diagnosis (24–48%).^{17–19}

Certain environmental factors, including pollen counts and climate zones have been associated with EoO in the adult and paediatric population.²⁰ A recent study on a cohort of 44 children and adolescents demonstrated that the onset of symptoms did not vary by season between 2001–2006, indicating that allergens triggering EoO are present all year round; however, all patients who had undergone the diagnostic endoscopy were initially placed on empiric PPI therapy for an average of up to 4 weeks, hence not enough time to substantiate effective treatment.^{21,22}

Due to current lack of consensus regarding seasonal variation and incidence of EoO among both adolescent and adults with non-PPI-ROE, the aim of our study was to evaluate the seasonal variation of the incidence

of EoO in non-PPI-ROE population in our single-centre cohort.

Methods

Study design

We retrospectively evaluated our electronic medical billing records of both adolescent and adult patients. We used the Current Procedural Terminology code for oesophagogastroduodenoscopy (OGD) and biopsy performed for symptoms of dysphagia, regurgitation, food impaction, and heartburn through the Digestive Disease Center at the University of Iowa Hospitals and Clinics from January 2003 to January 2013. The University of Iowa Hospital and Clinics Institutional Review Board approved this study.

Our pathology laboratory has coded for the last decade all oesophageal biopsies from the distal and mid-oesophagus with ≥ 20 eosinophils/hpf as EoO. Biopsies were obtained irrespective of the oesophageal mucosal appearance. A single microscopic field with the highest eosinophilic infiltration was used for diagnostic evaluation at magnification $\times 400$. The field of microscopic analysis equals 0.24 mm^2 . For every subject diagnosed with EoO, the following information was reviewed from their medical record: (1) age at diagnosis; (2) gender; (3) race; (4) presenting symptom(s); (5) medical history; (6) rural/urban locale; and (7) concurrent medication(s). Once we gathered all data we performed a subanalysis on a cohort that also had reported use of PPI ≥ 5 weeks prior to endoscopy. All presenting symptoms and allergy history were obtained from the initial primary care or gastroenterology clinic note. The use of PPI therapy was based upon prescriptions in our electronic medical record or documentation of such therapy in clinic notes, and only patients treated with high-dose PPI for at least 5 weeks were included in the study. Patients were excluded if they had known eosinophilic gastroenteritis, coeliac disease, inflammatory bowel disease, or hypereosinophilic syndrome or inadequate chart information from which to extrapolate the aforementioned data. Date of diagnosis was the date of first oesophageal biopsy showing ≥ 20 eosinophils/hpf. Patients were categorized by date of diagnosis into the 12 traditional calendar months and subsequently grouped into four seasons: winter, January–March; spring, April–June; summer, July–September; Autumn, October–December. To evaluate whether study results might be potentially influenced by the number of endoscopies (OGDs) performed in a given season or period, we also examined the number of OGDs carried out in our centre for the study period. The rate of OGDs grouped seasonally was

calculated and compared against the rate of cases diagnosed with EoO during the same period.

Statistical analysis

Both monthly and seasonal incidence were calculated using percentages based on date of diagnosis compared to total number of patients. Total number of patients per season was compared using the chi-squared test for equal proportions. Patient characteristics were analysed as follows: continuous variable of age using Kruskal–Wallis equation expressed as medians and quartiles and categorical/frequency variables (gender, race, rural/urban locale, presenting symptoms, medical history) with chi-squared test.^{23,24} If statistical significance was noted for any variable in the above analysis, the six seasonal subsets (Winter–Spring, Winter–Summer, Winter–Autumn, Spring–Summer, Spring–Autumn, and Summer–Autumn) were compared directly for that variable with a pairwise comparison. The Bonferroni correction was applied resulting in a statistical significance of $p < 0.0083$ when using a pairwise comparison for a given variable (traditional $p < 0.05$ was divided by the total number of subsets). SAS version 9.3 was used for statistical analysis (SAS Institute, Cary, NC, USA).

Results

A total of 20,718 patients were identified and their records evaluated. From this cohort, a total of 193 (0.93%) symptomatic patients had biopsy-proven oesophageal eosinophilia (≥ 20 eosinophils/hpf) and no seasonal variation was seen in the cohort (Table 1). However, only 57 (0.28%) had been adequately treated with PPI prior to diagnosis (i.e. non-PPI-ROE biopsy-proven EoO; ≥ 20 eosinophils/hpf) and a subanalysis was performed for this cohort (Table 2). The male/female ratio was 2:1 (39, 68.4% males and 18, 31.6% females). The age at diagnosis was (mean $\pm$ SD) 29.5 ± 17.0 years. Our population included 91.2% Caucasians, and 50.9% resided in a rural locale. The most common medical history components included asthma (12.3%) and food allergies (3.5%) and the most common presenting symptoms included dysphagia (50.9%) and heartburn (26.3%; Tables 3 and 4).

Incidence rates per month were as follows: January 10.9%, February 7.3%, March 5.2%, April 5.2%, May 9.3%, June 6.2%, July 8.8%, August 8.3%, September 9.3%, October 11.4%, November 8.8%, and December 9.3% ($p = 0.573$; Figure 1). Calculated seasonal variation as follows: winter 17.5%, spring 26.3%, summer 29.8%, and autumn 26.3% ($p = 0.393$; Figure 2).

Table 1. Characteristics of patients with oesophageal eosinophilia

	Total cohort	Winter	Spring	Summer	Autumn	<i>p</i> -value
No. of patients	193	45 (23.3)	40 (20.7)	51 (26.4)	57 (29.5)	0.393
Male	127 (65.8)	32 (71.1)	25 (62.5)	41 (80.4)	29 (50.9)	0.011
Age at diagnosis (years)	30.0 ± 16.5	30.7 ± 16.5	27.9 ± 16.4	30.4 ± 17.0	30.5 ± 16.4	0.849
Urban locale	81 (42.0)	19 (42.2)	16 (40.0)	25 (49.0)	21 (36.8)	0.632
Caucasian	176 (91.2)	37 (82.2)	35 (87.5)	49 (96.1)	55 (96.5)	0.035
Use of PPI at diagnosis	57 (29.5)	10 (22.2)	15 (37.5)	15 (29.4)	17 (29.8)	0.693

Values are *n* (%) or mean $\pm$ SD.

PPI, proton-pump inhibitor.

Table 2. Characteristics of patients with non-PPI-responsive oesophageal eosinophilia

	Total cohort	Winter	Spring	Summer	Autumn	<i>p</i> -value
No. of patients	57	10 (17.5)	15 (26.3)	17 (29.8)	15 (26.3)	0.703
Male	36 (68.4)	8 (80.0)	10 (66.7)	14 (82.4)	7 (46.7)	0.170
Age at diagnosis (years)	$29.5 \pm$	30.3 ± 19.2	26.0 ± 19.4	25.9 ± 16.0	25.8 ± 16.3	0.917
Urban locale	28 (49.1)	5 (50.0)	7 (46.7)	10 (58.8)	6 (40.0)	0.758
Caucasian	52 (91.2)	8 (80.0)	13 (86.7)	16 (94.1)	15 (100)	0.332
Duration of PPI treatment (months)	19.7 ± 31.4	33.3 ± 38.4	15.3 ± 20.1	20.6 ± 42.2	13.9 ± 19.1	0.450

Values are *n* (%) or mean $\pm$ SD.

PPI, proton-pump inhibitor.

Table 3. Medical history of patients with non-PPI responsive EoE

Condition	Total	Winter	Spring	Summer	Autumn	<i>p</i> -value
Asthma	7 (12.3)	1 (10.0)	2 (13.3)	1 (5.9)	3 (20.0)	0.687
Food allergy	2 (3.5)	1 (10.0)	0 (0.0)	1 (5.9)	0 (0.0)	0.540
Seasonal allergy	1 (1.8)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)	1.000
Allergic rhinitis	1 (1.8)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0.702

Values are *n* (%).

Table 4. Presenting symptoms of patients with non-PPI responsive EoE

Symptom	Total	Winter	Spring	Summer	Autumn	<i>p</i> -value
Dysphagia	29 (50.9)	7 (70.0)	6 (40.0)	10 (58.8)	6 (40.0)	0.346
Heartburn/reflux	15 (26.3)	4 (40.0)	6 (40.0)	4 (23.5)	1 (6.7)	0.124
Nausea/vomiting	13 (22.8)	1 (10.0)	4 (26.7)	5 (29.4)	3 (20.0)	0.715
Food impaction	10 (17.5)	3 (30.0)	3 (20.0)	1 (5.9)	3 (20.0)	0.387
Regurgitation	8 (14.0)	2 (20.0)	0 (0.0)	5 (29.4)	1 (6.7)	0.065

Values are *n* (%).

Figure 1. Monthly endoscopy and EoO frequencies at the University of Iowa Hospitals and Clinics from January 2003 to January 2013.

Although EoO rates and EoO numbers are higher in summer in spite of lower endoscopy numbers, there is still no statistical difference ($p = 0.4681$). Hence, there was no significant difference in the incidence between any of the months or seasons. Monthly and seasonal

trends were evaluated and there was no trend among months and seasons (p -values 0.438 and 0.322, respectively).

Interestingly, when the overall data period through 117 months was evaluated, a trend was found annually

Figure 2. Seasonal endoscopy numbers and incidence of eosinophilic oesophagitis at the University of Iowa Hospitals and Clinics from January 2003 to January 2013.

Table 5. Time trend tests for EoE rates in seasonal, monthly, annual, and overall study period

Time period	Cochran-Armitage test	p-value
Seasonal	−0.73	0.468
Monthly	−0.57	0.566
Annual	−2.30	0.022
Over study period	−2.36	0.019

($p=0.022$), and for the whole period for EoO rates in total endoscopy numbers (Cochran–Armitage p -value 0.019; Table 5). However, the monthly average endoscopy volumes were similar without a significant difference: January 1691, February 1534, March 1553, April 1732, May 1789, June 1836, July 1663, August 1809, September 1603, October 1920, November 1736, and December 1795.

Discussion

Our study did not demonstrate an increased incidence in any specific month or season in 193 patients with oesophageal eosinophilia. However, due to current consensus that definition of EoO includes nonresponse to at least 5–8 weeks of PPI treatment, we performed a

subanalysis on a cohort of 57 patients that could be defined as suffering from EoO. Several studies looked at the possibility of a seasonal variation in the incidence of EoO as a way to evaluate if aeroallergens truly are an aetiology. Unlike our study, these studies showed a trend towards a seasonal variation in the incidence of EoO. However, the individual studies differ in their conclusions regarding the precise season. Prasad et al.¹⁷ evaluated the incidence of EoO in a cohort of 78 patients (55 adults and 23 children) in Olmsted County, Minnesota over a 30-year period, concluding that the incidence of EoO was greatest in the late summer/autumn. A similar study in Florida on two separate cohorts of 41 adult patients primarily and 37 adult patients secondarily concluded that the incidence of EoO was greatest in the spring/summer months correlating with traditionally increased seasonal outdoor aeroallergens.¹⁸ A study on a cohort of 127 patients reported an increased diagnosis of EoO in the spring months correlating with pollen counts suggesting a potential role for aeroallergens.¹⁹ A recent study had evaluated the onset of symptoms in a cohort of children and adolescent under the age of 21 and found that they did not vary by season, hence indicating that allergens triggering EoO are present all year around.²¹ Another study on the incidence of EoO in the Netherlands similarly found no seasonal variation in the diagnosis of

EoO.²⁵ A few case reports had demonstrated de-novo onset of EoO after large volume allergen exposures.^{26,27}

Given the similarity in geographic locale to Olmsted County, Minnesota, and thus the likelihood that environmental factors would be relatively similar, we had postulated that our results would be supportive of previous findings.¹⁷ Hurrell et al.²⁸ had demonstrated that EoO has the highest prevalence in the cold and arid zones. However, unlike these studies conducted in the similar climate environments, we did not find an increased monthly or seasonal incidence in our population.

Our study cohort had a male predominance of the disease, a younger age at diagnosis, with atopic disorders, and most common presenting symptoms of dysphagia and food impaction, which is consistent with previously reported findings.^{29–32} Our study population encompassed a large, homogenous, mainly Caucasian (90.4%) upper midwest cohort similar to state of Iowa general population. According to the 2009 Census, 91.3% of the population of Iowa was Caucasian, 5.0% was of Hispanic or Latino origin, 2.9% was Black or African American, and all the rest were American Indian, Alaska Native, Asian, Native Hawaiian, or other Pacific Islander.³³ This represents one of the main strengths of our study, as few reports have investigated mainly Caucasian population mostly living in rural areas.

Our cohort had a lower rate of allergies compared to other studies. This may be explained by low population migration rate, which stabilizes a patient's exposure to the same allergens restricted to their environment prior to and during the development of EoO. According to the US Bureau of the Census, Iowa's net migration rate change in year 2000–2009 was between –2.8% and 1.2%.³³

Although no seasonal changes or trends were significantly seen, we found that winter months correlate with the lowest incidence in our study. These findings suggest that traditional seasonal aeroallergens may play a role in the pathogenesis of EoO and are continuously present to a certain degree throughout the year. Interestingly, a nonsignificant increased incidence in males in winter and summer compared to spring and autumn was also noted, and the significance of these finding remains unclear at this time. Sperry et al.³⁴ demonstrated that while age and dysphagia differed by gender and race among EoO patients, the majority of symptoms and findings were not different across groups, even after stratification by age.

Recently it has been shown that oesophageal squamous cells from gastro-oesophageal reflux disease and EoO patients express similar levels of eotaxin-3 when stimulated by Th2 cytokines. Omeprazole has been shown to block that eotaxin-3 expression, hence

suggesting that PPIs might have eosinophil-reducing effects independent of effects on acid reflux and that response to PPIs might not distinguish EoO from gastro-oesophageal reflux disease.^{35,36} In view of current data, the consensus is to include only non-PPI-ROE patients in any EoO study cohort; hence a trial of PPI therapy remains an important prerequisite to the diagnosis EoO.³⁷ Due to this consensus, we included only the group that had been treated with ≥ 5 weeks of PPI treatment prior to upper endoscopy (0.28%). According to latest guidelines, an 8-week trial of PPI is recommended prior to diagnosing non-PPI-ROE. However, there are few studies that have addressed specific PPI dosage and treatment duration as initial therapy for oesophageal eosinophilia.³⁵

Our study has some limitations. We had adopted the common method used in previous studies, defining the date of endoscopy and oesophageal biopsy as date of diagnosis. The actual date of endoscopy can be influenced by many factors, and may be delayed to a time much later than the peak severity of the symptoms. However, it would be difficult to correlate date of diagnosis with patient-reported symptom onset given lack of reproducibility for such a method.³⁸ Furthermore, gastro-oesophageal reflux disease was excluded by lack of response to high-dose PPI and not pH monitoring.^{39,40} Due to our strict inclusion criteria we cannot rule out the possibility that a larger sample size would have actually detected more obvious differences.

In summary, no monthly or seasonal trend was noted in our cohort of 57 patients with EoO. This could support the fact that traditional outdoor aeroallergens may either play less of a role in the pathogenesis of the disease or may be consistently present throughout the year. We are currently evaluating the role of specific allergens (pollen, wheat, corn, and other agricultural products) in the pathogenesis of EoO and believe that this may be the goal of future studies.

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Conflict of interest

The authors declare that there is no conflict of interest.

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