Eosinophilic esophagitis: studies on an emerging disease
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Chapter 2

Rapidly increasing incidence of eosinophilic esophagitis in a large cohort

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Abstract

**Background:** Recent literature has shown increasing incidence and prevalence rates of eosinophilic esophagitis (EoE). However, data are mainly based on small studies and come from centers dedicated to EoE. Aim of this study was to estimate the incidence rates of EoE by using a large database.

**Methods:** We performed a cross-sectional study of the pathology reports describing esophageal eosinophilia from 1996 through 2010, using the nationwide network and registry of histo- and cytopathology in The Netherlands (PALGA). All histopathology reports nationwide enter this database. We classified cases according to the diagnosis made by the pathologist. Annual incidence rates of EoE were estimated.

**Key Results:** Our search criteria yielded 8838 positive pathology reports. Eosinophilic esophagitis was diagnosed in 674 patients, of which 74% were men. In another 174 patients, no distinction was made between eosinophilia caused by gastro-esophageal reflux disease or EoE. The incidence of EoE increased considerably over the years, being 0.01 in 1996, 0.01 in 2000, 0.14 in 2005, and 1.31 per 100 000 persons in 2010. Eosinophilic esophagitis was diagnosed in all age groups, but in 2010 the highest incidence was seen in 20-29 years old males, in whom it was estimated to be 3.23 per 100 000 persons. The incidence in children was 0.73 per 100 000 in 2010. No seasonal variation in diagnosis of EoE was observed.

**Conclusions & Inferences:** In this large study, we found robust data on increasing incidence rates of pediatric and adult EoE in the past 15 years. This rapidly increasing incidence has not reached a plateau yet.
Introduction

Eosinophilic esophagitis (EoE) is an increasingly recognized disorder characterized by an abnormal accumulation of eosinophils in the esophageal mucosa associated with symptoms of dysphagia and esophageal food impaction.\(^1\) Diagnostic hallmark is the histopathological finding of mucosal eosinophilia. Current guideline recommendations state that 15 or more eosinophils per high power field (HPF) on hematoxylin and eosin (H&E) stain in at least one biopsy are adequate for diagnosis in the appropriate clinical setting.\(^1\)

Although epidemiological information on EoE is scarce, men, children and young adults seem to be most often affected.\(^1\) Furthermore, a large proportion of EoE patients has an atopic constitution, and seasonal variation in the diagnosis of EoE has been reported in several publications.\(^2-5\)

Recently, increasing prevalence and incidence rates of EoE in both children and adults have been reported in the literature.\(^2,6-9\) However, the fact that most studies were performed in relatively small populations could lead to bias and inaccurate incidence figures and therefore jeopardize the external validity.\(^7-9\) Moreover, reliable incidence figures from Western European countries remain scarce.\(^7,8,10\) Accurate and up-to-date incidence figures are essential to bring us closer to a better understanding of the extent of this disease in the general population.

Therefore, the main objective of this nationwide study was to estimate the incidence of EoE from January 1, 1996 to December 31, 2010 in children and adults in a large Western European population. Furthermore, age at diagnosis and seasonal variation in diagnosis were determined.

Materials and methods

Histopathology data collection

Data were retrieved according to the ethical guidelines ‘Code for proper secondary use of human tissue in the Netherlands’ established by the Dutch Federation of Medical Sciences (http://www.federa.org). Since 1971, all histopathology and cytopathology reports in The Netherlands are collected in a computerized national database (PALGA), which has national coverage since 1991.\(^11\) In this database, summaries of all histopathology and cytopathology reports of patients are collected and coded comparable to the Systematized Nomenclature of Medicine (SNOMED) issued by the College of American Pathologists.\(^12\) This creates unique possibilities for studying pathology-based incidence rates. Each office day on average 10 000 reports are added to the database. By the end of 2010, PALGA contained approximately 53 million reports on ample 11 million patients. These reports contain encoded patient data securing privacy of the patient, a report identifier, the type of sample, a morphological term, the conclusions, and a diagnostic code containing a topographic term.

Although the indication for the endoscopic procedure and details with regard to the number and intra-esophageal location of biopsies are not uniformly registered, each pathology
report can be traced to an individual patient. However, in PALGA it is not possible to access additional clinical data. Therefore, prevalence rates could not be estimated. We based our study on data recorded in the PALGA database from 1996 through 2010.

**Case identification**

We generated a database of reports of esophageal biopsies searching for the diagnosis code for esophagus in combination with the diagnosis code for eosinophilic inflammation, eosinophilic hyperplasia, or eosinophilia, or one of the search terms ‘eosinophi’ and ‘allerg’. Primary carcinomas were excluded from entering the database.

We detected all reports with esophageal eosinophilia and consequently classified them according to the degree of eosinophilic infiltration and the histopathological diagnosis made by the pathologist. In a few reports, the number of eosinophils was mentioned and could be separated into a group of <15 and a group of ≥15 eosinophils per HPF. In the other reports mentioning the degree of eosinophilia, ‘mild eosinophilia’ was considered to be <15 eosinophils per HPF. When the pathologist described the degree of eosinophilia in terms as ‘impressive’, ‘pronounced’, or ‘high’ (or words of similar meaning) the degree was interpreted as being >15 eosinophils per HPF by the investigators.

**Statistical analysis**

The entire population of The Netherlands was considered to be at risk for developing esophageal eosinophilia. Annual incidence rates of EoE were inferred from the total number of newly diagnosed cases and the corresponding population statistics in the 1996-2010 period (http://www.cbs.nl). Incidence rates were denoted for both genders, for children and adults (<18 resp. ≥18 years of age at diagnosis), and in 10-year age strata. To assess seasonal variation in the diagnosis of EoE, the date of first pathology report diagnosing EoE was taken as the date of diagnosis. The Rayleigh test for directional statistics was used to analyze whether or not the months of diagnosis were randomly distributed. We performed this statistical test in R, an open source statistical program for data analysis and graphics. All other statistical analyses were performed by using PASW Statistics 18.0.2 (SPSS Inc., Chicago, IL, USA).

**Results**

**Biopsy characteristics**

The PALGA query between January 1, 1996, and December 31, 2010 yielded 8838 pathology reports of 8321 patients positive for the selected search criteria. We identified esophageal eosinophilia in 3524 reports (Figure 1). In the other reports in which we found the term ‘eosinophilia’, the reported eosinophilia was not located in the esophagus or was described to be not present at all.
Of the 3524 reports in which esophageal eosinophilia was identified, the degree of eosinophilia was mild, pronounced or not described in 1116 (32%), 685 (19%) and 1723 (49%) reports, respectively. The degree of eosinophilia was described as mild in 40 (5%) and pronounced in 223 (29%) biopsies diagnosed with EoE. It was not described in 508 (66%) biopsies diagnosed with EoE by the pathologist.

Of the 685 biopsies in which pronounced eosinophilia was present, 223 (33%) were diagnosed with EoE, 161 (24%) with gastro-esophageal reflux disease (GERD), 102 (15%) with no clear distinction between GERD and EoE, and 46 (7%) with other diagnoses; no diagnosis was made in 153 (22%).

Esophageal biopsies showing eosinophilia had been diagnosed by the pathologist with GERD (1478), EoE (771), no clear distinction between GERD and EoE (196), or other diagnoses (269) – Barrett’s esophagitis, fungal esophagitis, or eosinophilic gastroenteritis. In 810 biopsy reports no clear conclusion had been drawn.

![Flow chart of case finding](image)

**Figure 1.** Flow chart of case finding. Some of the reports meeting the search criteria were incorrect or were revisions of previous reports. EoE: eosinophilic esophagitis; GERD: gastroesophageal reflux disease.

**Patient characteristics**

In the 1996-2010 period, we found 3218 patients with esophageal eosinophilia of which 2130 (66%) were men and 1088 (34%) were women (P<0.001). We found 540 (17%) children and 2678 (83%) adults.
From this group, 674 patients had been newly diagnosed with EoE in The Netherlands. Of those, 501 (74%) were men and 173 (26%) were women (P<0.001). We found 136 (20%) pediatric and 538 (80%) adult patients with EoE. Mean age at diagnosis was 36.9 (SD 20.0) years; it was not significantly different between men and women (P=0.073). Age distribution of EoE cases in 10-year strata is shown in Figure 2. Of all patients diagnosed with EoE, 56% were diagnosed in 2009 or 2010.

For 135 EoE patients, multiple histopathology reports describing esophageal eosinophilia were found. Forty three of these patients were diagnosed with EoE after having been diagnosed otherwise based on previous biopsies. In 13 of them no distinction between GERD and EoE was made on previous biopsies; 12 of them were diagnosed with GERD based on previous biopsies; 1 of them was diagnosed with fungal esophagitis and in 17 of them no clear conclusion was drawn. The pathologist could not make a clear distinction between GERD and EoE in 174 patients.

Incidence rates of EoE

According to the Central Bureau of Statistics Netherlands (CBS) the population in The Netherlands rose from 15 530 498 inhabitants in 1996 to 16 615 394 inhabitants in 2010. During this period, the male proportion of the population was stable between 49.44 and 49.50 percent. In the entire population, 674 patients were diagnosed with EoE, giving an average annual incidence of 0.28 (95% CI: 0.26-0.30) per 100 000 persons. Estimated incidence rates per year are shown in Figure 3. The incidence of EoE increased considerably.
with time, from 0.01 (95% CI: 0-0.02) in 1996 to 1.31 (95% CI: 1.13-1.48) per 100 000 persons per year in 2010. Eosinophilic esophagitis was diagnosed in all age groups, but the incidence was highest in 2010 in the 20-29 year age group for both men (3.23; 95% CI: 2.13-4.33 per 100 000 persons) and women (1.30; 95% CI: 0.59-2.00 per 100 000 persons) (Table 1). The incidence in 2010 was 0.73 (95% CI: 0.45-1.02) per 100 000 children and 1.45 (95% CI: 1.25-1.66) per 100 000 adults.

Seasonal variation of EoE

We found no seasonal variation in the diagnosis of EoE (Figure 4). The Rayleigh test for uniform distribution was non-significant (P=0.27), indicating a random distribution of the month of diagnosis through the year.
Table 1. Incidence per 100,000 persons per age group in 2010

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Male (95% CI)</th>
<th>Female (95% CI)</th>
<th>Total (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>0.65 (0.13-1.16)</td>
<td>0.45 (0.01-0.89)</td>
<td>0.55 (0.21-0.89)</td>
</tr>
<tr>
<td>10-19</td>
<td>1.56 (0.80-2.33)</td>
<td>0.31 (0.00-0.65)</td>
<td>0.95 (0.52-1.38)</td>
</tr>
<tr>
<td>20-29</td>
<td>3.23 (2.13-4.33)</td>
<td>1.30 (0.59-2.00)</td>
<td>2.27 (1.61-2.93)</td>
</tr>
<tr>
<td>30-39</td>
<td>2.54 (1.58-3.50)</td>
<td>0.94 (0.36-1.53)</td>
<td>1.74 (1.18-2.30)</td>
</tr>
<tr>
<td>40-49</td>
<td>2.37 (1.53-3.20)</td>
<td>0.86 (0.35-1.36)</td>
<td>1.62 (1.13-2.11)</td>
</tr>
<tr>
<td>50-59</td>
<td>2.43 (1.53-3.33)</td>
<td>0.88 (0.33-1.42)</td>
<td>1.66 (1.13-2.19)</td>
</tr>
<tr>
<td>60-69</td>
<td>1.05 (0.78-2.38)</td>
<td>0.52 (0.06-0.98)</td>
<td>0.79 (0.30-1.19)</td>
</tr>
<tr>
<td>70-79</td>
<td>0.94 (0.12-1.77)</td>
<td>0.48 (0.00-1.03)</td>
<td>0.69 (0.21-1.18)</td>
</tr>
<tr>
<td>80-89</td>
<td>0.46 (0.00-1.36)</td>
<td>0.26 (0.00-0.78)</td>
<td>0.34 (0.00-0.80)</td>
</tr>
<tr>
<td>Total</td>
<td>1.91 (1.61-2.21)</td>
<td>0.71 (0.53-0.90)</td>
<td>1.31 (1.13-1.48)</td>
</tr>
</tbody>
</table>

Figure 4. Rose diagram showing distribution of month of diagnosis of eosinophilic esophagitis. For each month, a sector is drawn corresponding to the percentage of cases.
Discussion

Our study is the largest incidence study of EoE. We found a rapid increase in the incidence rate of EoE in a Western European area over the last 15 years. Considering the stronger increase in the later time intervals of the study, it is not likely that this increase has reached a plateau yet, and the incidence of EoE may approach the incidence rates of Crohn’s disease in the near future.15

The estimated incidence rates in our study are lower than recently reported estimates from other Western European countries and the USA.6-8 Whereas our population of EoE patients resembles previously described EoE populations in age and gender, several other factors could account for the different incidence rates.6,8,16-18 First, we only included cases diagnosed with EoE by the pathologist. Diagnosing EoE requires awareness of this disease among pathologists and endoscopists, who need to take biopsies at multiple levels, even when no obvious endoscopic signs of EoE are present. In the 1990s little was known about EoE and esophageal biopsies were not regularly taken during upper endoscopy in patients with dysphagia. This will have caused an underestimation of the true number of EoE patients in our cohort, in particular in the first years. However, this would have also been the case in the other studies. A second explanation for the observed lower incidence rate may be more important. The use of a nationwide registry such as PALGA minimizes selection bias, which is a major drawback of smaller retrospective studies. The higher incidence rates reported by other groups come from centers with a special interest in EoE and it is possible that they represent an overestimation of the true rates.8 Thirdly, in our study we strictly included only the reports in which the pathologist’s conclusion was highly suggestive of EoE. We did not include the 174 cases in which the pathologist could not make a clear distinction between GERD and EoE due to a lack of clinical information available to the pathologist, such as localization of the biopsies taken. Furthermore, 161 biopsy reports mentioning pronounced eosinophilia had been diagnosed with GERD and 153 had no diagnosis; some of these may have been missed cases of EoE, which were also not taken into the analysis. This may have led to a slight underestimation of the incidence of EoE, making the finding of a rapidly increasing incidence even more convincing.

Interestingly, the incidence curves of pediatric and adult EoE differed considerably in our study. The increasing incidence rates of pediatric EoE in our cohort started several years before the rise of the adult incidence rates. In contrast, toward the end of our study the pediatric incidence rates seem to have reached a plateau, whereas the incidence among adults increased even stronger. This finding could suggest an earlier awareness among pediatricians compared to other physicians but could also indicate a difference in pathophysiological mechanism of the disease.

It is subject of debate whether the increase in incidence rate reflects a true increase due to environmental factors or merely increased awareness and recognition of the disease.6,9,19 The parallel rise in asthma and other allergic disorders such as atopic dermatitis and allergic rhinitis would be supportive of an environmentally driven increase of the incidence of EoE.20,21 Factors generally considered to be contributing to this trend are western lifestyle and a high level of hygiene, referred to as the ‘hygiene hypothesis’.22 Furthermore, the increasing prevalence of GERD over the past decades could also contribute to our finding of
a rising incidence of EoE, as GERD is more and more being considered a possible etiological factor for development of EoE.\textsuperscript{23-26} On the other hand, it is likely that the awareness of EoE among physicians and pathologists has increased during the time interval of this study. It is thus possible that the time trend in the incidence could be subject to bias. However, one can imagine that a ‘true’ environmentally driven increase would actually in itself give rise to better awareness of the disease as well.

Our study design entails some limitations. In the PALGA database, only histopathological and no clinical data are available. Information on the exact number of intraepithelial eosinophils was not present in the majority of the report conclusions. Therefore, to find patients diagnosed with EoE, the diagnosis made by the pathologist was leading in our study. Although we acknowledge that this is a suboptimal approach as compared to precise counting of the number of eosinophils per HPF, we think we were able to interpret correctly the severity of eosinophilia in our cases. Moreover, in a substantial number of cases the final diagnosis made by the pathologist could also be taken into account in relation to the clinical picture. Nevertheless, we have included some reports in which mild esophageal eosinophilia has led to a diagnosis of EoE. This group was relatively small and contained 30 (4%) of the 674 patients diagnosed with EoE. Since 2007, the international consensus recommends a peak count of 15 or more esophageal intraepithelial eosinophils per HPF for the diagnosis of EoE.\textsuperscript{27} In this small number of patients the certainty of the diagnosis of EoE is questionable. Close cooperation between clinicians and pathologists, and strict compliance with the diagnostic criteria could improve the certainty of the diagnosis. We suggest that every histopathology report describing esophageal eosinophilia should contain information on the exact peak number of eosinophils at multiple levels of the esophagus.

We observed no seasonal influence on the incidence of EoE in this study. Diagnosis dates were randomly distributed over the year. The debate on the presence or absence of a seasonal pattern in EoE is still open. Some authors have reported no seasonal variation in the onset of symptoms, suggesting that allergens triggering EoE are present during all seasons.\textsuperscript{28} Conversely, other authors have described that fewer patients were diagnosed during winter.\textsuperscript{3,4} Others have observed early summer/fall preponderance in the diagnosis of EoE.\textsuperscript{2,5} We know from previous studies that patients with dysphagia generally wait months if not years to present for endoscopy and biopsy taking, obscuring the actual date of onset of the disease.\textsuperscript{28,29} This diagnostic delay has probably influenced our data on seasonal variation; however, the same holds true for previous studies evaluating seasonal distribution.

In conclusion, we present the largest incidence study in EoE showing robust data on increasing incidence rates in both children and adults. Our results corroborate previous reports of rising incidence rates in the USA and Europe. The rapid increase of EoE over the past 15 years has not reached a plateau yet. It is hoped that the persistently increasing prevalence of EoE will trigger more research into pathophysiology and treatment of this disease, because there are currently no therapies registered for EoE and all drugs used for this disease are prescribed off-label.
References