Epidemiology of Eosinophilic Esophagitis

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Key Words

Eosinophilic esophagitis · Incidence · Prevalence · Epidemiology

Abstract

Eosinophilic esophagitis (EoE) is an allergy-associated disease defined clinically by esophagus-related symptoms in combination with a dense esophageal eosinophilia, both of which are unresponsive to prolonged acid suppression with proton pump inhibitors. Over the last two decades EoE has increasingly been recognized in various geographical areas (mostly industrialized countries) with high socioeconomic development. The prevalence rate is increasing and reaches up to 50 patients per 100,000 inhabitants in some indicator regions. Whether this increased prevalence is due to a real increase in incidence, a result of increased awareness by health care providers or because of the nonfatal nature of EoE adding more and more cases to the patient pool is still a matter of controversy. Several studies have consistently demonstrated a male predominance in EoE, with a male-to-female risk ratio of 3:1. The average age at diagnosis ranges between 30 and 50 years and suggests that EoE is a disease of the middle-aged man. It can affect patients of every race, but the disease is more common among Caucasians. In both children and adults, EoE has been clearly associated with allergies to food and aeroallergens, and most EoE patients present with a personal allergic background (e.g. asthma, rhinoconjunctivitis or oral allergy syndrome). In conclusion, knowledge of epidemiologic parameters of EoE is crucial for

identifying risk factors as well as pathogenic mechanisms, planning preventive measures and determining optimal treatment strategies.

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Eosinophilic Esophagitis: A New Esophageal Disease with Increasing Incidence and Prevalence

Epidemiology (Greek terms, ‘epi’ = among; ‘demos’ = people and ‘logos’ = study) characterizes factors affecting the health and the illness of a population. It serves as the foundation of any intervention made in public health as well as in clinical practice, and relies on a number of scientific disciplines such as medicine, biology, geography and social science. The clinical and socioeconomic relevance of any disease is determined by the knowledge of its epidemiologic parameters. In particular, it is the incidence and prevalence among a certain population. This knowledge is crucial for identifying risk factors as well as understanding pathogenetic mechanisms, planning preventive measures and optimizing treatment strategies.

Eosinophilic esophagitis (EoE) is a relatively new immune-mediated inflammatory disorder of the esophagus [1, 2]. It is clinicopathologically characterized by esophageal symptoms in combination with dense esophageal eosinophilia [3]. Several epidemiological reports have recently suggested that EoE is being diagnosed with a dramatically increasing frequency over the last years in westernized/industrialized countries. So far, the vast ma-

jority of studies addressing epidemiological questions in EoE rely on retrospective analysis of pathology reports with reexaminations of biopsy specimens or on analysis of endoscopy reports. In recent years, however, more and more population-based epidemiologic information from geographically confined regions with longitudinal analysis is being provided from which more substantive epidemiologic statements can be made.

Prevalence of Esophageal Eosinophilia

Eosinophils are found in concentrations of up to 350 cells/mm³ in the peripheral blood of healthy individuals and are present in the mucosa of all areas of the digestive tract, except the esophagus [4, 5]. The presence of eosinophils in the esophagus is therefore commonly associated with disease. Of note, esophageal eosinophilia is not exclusively limited to EoE. Eosinophilic infiltration of the esophagus has been reported in patients with gastroesophageal reflux disease, Barrett's esophagus and rare conditions such as drug-induced esophagitis, infectious and parasitic infection, vasculitis, Crohn's disease, and eosinophilic gastroenteritis affecting the esophagus. Esophageal eosinophilia therefore requires a process of differential diagnosis and cannot, *a priori*, be equated with EoE [4, 6].

A retrospective analysis and histologic reevaluation of pediatric esophageal biopsy specimens with reflux esophagitis obtained between 1982 and 1999 revealed a substantial number of patients who had >15 eosinophils/high-power field (HPF). This implicated that esophageal eosinophilia may have been an underrecognized finding already in the late 1980s and 1990s [7]. In a prospective cross-sectional population-based study of the adult Swedish population (mean age: 54 years, 49% men), the prevalence of esophageal eosinophils in the general population was determined by taking biopsies of the distal part of esophagus [5]. Eosinophilic infiltration of the esophageal epithelium was arbitrarily classified as 'low grade' when 1–4 eosinophils/HPF were found, 'possible EoE' with 5–14, 'probable EoE' with 15–20 and 'definite EoE' with ≥20. The prevalence of any eosinophil infiltration in the most distal parts of the esophagus was 4.8% in the general population, predominantly among men (63%), with 54% of these subjects reporting reflux symptoms. Therefore, the presence of esophageal eosinophils may be more common in the general population than expected. In only 4 subjects (0.4% of the general population) were ≥20 eosinophils/HPF found, and 3 of them reported trouble-

some reflux symptoms without any endoscopic characteristics of erosive esophagitis. Only 1 subject with 'definite EoE' presented with asthma and dysphagia, which suggests this patient was suffering from clinicopathologically defined EoE. 'Probable EoE' was present in 7 and 'possible EoE' in 25 subjects. On evaluation of two biopsy sites (taken at 2 cm above and at the Z-line), the presence of eosinophils was positively associated with erosive esophagitis, hiatus hernia, narrowing of the esophageal lumen and esophageal ulcer, thereby suggesting that the presence of esophageal eosinophils, especially in the distal esophageal portions, may be a manifestation of reflux disease. Conversely, patients with <15 eosinophils/HPF on histological evaluation may present with similar endoscopic findings and clinical symptoms as patients meeting the consensus definition of EoE. This raises an important question about the histological cutoff value of eosinophils/HPF for the diagnosis of EoE and, as a result, the pathophysiological contribution of esophageal eosinophilia to the development of EoE [8].

Incidence and Prevalence of EoE Based on Endoscopy and Histopathology Reports

Increasing prevalence of EoE has mostly been described by studies based on retrospective evaluation of pathological or endoscopic databases. Substantially increasing incidence rates in both pediatric and adult patients have been shown in a Dutch cross-sectional study using the nationwide network and registry of histopathology reports describing esophageal eosinophilia from 1996 through 2010 [9]. By the end of 2003, a prevalence rate of 43 per 100,000 children was reached in the pediatric population of Hamilton County, with a substantial increase in the years 2000–2003 [10]. Other studies on retrospective review of upper endoscopy procedure or histopathology reports of children also describe increasing prevalence rates during the last years [11–14]. In a prospective evaluation of children and infants in Southern Denmark (pediatric population of 256,164; age: 0–16 years) with symptoms of gastroesophageal reflux disease during an 18-month period, 6 patients were diagnosed with EoE, corresponding to an annual incidence rate of 1.6 per 100,000 children [15]. A recent review summarizing 25 epidemiological studies concerning incidence and prevalence of EoE in children showed that the incidence of EoE varied depending on the geographic location from 0.7 to 10/100,000 per person-year and the prevalence ranged from 0.2 to 43/100,000 children and increased over time.

The pooled prevalence of EoE was 3.7% in esophagogastroduodenoscopy performed for any indication, 24% in histologic esophageal disease, 2.3% in celiac disease and 2.6% in esophagogastroduodenoscopy performed for abdominal pain. The highest prevalence of EoE occurred in children with dysphagia and food impaction [16].

Similar findings have been reported from adult cohorts. A survey administered to members of the American College of Gastroenterology in 2008 (with a response rate of 17%) revealed an estimated prevalence rate of 52 patients with EoE per 100,000 inhabitants [17]. In a national pathology database (Caris Diagnostics, Irving, Tex., USA), 363 cases of EoE from a cohort of upper endoscopies were identified in more than 74,000 upper endoscopies. A prevalence rate of approximately 0.5% per endoscopy was calculated. The prevalence of EoE increased significantly during the study period [18]. A review of esophageal biopsy specimens from 1992 to 2004 (pathology database at the University of Pennsylvania) showed a cumulative prevalence of 1.7% (10 cases per 584 reviewed esophageal biopsies), but 9 of 10 cases were identified in the years 2001–2004 [19], again indicating an increasing prevalence of EoE. An unexpectedly high prevalence rate of EoE of 6.5% was reported in a prospective study with 400 consecutively enrolled adult patients who underwent a routine upper endoscopy [20]. Interestingly, when patients are referred for an upper endoscopy due to dysphagia, a diagnosis of EoE can be established in 10–15% of the cases [21, 22], with 11% due to food impactions [23]. Considerably higher rates are found when endoscopies were performed for the indication of bolus obstruction in children as an association with the diagnosis of EoE was found in up to 40% [24]. Patients older than 50 years with dysphagia are more likely to be diagnosed with EoE [21, 22].

Based on these studies, we can conclude that the incidence and prevalence of pediatric and adult EoE has been increasing throughout the last years. However, it still needs to be determined whether this increase is based on an accumulation of EoE cases as the mortality from EoE is low, or whether it is based on an increasing incidence, as suggested by recent studies in geographically confined areas.

Incidence and Prevalence of EoE in Geographically Confined Regions

Several longitudinal studies have evaluated geographically confined regions and will be discussed here [25–28]. In a retrospective and observational study in a geo-

graphically isolated community of 198,000 inhabitants in Townsville (Qld., Australia), adult residents were diagnosed with EoE after review of physician, computerized endoscopic and hospital records [26]. Up to September 2002, a total of 31 patients had been diagnosed with EoE: no patients between 1981 and 1994, 12 patients between 1995 and 2000, and 19 patients between January 2001 and September 2002. This clearly indicates an increasing incidence of EoE in this area. At the end of 2002, the prevalence of EoE reached 15.6 patients per 100,000 inhabitants.

Castilla-La Mancha is a rural area located in the center of Spain with a population of approximately 102,000 inhabitants [25]. No relevant demographic changes were noted during the 2005–2011 study period in the region. Two gastroenterological departments served as referral centers for family physicians and emergency departments with a high awareness for EoE. The mean annual incidence rate of EoE during the study period was 6.37 per 100,000 inhabitants. The prevalence reached 44.6 cases per 100,000 inhabitants by the end of 2011. Interestingly, an unexpectedly high male-to-female ratio of 19:1 with an average age of 29.4 years was observed.

The Olten County area is situated in the northwestern part of Switzerland [27, 29]. The area, which has an urban/suburban character, had no relevant demographic changes and no structural changes to its medical system within the past decades. About 90,000 inhabitants live in this geographically circumscribed and socioeconomically stable region. Since 1989, EoE patients with PPI-refractory esophageal symptoms, EoE-consistent endoscopic abnormalities and a peak infiltration of the esophageal epithelium with ≥ 24 eosinophils/HPF have been prospectively enrolled into a continuing community-based database. The diagnostic and enrolment procedures have remained almost unchanged over the past 20 years.

A recent analysis of this database showed that the incidence and prevalence of EoE has been substantially on the rise [27]. An annual incidence of 2.45 new EoE cases per 100,000 inhabitants per year was found with a pronounced increase in the last 6 years (4.4–7.4/100,000). The prevalence increased to 43 patients per 100,000 inhabitants in 2009. This increase occurred in the face of a constant diagnostic delay (defined as the time interval from the onset of EoE-attributed symptoms to EoE diagnosis) assessed in two time intervals from 1989 to 1999 and from 2000 to 2009, with a median diagnostic delay of 3 years (interquartile range: 2–5, range: 0–17; $n = 10$) and of 2 years (interquartile range: 1–7, range: 0–23; $n = 30$), as well as a lack of EoE awareness programs.

Comparable results have been reported from Olmsted County, a geographically confined region in Minnesota (USA) with a population of 120,000 inhabitants [28] that sociodemographically mirrors the US white population. Residents of this county receive their medical care almost exclusively from two group practices. EoE patients were identified through the medical records storage system for this region (Rochester Epidemiology Project database) by an electronic search using the terms 'esophagitis' and 'food bolus impaction'. Patients having ≥ 15 eosinophils/HPF on endoscopy with esophageal biopsies were included in the analysis. The cumulative age- and gender-adjusted incidence rate between 1976 and 2005 was calculated to be 2.39 (1.85–2.93) per 100,000 patient-years. The prevalence of EoE reached 55.0 per 100,000 inhabitants as of January 1, 2006. Analysis clearly indicated that the incidence of EoE increased over time, from 0.35 (1991–1995) to 9.45 per 100,000 person-years (2001–2005).

The results from these four studies indicate that the incidence and prevalence of EoE is increasing. The differences in the incidence and prevalence rates may be explained by the different threshold values for eosinophils per HPF used for the diagnosis of EoE, different geographical locations and different time frames when the studies were performed. Of note, by the end of 2002 the prevalence of EoE was approximately 16 patients per 100,000 inhabitants in Townsville County, 13 in Olten County, and 27 in Olmsted County. Considering the methodological differences between the three studies, it is roughly within the same range.

Demographic Profile of EoE Patients

Age Distribution

EoE can be found in all age groups, but most studies investigating adult EoE found the average age for subjects with EoE to be between 30 and 50 years, which suggests EoE is a disease of middle-aged adults [18, 20, 21, 26–28, 30].

Several studies have reported a substantial time lag between the onset of symptoms and diagnosis (diagnostic delay), which in some cases can be attributed to unawareness of sentinel features at endoscopy and, as a result, the absence of histological evaluation [26]. A substantial proportion of the diagnostic delay must be attributed to the patients who learn to cope with their swallowing difficulties with evasive maneuvers, thereby postponing a medical consultation. Therefore, age at diagnosis does not at all correlate with the onset of EoE-attributed symptoms.

Croese et al. [26] described an average diagnostic delay of 54 months (range: 0–180). The average duration between the onset of symptoms and diagnosis of EoE was reported to be 4.2 years (range: 0–44) [31] in a German study and 4.8 years (range: 0–22) in a study from Switzerland [29]. An updated analysis from the same Swiss database shows a median diagnostic delay of 3 years (1989–1999) and 2 years (2000–2009), which did not change significantly during the last two decades [27].

Gender and Social Parameters

EoE studies have concordantly demonstrated that males are significantly more affected with EoE than females, with 60–80% of all cases diagnosed being males. Analysis of studies with detailed demographic information of adult patients has shown that, on average, 76% of those affected were males, thereby suggesting a male-to-female risk ratio of 3:1 [32].

Patients with EoE have been reported worldwide, but the vast majority of EoE cases and cohorts are reported from industrialized and westernized countries, such as the USA, Europe and Australia, whereas almost no reports come from tropical areas and/or developing countries [32]. EoE has been identified in a variety of ethnic backgrounds, including Caucasians, African Americans, Hispanics and Asians. So far, most studies have shown that Caucasians are the most frequently diagnosed group with EoE, but there is still insufficient epidemiological information about geographic variations of prevalence and it remains unclear whether clinical presentation of EoE is associated with any particular ethnic or racial background [33, 34]. Interestingly, a prospective evaluation of routine endoscopy at a tertiary care military hospital in the USA revealed there was no significant difference between Caucasians (60%) and African Americans (40%), with no cases of EoE found among Hispanics or Asians [20]. However, because of this study's high overall EoE prevalence rate of 6.5% on routine upper endoscopy, these data should be interpreted with caution due to a possible selection bias, especially as other studies have not reported such high EoE prevalence rates on routine endoscopy.

EoE patients tend to live in affluent environments, are better educated and reside more often in urban/suburban areas when compared to the control groups; nevertheless, after adjustment for race and gender, these differences could no longer be confirmed [35]. These results notwithstanding, data from socioeconomic distribution are sparse and more systematic evaluations are needed to address the important questions of the contribution of environmental influences for the development of EoE.

Symptoms of Esophageal Dysfunction

The most common presenting symptom of adult EoE is dysphagia for solids, sometimes leading to food impaction. Dysphagia is present in 70–100% of patients with EoE [18, 28, 29, 31]. Children may present with a variety of symptoms. In addition to dysphagia and bolus obstruction, feeding disorder, failure to thrive, abdominal pain, heartburn and vomiting may occur [10, 13, 36, 37]. Food impaction and/or the necessity for bolus removal ranges between 30 and 50% in most studies [20, 26, 28, 29, 38]. As a consequence of EoE's male predominance, it is not surprising that food impaction occurs more frequently in men [38, 39]. Interestingly, patients evaluated for dysphagia or food impaction are reported to have EoE with a prevalence of 10–15%, and are at a higher risk of being diagnosed with EoE if they are older than 50 years [21, 22]. Patients presenting with dysphagia have been observed to have a significantly higher peak eosinophil count on biopsy specimens [18]. These prevalence rates may still underestimate the incidence of EoE as only 27% of patients with esophageal foreign body impaction had esophageal biopsies [40]. Symptoms resembling gastroesophageal reflux disease have been reported in different studies and range from 16 to 54% for EoE patients [18, 26, 28, 29, 31]. Symptoms of swallowing-associated chest pain and abdominal pain have also been reported in the literature. In summary, EoE is a leading cause of dysphagia and food impaction, especially in middle-aged men.

Allergic Predisposition

It has been proposed that in EoE eosinophils migrate to the esophagus in response to various ingested and/or inhaled allergens [41]. The specific patterns of cytokine expression resemble the findings of Th2-type inflammatory disorder also reported in other allergic diseases [42, 43]. Food allergens as well as aeroallergens have been implicated as contributing factors in inducing and maintaining the eosinophilic inflammation [32, 44, 45]. Indeed, patients with EoE show a history of seasonal allergies (40–50%), asthma (30–40%) and food allergies (10–40%) [20, 21, 26, 28, 29]. In a prospective evaluation, the prevalence of asthma was significantly higher in patients with EoE than in unaffected controls [20]. Similarly, though not significantly different, seasonal allergies and food allergies had a higher prevalence among the EoE-positive group. A case series of 23 adult EoE patients

described a high degree of atopy with atopic diathesis in 18 of the 23 patients, with allergic rhinitis being the most common, and polysensitization to several environmental allergens in 17 of the 23 patients [46]. Multiple intervention studies in pediatric and adult EoE patients have identified food allergens as pathogenic factors of EoE. Specific skin-based elimination and six-food elimination diets have resulted in the resolution of symptoms and histological improvement in >60% of affected pediatric and adult patients [47–55]. Amino acid-based elemental diets have been reported with even better success rates, but long-term adherence to these diets is difficult [56–58]. Overall, food elimination diets show better success rates in children than in adults, and suggest that the pathophysiology of EoE in adults is more complex with frequent sensitization to aeroallergens [59]. This is consistent with the findings in a small case series of 6 adult EoE patients with known sensitization to wheat and rye where an elimination diet did not improve symptoms or endoscopic findings of EoE [60].

EoE and Seasonal Distribution

There is evidence that airborne antigens play a crucial role in the pathogenesis of EoE, and some reports have suggested a seasonal variation of EoE with EoE being more frequently diagnosed in the spring and summer seasons [36, 61, 62]. This is further supported by the observation that EoE varies by climate zones in the USA [63]. A confirmation of a seasonal dependency of EoE would be an indicator that external seasonal factors (especially pollen) could play a substantial role in the pathogenesis of this Th2-type inflammation. Indeed, one study has shown a significant correlation with the peak grass pollen count and diagnosis of EoE in the spring; however, only a coincidental association with the peak pollen counts of tree or weed was found [64]. It is important to consider that there is a substantial gap between the onset of symptoms (i.e. likely onset of disease) and endoscopic and histological diagnosis. Furthermore, the onset of disease often does not correlate with the date of diagnosis. Taken together, there is currently no solid proof that either the first onset of EoE or the course of its inflammation show a seasonal variation, or that pollen exposure could play a significant pathogenic role. One might speculate that patients with seasonal allergies would be more susceptible to aeroallergens and might therefore be more likely to develop symptoms of esophageal dysfunction. However, prospective studies are needed using either a systematic

assessment of the symptom course or of EoE's inflammatory activity in correlation to the pollen exposure to answer this question.

Summary

Over the last decade there have been multiple indications of a true and constant increase in the prevalence of EoE worldwide. Whether this increased prevalence is due to a real increase in incidence, the result of increased awareness by health care providers or because of the non-fatal nature of EoE adding more and more cases to the patient pool is still a matter of controversy. The best evidence for a true escalation comes from recent data from Switzerland [27]. These data suggest that these changes in incidence and prevalence most likely reflect a true increase as it has occurred in the face of a constant diagnostic delay and in the absence of any EoE awareness programs. These findings are comparable with retrospective analyses from other geographically confined regions in the United States, Europe and Australia and therefore

provide solid evidence for a significant increase in EoE incidence [10, 12, 25, 26, 28]. However, there are also reports in the literature that the rising incidence of EoE is associated with increasing biopsy rates and that the diagnosis of EoE is still being missed or misinterpreted [65]. It was shown that diagnostic failure is frequently due to a delayed request for endoscopy in patients with dysphagia, poor recognition of typical endoscopic appearances of EoE, and failed recognition or recording of maximal eosinophil concentrations within biopsies [66]. This indicates that in spite of established consensus recommendations for the diagnosis of EoE, health care professionals such as gastroenterologists, allergists, general practitioners and pathologists who encounter EoE need to increase the awareness to facilitate diagnosis of this still relatively new disease.

Disclosure Statement

The author has no conflicts to declare regarding this article.

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