

Prevalence of eosinophilic oesophagitis in adult patients in a central region of Spain

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Background and study aims Eosinophilic oesophagitis (EoE) is a common cause of oesophageal disease. Limited data have been reported on its epidemiology in Europe as the only available information has been estimated for Swiss adult patients, among whom a prevalence of 42.9 per 100 000 was calculated. We estimate for the first time the prevalence of EoE in adult patients in two healthcare areas located in a central region of Spain.

Patients and methods All patients older than 16 years of age and living in the study areas appointed to two hospitals located in a central region of Spain who were consecutively diagnosed with EoE between 2005 and 2011 were analyzed retrospectively. Annual incidence and period prevalence were estimated along with a confidence interval (CI) of 95%.

Results Between January 2005 and December 2011, 40 adult patients were diagnosed with EoE in our areas, with an average overall adult reference population of 89 642. No significant differences in clinical data or prevalence figures were found between both hospitals. The average age was 29.4 years (range 16–53), 80% of patients being younger

than 40 years of age. The estimated mean annual incidence of adult EoE for the study period was 6.37 per 100 000 (95% CI: 6.31–6.44) and remained relatively stable during the study period. The period prevalence was 44.6 cases per 100 000 inhabitants (95% CI: 30–59), with a male/female ratio of 19:1.

Conclusion EoE was highly prevalent in adults from central Spain, being diagnosed in one out of 2250 inhabitants older than 16 years of age. *Eur J Gastroenterol Hepatol* 00:000–000 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

European Journal of Gastroenterology & Hepatology 2012, 00:000–000

Keywords: adult, eosinophilic oesophagitis, epidemiology, incidence, prevalence

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Received 1 August 2012 Accepted 10 September 2012

Introduction

Eosinophilic oesophagitis (EoE) is a chronic immune/antigen-mediated inflammatory clinicopathological entity characterized by the presence of large numbers of intra-epithelial eosinophils in oesophageal biopsies and recurrent symptoms of oesophageal dysfunction [1].

First characterized about 20 years ago [2,3], EoE is no longer a rare disorder; in fact, it has been recently identified as a common cause of oesophageal disease and its diagnosis has rapidly increased, especially in the last 10 years. EoE is now considered the most common cause of dysphagia and chronic oesophagitis behind gastro-oesophageal reflux disease and represents the most common eosinophilic gastrointestinal disorder. Currently, EoE represents between 12 [4] and 15% [5] of diagnosis in patients explored with upper endoscopy because of nonobstructive dysphagia. Thus, in 2006, the prevalence of paediatric EoE in Australia was estimated to have increased 18-fold over the previous 10 years [6] and in Philadelphia (USA), this increase was 35-fold [7].

Limited knowledge is available on the exact epidemiology of the disease in many settings, and most epidemiological studies on EoE are from USA and involve paediatric populations. In a retrospective study carried out in a

region of Ohio, the incidence of paediatric EoE during the period between 2000 and 2003 was calculated by Noel *et al.* [8] to be nine to 13 new cases per 100 000 children, whereas the prevalence among children for the same period was estimated to be 42.9 per 100 000 inhabitants of up to 19 years. Retrospective analysis on the overall epidemiology of EoE over three decades in Minnesota had found a progressive increase in prevalence of up to 55 cases per 100 000 inhabitants [9]. Finally, a recent survey-based study estimated an overall prevalence of EoE in the USA of 52 cases per 100 000 inhabitants [10] in 2010, being higher in urban areas than in suburban and rural settings, and geographically more common in the north-western states.

With respect to Europe, limited epidemiological data exist; prevalence among paediatric patients has been reported exclusively in Danish infants and children [11], whereas for adults prevalence has been reported only among Swiss patients. In a 5-year period, the annual incidence increased from 1.4 [12] to 2.45 [13] cases per 100 000 inhabitants. In parallel, the prevalence of adult EoE also increased in the same period from 23 to 42.8 per 100 000.

There is a lack of studies that estimate the epidemiology of EoE in other European regions, and no specific studies

have been carried out in Spain to date. The aim of this research was to evaluate the prevalence of EoE diagnosis in adult patients in a specific geographical area in a central region of Spain between 2005 and 2011.

Materials and methods

Study setting

The recruitment areas of Tomelloso General Hospital (Hospital #1) and Virgen de Altagracia Hospital (Hospital #2) are located in the centre of Spain in the autonomous region of Castilla-La Mancha. The study areas are predominantly rural, with an overall reference population of roughly 101 882 inhabitants, of whom 89 642 (83%) are at least 16 years of age (average data from 2005 to 2011). No relevant demographic changes were noted in our region during the study period. These hospitals are exclusively in their respective areas and offer universal coverage for adult specialist gastroenterology services as no additional private gastroenterology, endoscopy nor pathology clinics exist. The departments of gastroenterology of both hospitals are considered referral centres for EoE in adults in the area. Patients are usually referred to them by family physicians or emergency departments when necessary. Experienced gastroenterologists and pathologists with a high awareness of EoE serve our areas and have been using the same diagnostic procedures and criteria for the entire study period.

Patients and diagnostic criteria

All newly diagnosed adult EoE patients at two hospitals between 1 January 2005 and 31 December 2011 were analyzed retrospectively. The patient search was carried out by reviewing the databases of the departments of gastroenterology and pathology from both hospitals. All clinical records and histological slides were reanalyzed to ensure EoE diagnosis. A patient was considered to be an adult if he or she was 16 years of age or older.

The diagnosis of EoE was based on the following accepted criteria [1]: (a) infiltration of oesophageal epithelium by 15 or more eosinophil leucocytes per high-powered field (HPF) on light microscopy; (b) absence of eosinophilic infiltration in biopsy specimens from gastric and duodenal mucosa; (c) exclusion of gastro-oesophageal reflux as a cause of eosinophilia either by ambulatory 24-h pH-metry or by persistence of eosinophilic infiltration after an 8-week treatment with antisecretory drugs (omeprazole 20 mg/twice a day or equivalent); and (d) ruling out of drug intake, parasites, oesophageal caustications, haematologic neoplasm or other events in the patient's medical history as possible causes of oesophageal eosinophilia.

The reference populations of the areas analyzed were obtained from official databases from the National Institute of Statistics (Instituto Nacional de Estadística or INE) for the same study period.

Clinical data

Age at diagnosis, symptoms and its evolution time, sex, endoscopic findings, personal and familiar atopic backgrounds and the mean eosinophil count in oesophageal samples were determined for all included patients (Table 1).

Data analysis

The prevalence period was estimated as the proportion of adult individuals with the disease during the period 2005–2011 along with the confidence interval (CI) of 95%. Results were expressed as mean and SD (quantitative variables) or as percentages (qualitative variables). We compared the qualitative variables using the χ^2 -test (Fisher's exact test, where appropriate) or the Mann–Whitney *U*-test. A 0.05 level of significance was used throughout. Analyses and summaries were produced using the PASW statistical program, version 18.0 (SPSS Inc., Chicago, Illinois, USA).

Ethics

This study was approved by the Institutional Research Committee at Tomelloso General Hospital.

Results

Between 1 January 2005 and 31 December 2011, a total of 40 patients 16 years of age and older and resident in our recruited areas were diagnosed with EoE (28 cases in Hospital #1 and 12 cases in Hospital #2). No significant differences were found between patients from the two hospitals in the demographic, clinical and epidemiological characteristics; thus, the data were combined and summarized for a combined analysis (Tables 1 and 2). The incidence of EoE was lower in women than in men, with a male/female ratio of 19:1.

The mean age at the time of diagnosis was 29.4 years (SD 10.8, range 16–53), indicating that over 80% of patients were aged between 16 and 40 years (Figs 1 and 2).

The average duration of symptoms before diagnosis was around 51 months (range 1–168), with no significant differences between both hospitals. The main symptoms leading to a diagnosis of EoE were food impaction (80%) and dysphagia (67.5%). An atopic background was present in 80% of patients and almost half of them also had a familiar background of allergy (Table 1).

The mean reference population aged at least 16 years in our areas for the study period comprised 89 462 inhabitants, with no significant changes over time (Table 2); of these, 45 245 (50.47%) were males and 44 397 (49.53%) were females. All diagnosed adult EoE patients were alive in our reference areas during the study period and no patient with a previous diagnosis of EoE had relocated from other regions. No patients were missed at follow-up during the study period.

The mean annual incidence of adult EoE for the period 2005–2011 was 6.37 per 100 000 (95% CI: 6.31–6.44).

Table 1 Clinical characteristics of adult eosinophilic oesophagitis patients from two Spanish hospitals included in our study

Characteristics	Total (n=40)	Hospital #1 (n=28)	Hospital #2 (n=12)	P
Mean age (SD), rank	29.38 (10.81), 16–53	27.5 (10.6), 16–53	33.75 (10.45), 23–52	0.06 ^b
Sex (male/female)	38 (95%)/2 (5%)	26 (92.9%)/2 (7.1%)	12 (100%)/0 (0%)	1 ^a
Time of evolution (months)	51.05 (45.15) 1–168	44.64 (42.86) 1–120	66 (48.68) 12–168	0.088 ^b
Symptoms				
Food impaction	32 (80%)	21 (75%)	11 (91.7%)	0.396 ^a
Dysphagia	27 (67.5%)	18 (64.3%)	9 (75%)	0.716 ^a
Abdominal pain	11 (27.5%)	10 (35.7%)	1 (8.3%)	0.124 ^a
Vomiting	4 (10%)	4 (14.3%)	0	0.297 ^a
Pyrosis	6 (15%)	4 (14.3%)	2 (16.7%)	1 ^a
Weight loss	2 (5%)	2 (7.1%)	0	1 ^a
Calibre (normal/reduced)	32 (80%)/8 (20%)	24 (85.7%)/4 (14.3%)	8 (66.7%)/4 (33.3%)	0.211 ^a
Mucosal appearance				
Normal	5 (12.5%)	3 (10.7%)	2 (16.7%)	0.627 ^a
Longitudinal furrows	32 (80%)	22 (78.6%)	10 (83.3%)	1 ^a
Crepe-paper appearance	14 (35%)	12 (42.9%)	2 (16.7%)	0.157 ^a
Rings	26 (65%)	17 (60.7%)	9 (75%)	0.484 ^a
White plaques	12 (30%)	10 (35.7%)	2 (16.7%)	0.285 ^a
Atopic personal history				
Allergic rhinitis	28 (70%)	20 (71.4%)	8 (66.7%)	1 ^a
Drug sensitivity	6 (15%)	5 (17.9%)	1 (8.3%)	0.648 ^a
Bronchial asthma	23 (57.5%)	15 (53.6%)	8 (66.7%)	0.443 ^a
Dermatitis	1 (2.5%)	0	1 (8.3%)	0.3 ^a
Food sensitivity	11 (27.5%)	6 (21.4%)	5 (41.7%)	0.254 ^a
Atopic family history				
Allergic rhinitis	11 (27.5%)	7 (25%)	4 (33.3%)	0.704 ^a
Drug sensitivity	2 (5%)	2 (7.1%)	0	1 ^a
Bronchial asthma	10 (25%)	7 (25%)	3 (25%)	1 ^a
Dermatitis	1 (2.5%)	0	1 (8.3%)	0.3 ^a
Food sensitivity	6 (15%)	3 (10.7%)	3 (25%)	0.341 ^a
Mean intraepithelial eosinophils				
Cells/HPF (SD)	218.99 (113.72)	212.94 (127.51)	233.1 (75.05)	0.215 ^b
HPF (SD)	46.43 (24.11)	45.14 (27.03)	49.42 (15.91)	0.215 ^b

HPF, high-power field.

^a χ^2 -test.^bMann–Whitney *U*-test.**Table 2 Cumulative annual prevalence of eosinophilic oesophagitis in adult patients in two hospitals in central Spain between 2005 and 2011**

Year	Total (N=40)			Hospital #1 (n=28)			Hospital #2 (n=12)		
	Overall prevalence	Male prevalence	Female prevalence	Overall prevalence	Male prevalence	Female prevalence	Overall prevalence	Male prevalence	Female prevalence
2005	0	0	0	0	0	0	0	0	0
2006	3.44	4.56	2.31	1.9	0	3.83	5.79	11.6	0
2007	11.43	20.49	0	7.58	11.28	0	17.29	34.61	0
2008	19.76	39	0	19.73	35.12	0	22.64	45.24	0
2009	28.34	55.87	0	30.28	55.84	0	28.09	55.91	0
2010	34.65	68.36	0	40.46	75.82	0	28.17	56.21	0
2011	43.21	81.23	4.37	49.01	89.39	7.13	33.87	67.82	0
Total (95% CI)	44.62 (30–59)	84.0 (56–112)	4.5 (0.5–16.3)	51.26* (31–71)	93.76† (56–132)	7.44* (1–27)	34.27* (13–58)	68.51† (27–110)	0*

CI, confidence interval.

**P* = 0.32; †*P* = 0.46; #*P* = 0.68.

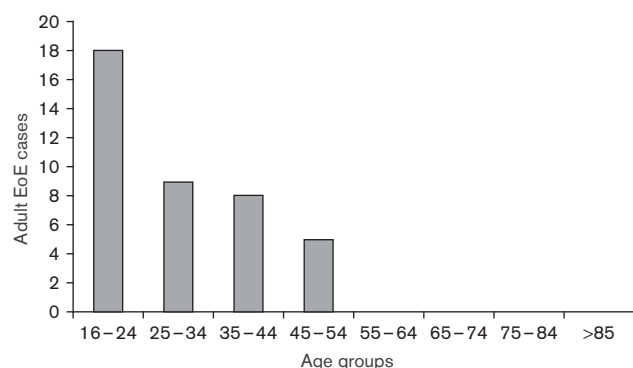
The period prevalence from 2005 to 2011 was 44.62 new adult EoE cases diagnosed per 100 000 adult inhabitants (95% CI: 30–59). For males, the period prevalence was 84 per 100 000 (95% CI: 56–112) and in females, it was 4.5 per 100 000 (95% CI: 0.5–16.3) (Table 2).

Discussion

Our data show that EoE is a prevalent disorder among adult Spanish patients, affecting about one case out of 2250 adult inhabitants living in two areas in central Spain. The disease affected predominantly young male patients,

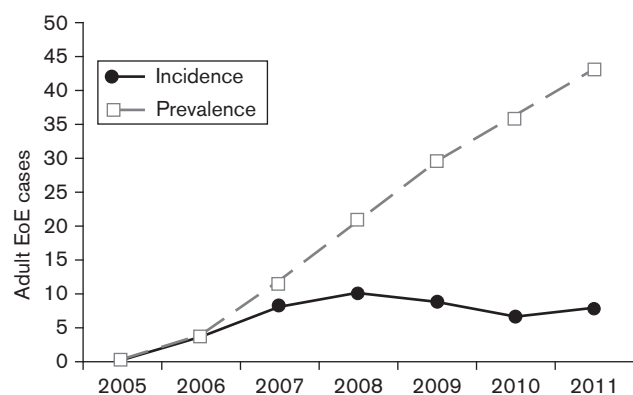
younger than 40 years of age in 80% of the cases. Our cumulative prevalence figure of 44.6 cases per 100 000 inhabitants for the study period parallels that of the recently reported results from Switzerland of 42.8 per 100 000 and shows that EoE in adults is also a prevalent disorder in Europe as reported in North America and Australia. Data from retrospective analysis [9] and compiled through nationwide surveys, especially when low response rates were achieved [10], may have underestimated the actual prevalence of the disease. In this case, our registry was started in two health areas in which

Fig. 1



Age distribution of patients at least 16 years of age diagnosed with EoE in a central region of Spain between 2005 and 2011. EoE, eosinophilic oesophagitis.

Fig. 2



Diagnostic incidence and cumulative prevalence of EoE per 100 000 adult inhabitants per year in a central region of Spain during the period 2005–2011. EoE, eosinophilic oesophagitis.

all the gastroenterology, endoscopy and pathology facilities were exclusively provided by our two community hospitals, with no differences in findings between them.

In terms of the incidence of EoE among adults, significantly higher figures than reported previously were also found from our research. Our mean annual incidence for the period 2005–2011 was 6.37 new adult EoE cases per 100 000 inhabitants, and remained relatively stable over the years. This figure contrasts with that reported recently by Hruzp *et al.* [13] for Switzerland, where EoE presented in 2.45 per 100 000 new cases annually, and exceeds the available estimations for the last decade in Spain; according to that, adult EoE incidence varied between 1.4 [14] and 2.13 [15] new cases per 100 000. A plausible explanation may be the diagnostic delay of EoE in our region, with no cases diagnosed before 2006 and a subsequent recovery up to prevalence figures similar to that reported for regions with a long tradition in caring for

EoE patients. The future trend of our incidence will confirm our hypothesis.

Additional comments are required after reporting our results: most of our patients were male, as usually reported in the literature. However, and in contrast to Straumann's group results [13], who reported a male/female ratio of 3:1, we found this ratio to be 19:1, which is higher than the previously reported proportion of around 3–4:1 in favour of the male sex. The larger published epidemiological registry did not provide the sex distribution for American EoE patients [10]; thus, additional studies on differences in the symptoms' severity and tolerance to them between males and females are required.

The referral areas of our two hospitals are predominantly rural, with the local economy based mainly on agriculture, farming processing industries and community services. The previously mentioned American epidemiological registry identified a higher prevalence of EoE in urban areas compared with suburban and rural settings [10], a finding that was not obtained in preceding reports. In this respect, Noel *et al.* [8] documented that EoE distributed homogeneously according to population distribution, with no urban–rural gradient. The distribution of EoE in Western Australia was in agreement with this, and in addition, the authors did not observe any association with the socioeconomic gradient [6]. Unfortunately, our study is the first one to be carried out in Spain and no data are available from other regions in our country to corroborate the relationship between EoE and urban settings.

Our registry included only adult patients, as we could not ensure that all paediatric cases were correctly recruited and diagnosed, as paediatric gastroenterology assistance is not fully provided in our hospitals. However, given the high concordance in prevalence that we have observed between different geographical areas, the figures provided for American children from Ohio [16] of around 42.9 per 100 000 could be easily assumed for our region as well. Therefore, after extrapolating that prevalence figure to our 17% of inhabitants aged 16 years or younger, we found that 44.31 of our entire population could have EoE in central Spain. This was comparable to the prevalence figures of 52 [9] to 55 [10] per 100 000 inhabitants of all ages reported from the USA; EoE in Spain seems to be slightly less prevalent, but still a major disorder.

In addition to Switzerland and Spain, EoE series have also been described from several European countries [17,18]; after our reports, we could estimate that a diagnosis of EoE may be made in around 0.4% of European inhabitants of all ages. These figures are much lower than those reported from Sweden in the population-based Kalixandra epidemiological study, in which the authors found that the adult Swedish population presented histopathological findings compatible with EoE (defined

by 20 or more eosinophils/HPF in biopsies from lower oesophageal thirds), with a prevalence of ~1% [19], independent of the presence of oesophageal symptoms. However, some caution should be exercised when comparing these figures (1 and 0.4%), as discussed below.

Our epidemiological study limited our EoE diagnosis to patients who sought assistance because of the symptoms of oesophageal dysfunction, and were diagnosed after referral to the gastroenterology departments at our hospitals. In accordance with previous reports, a considerable diagnostic delay existed for adult EoE patients, likely because of symptoms that can fluctuate over time and are frequently unspecific. Thus, we can assume that only the most symptomatic patients would have been consulted because of their symptoms or referrals to hospital for additional studies by family physicians, and possibly some young patients with nonalarming gastro-oesophageal reflux disease-related symptoms who received empiric antisecretive therapy or refused the carrying out of digestive endoscopy. In this scenario, the finding of a pathological eosinophilic infiltration over the EoE diagnostic threshold described in Sweden during the Kalixandra study [19] would really reflect the actual magnitude of EoE. As we lack a definitive noninvasive marker for the diagnosis of EoE even in scarcely symptomatic patients, an exact estimation of the real incidence and prevalence of the disease is not achievable at present. In any case, we should keep in mind that EoE is a frequent disorder in our country that should be always considered in the differential diagnosis of every patient with oesophageal symptoms.

Acknowledgements

We would like to thank Dr Jose María Tenias Burillo for his helpful comments on the manuscript and insight in this study.

Conflicts of Interest

There are no conflicts of interest.

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