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ORIGINAL ARTICLE

Are patients with eosinophilic esophagitis treated at an academic hospital comparable to a patient from a population-based cohort? Not in Denmark

Dorte Melgaard,*,† Inger B Andersen,‡ Line T Frandsen,§ Christian Mortensen,‡ Line E M Hansen* and Anne L Krarup†,¶

*MechSense, Department of Gastroenterology and Hepatology, §Department of Gastroenterology and Hepatology, ¶Department of Emergency Medicine and Trauma Center, Aalborg University Hospital, †Faculty of Clinical Medicine, Aalborg University, Aalborg and ‡Gastro Unit, Medical Division, Hvidovre University Hospital, Copenhagen, Denmark

Key words
eosinophilia, eosinophilic esophagitis, esophagus, gastro-esophageal reflux, population-based, register-based.

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Correspondence
Anne L Krarup, Department of Emergency Medicine and Trauma Center, Aalborg University Hospital, Hobrovej 18-22, DK-9000 Aalborg, Denmark.
Email: apslk@rn.dk

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Abstract

Background and Aim: Little are known about differences in eosinophilic esophagitis (EoE) patients in the general population compared with patients treated at academic hospitals. This might affect the generalizability of study results. The aims of the study were to compare clinical features, and complications of EoE between patients from a population-based cohort (DanEoE) and patients from an academic hospital cohort in Copenhagen (EoE-Cph).

Methods: The DanEoE cohort is a population- and register-based cohort including all 236 adult EoE patients diagnosed in the North Denmark Region in 2007–2017 previously described in detail. The new EoE-Cph cohort consists of 245 consecutively referred adult patients to a dedicated EoE center in an Academic Hospital in the Danish capital in 2013–2020. Data were collected from medical registries and medical files.

Results: Patients in the academic cohort were at symptom debut 12 (SD 16) years younger ($P = 0.001$). At the time of diagnosis they were 5.4 (SD 15) years younger ($P < 0.001$). Where Gastro-esophageal reflux disease (GORD) was present in one-third of the population-based cohort, this was only observed in 14% of the EoE-Cph group ($P < 0.05$). Food bolus obstruction before diagnosis was 24% less common in the EoE-Cph patients ($P < 0.001$).

Conclusion: Results indicated that EoE patients referred to a Danish EoE center is a selected subgroup with disease debut at a younger age, less comorbid GORD, and rarely food bolus obstruction before diagnosis. This suggests that study results from academic hospitals might not have generalizability to the average EoE patient in a population.

Introduction

Eosinophilic esophagitis (EoE) is a chronic disease of eosinophilic inflammation in the esophageal mucosa in combination with esophageal dysfunction.[1] It causes a range of symptoms but predominantly dysphagia and food impaction in adults, resulting in decreased quality of life.[2] Many observational studies of EoE are based on data from academic centers. However, results from such studies may not reflect the general patient population due to selection bias. Examples of this problem have been shown in other inflammatory gastrointestinal diseases: A German study of Crohn's disease suggested that academic hospitals were more likely to have early onset disease, needed more aggressive treatment, and were more prone to fistulizing complications.[3] If treatment recommendations are being based on study results from patient populations at academic center, they may end up being too aggressive when treating patients from nonacademic centers. There are no studies of EoE patient populations and their clinical course in academic hospitals compared with nonacademic hospitals. In Denmark, EoE patients are treated by surgeons and gastroenterologist in academic hospitals, in nonacademic hospitals, and in private practices. In Denmark, there is equal and free access to medical treatment for all citizens, and high-quality medical registries. This makes it possible to estimate the differences in disease characteristics in a population setting compared with an academic setting, to estimate the level of selection bias as described above.

DanEoE is a population- and register-based database of EoE patients in the North Denmark Region (NDR).[4] Hvidovre University Hospital is an Academic Hospital in the Danish

capital Copenhagen. They have a dedicated EoE clinic and have started a cohort with all referred EoE patients since 2013. Both databases include data on patient age, sex, diagnostic workup, treatments, and complications. We hypothesize that the disease course was more severe, or complication rates were higher in cohorts of EoE patients from academic center based cohorts compared with population-based, and that this difference could be measured in Danish patients. We therefore aimed to measure and compare clinical features, and complications in EoE patients from a population-based cohort (DanEoE) in the NDR and compare them to patients in a new academic hospital cohort in an EoE center in Copenhagen (EoE-Cph).

Materials and methods

The study databases were approved by the Danish Data Protection Agency (ID number 2018-59) and as a quality project by all hospitals involved (ID-21024729-8 604 783 and 2017-011259).

Data sampling. Data for the cohort were collected using the unique social security number assigned to all Danish citizens. With that number, it is possible to access all national health registries including medical records and pathology findings.[5,6] Descriptive information as well as allergy status, treatment, response, and complications were sampled. Variables collected are shown in Tables 1–3. The index endoscopy was defined as the first endoscopy where a sampled biopsy showed esophageal eosinophilia.

DanEoE cohort: A population-based cohort in the NDR. The population- and registry-based DanEoE cohort has previously been described in detail.[4,7–10] All patients with esophageal eosinophilia for the first time and living in the NDR in 2007–2017 were included regardless of where they were diagnosed and treated, including patients not treated at all. Follow-up continued until 31 December 2018.[7] Two EoE experts evaluated and entered all data in the cohort.

EoE Copenhagen cohort: A Danish academic hospital based cohort. The EoE-Cph cohort was initially established to evaluate the quality of EoE treatment. All patients were treated by the two experts running the center. Patients were included prospectively with no exceptions from May 2013 to December 2020. Inclusion criteria were adults with dysphagia in combination with at least one biopsy with 15+ eosinophiles per high power field (eos/hpf) in an esophageal biopsy and referred to the "Gastro Unit" at Hvidovre University Hospital. Exclusion criteria were other causes of eosinophilia in esophagus excluding EoE. Since 20 October 2017, the extent of data collected was increased to match that of the DanEoE cohort.[4] Data were entered by the treating EoE experts.

Patient groups in both cohorts. EoE patients were diagnosed according to the AGREE2 consensus[1]: Symptoms of esophageal dysfunction and eosinophilic inflammation with ≥15 eos/hpf (~60 eos/mm^2) in at least one esophageal biopsy.[11] The EoE group was subgrouped according to whether they had comorbid GORD (EoE + GORD) or not (Pure EoE).

EoE + GORD was defined as EoE patients with a clear EoE phenotype but also objective findings of GORD: Esophagitis, abnormal pH testing, or Barrett's esophagus. Barrett's esophagus was defined as intestinal metaplasia in salmon colored esophageal mucosa.[12] Esophagitis was defined according to the LA classification and grouped into mild (LA-grade A + B) or moderate to severe (LA grade C + D).[13]

Pure EoE was defined as patients having EoE without GORD.

Statistics. Descriptive statistics were given as median and range (25–75 percentile [IQR]) for continuous variables or mean (SD) as appropriate. For categorical variables, counts and percentage were displayed. Comparison of the groups, pure EoE with EoE + GORD, was done using one-way ANOVAS and results were given as mean and 95% confidence interval (95% CI). The data management and statistics was done using SAS enterprise guide 71 (SAS Institute Inc., Cary, NC, USA), and figures using Sigmaplot 11.0 Build 11.1.0.102 (Systat Software Inc., CA, USA).

Results

Patient groups and descriptive data. Table 1 shows patient characteristics of the EoE-Cph patients. In Table 2, data from the pure EoE patients on both cohorts were compared (Fig. 2). Data showed that the academic hospital cohort was diagnosed at a younger age but had similar 10–11 years diagnostic delay (Fig. 1). They were less inflamed and more often had comorbid asthma or allergy. Table 3 documents that the endoscopist diagnosing the EoE-Cph cohort patients were less likely to choose "possible EoE" as indication compared with the endoscopists in the NDR, and less likely to sample enough biopsies according to guidelines. Patients having comorbid reflux disease were also more rare in the academic hospital cohort (Fig. 2). Another very interesting finding was that food bolus obstruction was a very rare finding in the EoE Copenhagen cohort compared with the population-based cohort (Fig. 2). Just 1% had been hospitalized with a food bolus obstruction before being diagnosed, whereas this was 16% in the DanEoE cohort (Table 4). Dilations were rarely done in either cohort but dilations after diagnosis was more frequently performed in the EoE-Cph cohort (Table 4, Fig. 2).

Discussion

This is to our knowledge the first cross-sectional study comparing clinical characteristics of EoE patients from a population- and registry-based cohort with an academic hospital based cohort. We found that the patients from the academic hospital EoE-Cph cohort were, on average, 5 years younger at diagnosis, were less inflamed, and did not have comorbid reflux disease as often. The endoscopists in the capital of Denmark less often choose EoE as an indication, or biopsied according to the EoE guideline, compared with endoscopists in the DanEoE cohort. Interestingly hospitalization due to food bolus obstruction was almost nonexisting in the EoE-Cph cohort compared with the DanEoE cohort, whereas dilations were performed more often after diagnosis.

Table 1 Descriptive data of the EoE-Cph cohort of adults with eosinophilic esophagitis referred to an academic hospital in the capital of Denmark in 2013–2020

	All EoE patients (subgroups in gray)			After 20 October 2017
	All EoE	Pure EoE	EoE + GORD	Pure EoE
Proportion of group				
Of all 245 patients EoE: %, *n*	100, *n* = 245	86, *n* = 210	14, *n* = 35	*n* = 95
Ratio w:m	1:2.7	1:2.5	1:4.0	1:2.2
Age at diagnosis: Mean (SD) years, *n*				
All	41 (15), *n* = 224	40 (15), *n* = 189	48 (16), *n* = 35	39 (14), 93
Men	41 (15), *n* = 165	40 (15), *n* = 137	46 (14), *n* = 28	39 (13), 64
Women	43 (17), *n* = 59	41 (15), *n* = 52	56 (20), *n* = 7	40 (15), 29
Age at symptom debut: Mean (SD) years, *n*				
All	25 (16), *n* = 118	24 (16), *n* = 97	28 (20), *n* = 21	27 (16), 67
Men	23 (16), *n* = 89	22 (15), *n* = 70	25 (18), *n* = 19	25 (15), 47
Women	30 (18), *n* = 29	29 (17), *n* = 27	56 (23), *n* = 2	31 (18), 20
Diagnostic delay: Mean (SD) years, *n*				
All	12 (12), *n* = 196	11 (10), *n* = 164	18 (17), *n* = 32	10 (9.8), 72
Men	14 (13), *n* = 146	12 (11), *n* = 120	20 (18), *n* = 26	12 (10), 49
Women	8.2 (9.0), *n* = 50	7.7 (8.2), *n* = 44	12 (14), *n* = 6	7.0 (8.1), 23
Inflammation at debut: Eos/hpf	36 (20; 50), 223	40 (20; 53), 191	25 (20; 40), 32	40 (25; 51), 88
Phenotype: % of all, *n*				
Allergy or asthma	55%, *n* = 134	53%, *n* = 112	63%, *n* = 22	60%, *n* = 57
Allergy	52%, *n* = 127	48%, *n* = 55	57%, *n* = 8	55%, *n* = 52
Asthma	NA	NA	NA	26%, *n* = 20
Treatment: % of group, *n*				
No treatment started	13%, 31	14%, 30	3.0%, 1	6.3%, 6
PPI started first	79%, 194	77%, 161	94%, 33	83%, 79
Diet started first	1.2%, 3	1.4%, 3	0.0%, 0	2.1%, 2
Topical steroid started first	6.9%, 17	7.6%, 16	3.0%, 1	8.4%, 8

EoE, eosinophilic esophagitis; eos/hpf, eosinophilic granulocytes per high power field; GORD, gastro-esophageal reflux disease; Id, identification number; IQR, inter-quartile range; *n*, number.

Table 2 Comparison between the population-based DanEoE cohort and the EoE-Cph cohort

		Pure EoE patients (no comorbid GORD)	
	EoE-Cph *n* = 210	EoE-Cph-DanEoE Difference DanEoE *n* = 170	*P* value
Age at diagnosis: Mean (SD) years, *n* EoE-Cph, *n* DanEoE			
All	40 (15)	−5.4 (15), 189, 152	0.001
Men	40 (15)	−6.9 (15), 137, 111	<0.001
Women	41 (15)	1.4 (15), 52, 41	0.7
Age at symptom debut: Mean (SD) years, *n* EoE-Cph, *n* DanEoE			
All	24 (16)	−12 (16), 97, 115	<0.001
Men	22 (15)	−16 (16), 70, 83	<0.001
Women	29 (17)	−2.9 (4.3), 27, 32	0.5
Diagnostic delay: Mean (SD) years, *n* EoE-Cph, *n* DanEoE			
All	11 (10)	1.3 (11), 166, 115	0.4
Men	12 (11)	2.1 (11), 120, 83	0.2
Women	7.7 (8.2)	−1.9 (9.1), 44, 32	0.4
Inflammation in esophagus: median (IQR) eos/hpf			
At debut	44 (30)	−9.1 (41), 191, 151	0.04
Phenotyping			
Any type of allergy or asthma	53%	9.0%, 112, 74	0.047
Dysphagia without stenosis	58%	−28%, 122, 146	<0.001
Food impaction before diagnosis	1.0%	−24%, 2, 40	<0.001

t-test and Fischer's exact (proportions).

EoE, eosinophilic esophagitis; eos/hpf, eosinophilic granulocytes per high power field; GORD, gastro-esophageal reflux disease; IQR, inter-quartile range; *n*, number.

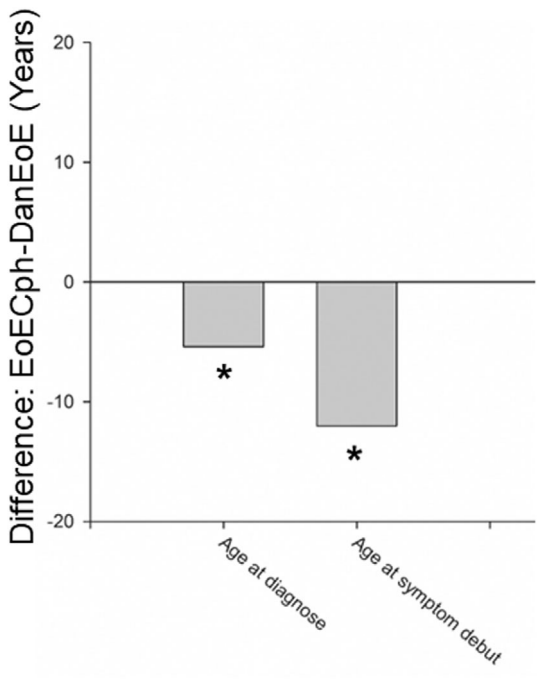

Figure 1 Eosinophilic esophagitis (EoE) patients from the academic center based EoE Copenhagen cohort were younger at diagnosis, and at symptom debut (*$P < 0.05$).

The patient population in this cohort was primarily referred from specialized practitioners (gastroenterologists) and from non-academic hospitals in Copenhagen and Northern Zealand. This pattern of referral should give an expected high generalizability of our results to patients treated in other academic hospitals. It was a strength that (i) the EoE-Cph cohort adapted to using the same database as the DanEoE in 2017, so the patients were identically described and could be compared with high precision, (ii) a prospective design with full inclusion of all patients was possible within Danish law, (iii) that only two EoE experts treated all patients in the EoE-Cph cohort, and lastly, (iv) that the description of DanEoE cohort was not published until 2021 and therefore not likely influencing the EoE-Cph cohort. Limitations were that the EoE-Cph sampled fewer information about their patients until 2017, and that inclusion required the symptom dysphagia until the publication of the AGREE2 conference. However, as the cohort included only adults, the risk of excluding EoE patients until 2018 was expected to be very low. We did not register the referral pattern for the EoE-Cph cohort. In Denmark, a patient will always start with a contact to a primary care physician unless they present with a food bolus obstruction directly at the hospital. A weakness of the current study is therefore that we have not registered how large a proportion has been referred directly from a primary care physician, from a private endoscopy clinic, or directly from the Department of Emergency Medicine.

The registry-based approach using the national unique identification number assigned to all Danish citizens was a strength.[5,6] As the quality of the Danish Pathology Registry is high, we were certain to find all cases of esophageal eosinophilia in the area, and the external validity is expected to be high.[14] Combined with medical files, the patient phenotype was possible to determine in 97% of cases, which had never been done on a population-based cohort before.

We expected the patients referred to the academic center in Copenhagen to be older and more inflamed. This was not the case and suggests a large portion of EoE patients never walk inside an EoE center in the capital region. Compared with the DanEoE cohort, this suggested that the older patients, patients with food bolus obstruction before the diagnosis of EoE, or EoE patients having comorbid GORD were never referred to the academic EoE center but treated elsewhere or not treated at all.[4,7] The latter would fit well with both a recent Danish epidemiological study showing a lower incidence of EoE in the capital

Figure 2 Comorbid gastro-esophageal reflux disease and food bolus obstruction were less common in the academic hospital based eosinophilic esophagitis Copenhagen cohort compared with the population-based DanEoE. In contrast, dilations were performed more often (*$P < 0.05$).

Table 3 Description of the index endoscopy for adults with eosinophilic esophagitis and no comorbid gastro-esophageal reflux disease in the EoE-Cph cohort after October 2017 compared with the population-based DanEoE cohort

	Pure EoE patients (no comorbid GORD)		
	EoE-Cph $n = 95$	EoE-Cph-DanEoE difference DanEoE $n = 170$	*P* value
Endoscopies before the index endoscopy: %, *n*			
Information available	97%, $n = 93$	59%	>0.001
No previous endoscopies	77%, $n = 72$	52%	>0.001
One or more endoscopies	19%, $n = 18$	9.6%	>0.001
Of these >4 endoscopies	10%, $n = 3$	5.3%	0.7
Mean number of previous endoscopies if any	2.3 (1.6)	0.6 (1.3)	0.2
At the index endoscopy			
On PPI, % of all with information of PPI	14%, $n = 12$ of 85	0.0%	1.0
Indication for index endoscopy: Proportion of patient group in %, *n*			
EoE symptoms, any	97%, 92	0.0%	1.0
"Probable EoE" in the file	11%, 10	−58%	<0.001
Dysphagia	70%, 66	6.0%	0.4
Food impaction	31%, 29	7.0%	0.4
GORD	2.2%, 2	−4.9%	0.08
Barrett control program	0.0%, 0	0.0%	1.0
Other indications	0.0%, 0	−2.4%	0.3
Sedation at the index endoscopy: Proportion of patient group in %, *n*			
No sedation or local anesthetics	1.1%, 1	−41%	<0.001
Local anesthetics	55%, 52	47%	<0.001
IV sedation	58%, 54	49%	<0.001
General anesthesia	22%, 21	2.0%	0.8
Missing	11%, 10	8.6%	0.008
Macroscopic changes at the index endoscopy: Proportion of patient group in %, *n*			
Macroscopic normal	34%, 32	−2.0%	0.7
Any endoscopic EoE sign (edema, rings, exudates, furrows, strictures)	55%, 52	11%	0.08
Rings	23%, 22	1.0%	0.8
Strictures, All	14%, 13	2.0%	0.9
Furrows	18%, 17	6.0%	0.2
Edema	17%, 16	11%	0.01
White dots	9.4%, 8	6.5%	0.07
Laceration	5.3%, 5	3.5%	0.2
Esophageal ulcer	0.0%, 0	−3.5%	0.1
Biopsy sampling at the index endoscopy			
Number of biopsies if dysphagia, median (IQR), *n*			
All	8.0 (4.0; 8.0), $n = 89$	0.6 (3.0)	0.2
4 cm	4.0 (3.0; 4.0), $n = 77$	0.3 (1.7)	0.4
14 cm	4.0 (3.0; 4.0), $n = 74$	−0.3 (1.6)	0.4
Proportion % of biopsy sampling following guideline in %, *n*			
DK guidelines (≥8 biopsies)	50%, $n = 47$	−11%	0.07
EUREOS guidelines (≥6 biopsies)	63%, $n = 60$	−13%	0.03
Treatment initiated within 3 months			
With PPI	90%, $n = 85$, 152	−1.0%	1.0

EoE, eosinophilic esophagitis; IQR, Intra quartile range; IV, Intra venous; *n*, number; PPI, proton pump inhibitor.

region,[15] and that the referring endoscopists less frequently identified EoE as the indication for sampling biopsies at the index endoscopy.

Food bolus obstruction was more often seen in the population-based DanEoE cohort compared with the EoE-Cph (16% *vs* 1%). Prior literature estimates that EoE is diagnosed in up to half of patients presenting with food bolus obstruction.[16] Management of acute food bolus obstruction is mainly done by surgeons. Chang et al. found in a single-center study of a tertiary medical center in Michigan that esophageal biopsies are not routinely taken and were only obtained in 34% of urgent endoscopy for food bolus obstruction.[16] This indicates an underdiagnosis of EoE patients when presenting with acute food bolus obstruction as a symptom. In the DanEoE cohort, patients were more often biopsied according to the national guideline and more often referred with "possible EoE," indicating a greater knowledge of EoE in the NDR where an initiative was done in 2011 to find more EoE patients. It is therefore suspected that the surgeons in the NDR are more aware of biopsying patients with food bolus obstruction and therefore finding more patients with EoE.

Table 4 Complications of EoE

	Pure EoE patients (no comorbid GORD)		
	EoE-Cph $n = 95$	EoE-Cph-DanEoE	*P* value
Food bolus obstruction (FBO): Proportion of patient group, *n*			
Never FBO before, during, or after the debut endoscopy	97%, 92	30%	0.01
FBO at any time before or after the index endoscopy	3.4%, 3	−24%	<0.001
FBO at the index endoscopy	1.1%, 1	−13%	<0.001
FBO before the index endoscopy			
Once	1.1%, 1	−16%	<0.001
Twice	1.1%, 1	−3.0%	0.3
3 or more times	0.0%, 0	−2.4%	0.3
FBO after the index endoscopy			
Once	1.1%, 1	−6.0%	0.04
Twice	0.0%, 0	−0.6%	1.0
3 times	0.0%, 0	−0.6%	1.0
Patients having strictures dilated or perforations: Proportion of patient group, *n*			
Patients dilated in total	9.5%, 9	2.4%	0.5
Before the index endoscopy	2.1%, 2	0.3%	1.0
At the index endoscopy	0.0%, 0	−2.9%	0.2
After the index endoscopy	8.4%, 8	6.0%	0.03
On PPI treatment	4.2%, 4		
Perforation of esophagus, ever	0.0%, 0	0.0%	1.0

The differences between complications served in the academic of the EoE-Cph after October-2017 ($n = 95$) compared with the population-based DanEoE cohort ($n = 170$).

EoE, eosinophilic esophagitis; FBO, food bolus obstruction; GORD, gastro-esophageal reflux disease; *n*, number.

Despite the long diagnostic delay in both cohorts, a need for dilation before or at the diagnosis was rare (<5%).[4] We had expected a difference in dilations between the population-based and the EoE-center-based Danish cohorts. This anticipation was based on the lower number of dilations in population-based Swiss cohorts (13–36%)[17,18] compared with several academic cohorts (24–56%).[19–21] That we did not see such a difference might suggest that EoE has a milder course, or that stenosis is not recognized in Denmark, and dilations therefor not performed before arrival to an EoE center at an academic hospital.

Conclusion

In this study, the new academic hospital based EoE Copenhagen cohort was described clinically in detail and compared with the population-based DanEoE cohort. Results indicated that EoE patients referred to a Danish EoE center is a selected subgroup with disease debut at a younger age, less comorbid GORD, and rarely food bolus obstruction before diagnosis. It also indicates that many older EoE patients, EoE patients with previous food bolus obstruction or comorbid GORD, are treated elsewhere. In summary, this suggests that study results from academic hospitals might not have generalizability to the average EoE patient in a population.

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