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DIAGNOSTIC DELAY IN PATIENTS WITH EOSINOPHILIC ESOPHAGITIS HAS NOT CHANGED SINCE FIRST DESCRIPTION 30 YEARS AGO

Diagnostic delay in eosinophilic esophagitis

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Abbreviations:

EoE	Eosinophilic esophagitis
DD	Diagnostic delay
GI	Gastrointestinal
IQR	Interquartile range
SEED	Swiss EoE database

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Abstract

Background and aims: Eosinophilic esophagitis (EoE) is a chronic-progressive disease. Diagnostic delay (DD) is associated with increased risk of esophageal strictures and food impactions. We aimed to assess the evolution of DD since EoE's first description in 1993 until 2021.

Methods: We analyzed data from patients prospectively included in the Swiss EoE Database. DD was calculated as time-interval between the first occurrence of EoE-symptoms and the confirmed diagnosis. DD was analyzed annually over time (1989-2021) and according to mile stone publications in the field (1993: first description; 2007: first consensus recommendations; and 2011: updated consensus recommendations). In addition, a cox proportional hazards model has been used to describe the relation between diagnostic delay and covariates.

Results: Complete data of n=1152 patients (male = 857, 74%; median age at diagnosis = 38 years, interquartile range (IQR): 28-49, range, 1-86) were analyzed. Overall, median DD was 4 years (IQR: 1-11, range, 0-56) with DD ≥10 years in 32% of the population. Over time, DD did not significantly change, neither annually, nor according to release dates of mile stone publications with a persistently stable fraction of roughly a third of all patients with a DD of ≥10 years. Both, age at diagnosis ($p<0.001$, with an increase in DD up to the age of 31-40) and at symptom onset (younger patients had a longer DD; $p<0.001$) were significantly associated with DD.

Conclusions: DD has not changed since EoE's first description almost 30 years ago and remains substantial. Even today a third of patients has a persistently high DD of ≥10 years. Substantial efforts are warranted to increase awareness for EoE and its hallmark symptom, solid-food dysphagia, as an age-independent red-flag symptom amongst health-care professionals and presumable the general population alike in order to lower risk of long-term complications.

Key words: Eosinophilic esophagitis; diagnostic delay; solid-food dysphagia; Esophagus

INTRODUCTION

Eosinophilic esophagitis (EoE) has emerged as one of the major disease states in gastroenterology, causing a variety of upper gastrointestinal (GI) symptoms. EoE is the major cause of solid food bolus impaction (1), which may result in serious complications like esophageal perforation or aspiration pneumonia. However, the broad clinical picture may also consist of only mild symptoms. Incidence rates are continuously increasing, presumably due to yet insufficiently identified environmental factors and altered compositional food intake, rather than an increase in awareness or esophageal biopsy rates (2, 3). As of today, the overall pooled prevalence is estimated around 34 cases/100,000 with considerable geographic- and population-based heterogeneity (1, 4).

Untreated disease results in remodeling of the esophagus with progressive increase in esophageal wall stiffness and stricture formation in direct correlation with the length of diagnostic delay (DD) (5, 6). Every additional year of DD increases the risk of fibrostenotic changes in the esophagus by 5% (7). This not only impacts on potential serious clinical sequelae including food impaction, but also on therapeutic management, as early disease changes with mucosal inflammation may more readily respond to anti-inflammatory measures such as elimination diets or medical treatment, whereas later stages often require invasive treatment strategies (1). In Inflammatory bowel disease – a group of chronic immune-mediated inflammation of the luminal gastrointestinal tract – a similar increase in risk of complications and lower response rates to medical treatment with increased DD has been robustly demonstrated (5, 8, 9).

The wide spectrum of clinical presentation including symptoms and at times mild endoscopic appearance might prolong the physician-attributed delay. However, according to a large retrospective long-term analysis from Italy, a large portion of the overall DD appears to be attributed to patients (10). This could be, amongst others, explained by a lack of awareness as

well as symptoms, modifiable by behavioral adaptations, such as avoidance of certain foods or reduced velocity of food intake.

In recent years, EoE has emerged as an increasingly more prominent topic in gastroenterology in general, and published literature as well as educational events in specific. However, little is known on whether increased awareness and efforts to educate health professionals about EoE translate into decreasing diagnostic delay over time. The purpose of this study was, therefore, to assess the evolution of DD in Switzerland from 1993 to 2021 and to examine potential influence of mile stone publications including first description of EoE in 1993 (11, 12) and consensus recommendations in 2007 and 2011 (13, 14) as well as patient- and disease-specific characteristics on DD. We also examined whether DD in patients with typical EoE symptoms but not fulfilling diagnostic criteria for EoE and hence categorized as EoE-like disease or lymphocytic esophagitis (15, 16) differs from DD in EoE patients.

METHODS

Study design and patient population

We conducted a retrospective observational study of EoE patients of all age groups included in Swiss EoE database (SEED) initiated by one of the co-authors (A.S.) of this manuscript and continued by the EoE clinic of the University Hospital Zurich (Switzerland). At the time of analysis (November 2021), the SEED included 1380 patients (first patient diagnosed in 1989). All included patients were diagnosed according to established EoE criteria (1, 17). A detailed description of the SEED was published previously (18). Before inclusion, all patients gave their written consent, and the study was approved by the Ethics Commitee (EKNZ 2006/058). Inclusion criteria for this analysis were known year of first appearance of EoE symptoms, and known year of EoE affirmative diagnosis. In case of missing data, a retrospective chart review was conducted. DD was defined as the interval between first occurrence of EoE symptoms and confirmed diagnosis.

In order to further evaluate the sources of the DD we additionally performed a subanalysis focusing on the first medical contact after disease manifestation, the first contact with a gastroenterologist and the number of esophagogastroduodenoscopies (EGD) prior to diagnosis. Since these information are not included in the SEED, we randomly selected patients from each 5 year time-interval (whenever possible 20 patients) and searched their medical records for the aforementioned data.

Statistical analysis

Statistical analysis war performed by R statistical software (version 4.0.3). Normal-Quantile-Quantile-Plots were applied to visualize quantitative data distribution. Non normally distributed data were presented as median, interquartile range (IQR) and range. For reasons of overview, age at symptom onset and at diagnosis was additionally grouped by 10-year

intervals. Differences of numeric non-normally distributed data by (sub-) groups were analyzed by Kruskal Wallis test. Categorical data were presented as number (n) and percentage (%) of group totals. A multivariable analysis was performed as a cox proportional hazards analysis with diagnostic delay, patients' characteristics and years (including the interaction term age*atopic disease). $p < 0.05$ was regarded as statistically significant.

RESULTS

Patient characteristics

At time of the analysis, the SEED included 1380 patients. After excluding missing data on symptom onset and/or date of confirmed diagnosis (n=208 patients) as well as patients diagnosed incidentally and labeled asymptomatic (n=20), 1152 patients were included in the analysis. The majority of patients were male (male = 857, 74%; median age at diagnosis = 38 years, IQR: 28-49, range: 1-86). Age at diagnosis showed a normal distribution with its peak between 30 and 40 years with 25% of the study population being diagnosed with EoE during that period (figure 1). Median age at symptom onset was 30 years (IQR: 18-43, range: 0-85). Fifty one percent of patients first experienced EoE-symptoms in between the ages of 10 and 30 years. Individuals up to 10 years old and 51 years or older were less likely to first experience EoE symptoms when compared to those between 11 and 50 years of age (figure 1).

Overall diagnostic delay and its evolution over time

The median DD during the entire observational period of the study (1989-2021) was 4 years (IQR: 1-11, range, 0-56). Of note, a third of the population (n= 363, 32%) had a DD of ≥10 years. Over time, DD did not change, neither when examined on yearly basis (p=0.716, figure 2a), nor when DD was stratified into periods (1993-2007, 2008-2011, and 2012-2021) based on aforementioned EoE milestone publications (p=0.387, figure 2b). In addition, in all three time intervals a persistently stable fraction of roughly one third of all patients had a DD of ≥10 years (1993-2007: n=85, 32%; 2008-2011: n=124, 33%; 2021-2021: n=154, 30%).

Diagnostic delay, gender and age at the time of diagnosis

Overall, DD did not differ between sexes (figure 3). However, length of DD differed with age at the time of diagnosis. DD increased from a median of 0 years for persons of 10 years of age or younger to 5 years for persons between 31-40 years of age ($p<0.001$, figure 3).

When examining variation in DD based on age at symptom onset, we observed an inverse association of age at symptom onset and DD ($p<0.001$, figure 4), with longest DD observed in children.

Diagnostic delay and food bolus impaction prior to EoE diagnosis

A third (n=361, 31%) of the study population suffered from at least one food impaction requiring endoscopic removal prior to diagnosis. DD was longer in patients requiring endoscopic disimpaction prior to diagnosis when compared to patients that did not undergo endoscopic disimpaction (with endoscopic disimpaction median DD of 6 years, IQR: 2-14, range: 0-45; without endoscopic disimpaction: median DD of 3 years, IQR: 1-10, range: 0-56, $p<0.001$).

Diagnostic delay according to concomitant atopic diseases

Three quarters (74%, n=853) of the population had confirmed atopic conditions other than EoE. In the remaining patients, it was either not known if patients had other atopic conditions (n=146, 13%), or else patients did not suffer from concomitant atopic conditions (n=153, 13%). When compared to patients without concomitant atopic conditions, patients with concomitant atopic conditions were younger at the time of symptom onset (with concomitant atopic condition: median = 29 years of age, IQR: 17-41, range: 0-81; without concomitant atopic condition: median = 34 years of age, IQR: 21-50, range: 0-85, $p<0.001$ as well as at time of diagnosis (with concomitant atopic condition: median = 38 years of age, IQR: 28-47,

range: 1-82; without concomitant atopic condition: median = 41 years of age, IQR: 28-54, range: 3-86, p<0.001. DD for patients without concomitant atopic conditions was shorter (median = 3 years of age, IQR: 1-9, range: 0-45 versus median = 5 years of age, IQR: 2-12, range: 0-56, p<0.001).

Cox proportional hazards model

The multivariable analysis confirms the longer DD in patients with food bolus impaction. For details on all included variables see table 1.

Diagnostic Delay in EoE-variants

Two percent (n=23) of the study population were diagnosed with EoE-like disease or lymphocytic esophagitis. Compared to classic EoE, DD in EoE-variants did not significantly differ (classic EoE: median = 4 years, IQR: 1-11, range, 0-56; EoE-variants: median = 3 years, IQR: 2-6.5, range: 0-23, p=0.704).

Analysis of patient- and gastroenterologist-diagnostic delay

In a subanalysis we reviewed the medical charts of n=123 patients, accounting for 10.7% of the entire cohort (male = 97 (79%), median age 38 years, range: 11-79). No robust data was found concerning the first medical consultation (with any type of physician) after the manifestation of symptoms. In this subgroup, 38 patients (31%) were evaluated by a gastroenterologist prior to diagnosis (gastroenterologist-diagnostic delay). Thirty-five of these patients (97%) received at least one EGD (range 1-5) with biopsies taken in 17%. In the remaining 85 patients (69%), diagnosis was made at the first contact with a gastroenterologist (patient-related delay).

DISCUSSION

In our study, we demonstrated that, despite considerable research (>2000 publication on EoE on www.pubmed.gov since 2014) and numerous educational events in recent years, the DD has not changed since first description of EoE almost 30 years ago. In fact, DD remains substantial with an overall median delay of 4 years, comparable to that described in previously published studies from Europe and the US (5, 19-21). In addition, about one third of EoE patients have a DD of ≥10 years. Bearing in mind that EoE is a chronic and progressive disease, that, if left untreated, leads to esophageal structuring ultimately causing food impaction, the results of our analysis are a cause for concern (5, 20, 22).

Esophageal remodeling not only causes symptoms like dysphagia, but also are responsible for food bolus impactions (20, 23). Importantly, the length of DD (untreated disease) directly correlates with the occurrence of esophageal strictures (5). Schoepfer et al. showed that the prevalence of strictures increases from 17% to 71% in patients with a delay between 0-2 years and >20 years ($p<0.001$) (5). Esophageal strictures were present in around 38% of patients with a delay between 8-11 years, a delay that is prevalent in about one third of our study population. However, even a median delay of 4 years resulted in strictures in around 31% of untreated patients (5). This was just recently confirmed by Lenti et al., who reported a significantly longer median DD in patients with EoE complications (complications present in 14% of the study population; 92% of these were strictures) when compared to patients without EoE complications (60 vs. 35 months) (10). The risk of esophageal strictures seems to increase by as much as 9% with each year of untreated EoE (20). Thus, reducing the DD in EoE patients is of importance.

One reason for the persisting long DD might be the patient-dependent delay, defined by the time period from the occurrence of first symptoms to the initial medical evaluation. In a recently published retrospective, multicenter study including 261 consecutive Italian patients over a time period of 5 years (10), the overall DD was 3 years (IQR 12-88; DD >10 years in

15% of the population). The patient-dependent delay was significantly longer (median = 18 months, IQR 5-49) than the physician-dependent delay (median = 6 months, IQR 1-24), giving evidence that part of the observed overall delay results from patients coping with (i.e., changes in diet and/or eating behavior) or denying symptoms – sometimes for years. There is a lack of information regarding the first medical contact due to EoE-like symptoms in our database, which hinders us to state on the patient-dependent delay. This is unfortunate, since in our personal experience the patient-dependent delay plays a critical role in the overall DD. However, in our subsequently conducted extensive subgroup analysis we were able to deduce that patients (or a physician other than a gastroenterologist) are responsible for the largest part of the overall DD. This fact indicates that future efforts should target the general population, and potentially primary physicians, to strengthen the awareness for EoE as a potential underlying condition in patients with dysphagia. Regarding the patient-dependent delay, future studies should also try to analyze the type of coping behavior and its influence on the delay. Nowadays even a substantial change in diet may not necessarily suspicious for underlying dysphagia. However, a change in eating behavior, especially in cases with prolonged chewing, slow swallowing or even the necessity of drinking fluids after swallowing of solid food, should raise suspicion also in the general population.

Analyzing age at symptom onset (51% <31 years of age and 30% <21 years of age), once more illustrate that EoE affects young individuals. This is of major clinical relevance, since young age (at onset of symptoms and at diagnosis) was associated with long DD confirming previously published data (5, 20). It is likely that young patients (age <10 years at symptom onset in 10% of patients in our population) face many hurdles that undoubtedly lead to increased length of DD in this population. They may have difficulties reporting their symptoms. Whilst in adolescent and adult EoE-patients solid-food dysphagia is the most common symptom, younger children may also experience regurgitations, emesis, abdominal

pain, failure to thrive, and food refusal (20, 24). Lastly, the standard clinical management of young patients differs from adults, and when compared to adult population endoscopic investigations are performed less frequently in the pediatric population for safety and logistic reasons (i.e., necessity of general anesthesia). Nevertheless, solid food dysphagia should be regarded as an alarm symptom in all age groups and should lead to endoscopic examination.

Just as in our analysis, Lenti et al. reported patients who experienced food bolus impactions have longer DD than patients who did not (10). It is likely that EoE diagnosis is missed in individuals that might have relatively mild endoscopic presentation and are not biopsied. However, in our own experience this patient group often consists of patients that are specifically at risk to notoriously and stoically cope for years with dysphagia using various behavioral adaptations. In addition, history taking in these patients may unfortunately often be only superficial and inadequate. In these individuals, untreated EoE ultimately leads to strictures and food impactions, which often (in our experience) resemble the first contact to a gastroenterologist.

Concomitant atopic conditions are known to be associated with the diagnosis of EoE, in all age groups, including the very young children (25, 26). Especially in children with a symptom complex of atopy and vomiting or failure to thrive, further diagnostic workup to rule out EoE should be considered (25). In our study population, three quarters (74%) had atopic features, confirming the association of atopy and EoE. Median DD in patients without atopy seemed to be shorter than in patients with atopy. However, after adjusting for age, the difference in DD between the two groups was not significant anymore, which is most likely explained by the significant younger median age of patients with atopy, which was shown to be associated with a longer DD. The last objective in our analysis were EoE-variants. Those manifest clinically just as the classic EoE and therefore lead to similar diagnostic management, explaining similar lengths of DD in both groups.

The reasons for the persisting long DD are multifactorial. Lenti et al. argued that the vast clinical picture of EoE with differing symptoms is probably the most important influencing factor (10), but that argument is more likely to be relevant for pediatric than adult EoE patients. In addition, the urge to seek medical advice due to symptoms suggestive for gastroesophageal reflux disease (GERD), a condition not always easily distinguishable from EoE, is influenced by symptom- and patient-related factors (27, 28). Mild symptoms, for example, lead to the underestimation of symptoms, both by patients and physicians. Especially if behavior changes (i.e., diet or drinking of water with solid food) decrease severity of complaints to some extent, patients do not seek medical advice. Even if they do, physicians might not schedule further, potentially invasive diagnostic workup (biopsies) in those cases. In addition, typical symptoms of GERD can be mimicked by EoE (inflammation can induce acid hypersensitivity) and the standard GERD therapy with proton-pump inhibitors can also reduce symptoms caused by EoE (29-31). One additional physician-related factor contributing to the persisting long DD is that physicians do not obtain esophageal biopsies during upper endoscopy for the purposes of diagnostic exploration even in the event of prior food impaction in an apparent "healthy" patient. Endoscopic findings are often prematurely rated as normal or else are normal during index endoscopy resulting in a missed chance for diagnosis and loss to follow up (in up to 50% of patients) (32, 33). In fact, it is of utmost importance to keep in mind that endoscopic features of EoE vary, ranging from classic features like exudates, rings, edema, furrows, stricture (EREFS), narrowing or crepe-paper mucosa to completely normal appearing mucosa (1, 34). Additionally, endoscopic findings of whitish plaque-like lesions may be interpreted as esophageal candidiasis or as white exudates, both potentially expressing similar symptoms (35). Because specificity of endoscopic diagnosis of Candida is at most 80%, histopathologic confirmation essential (35, 36). In addition, patients with esophageal motility disorders are at risk to develop esophageal,

adding another argument to take biopsies whenever the endoscopist sees white exudates and especially if the leading symptom is dysphagia (37). Krarup et al. recently demonstrated (34) that prospectively implementing a biopsy protocol during the diagnostic work-up for patients with dysphagia, regardless of the endoscopic appearance of the esophagus, resulted in doubling of the number of biopsies taken per patient, and the EoE detection rate increased 50-fold per year. Remarkably, one third of all EoE patients had a macroscopically normal appearing esophagus, but eventually received diagnosis and treatment as a consequence of the biopsies taken.

We unfortunately do not have a precise understanding on a potential influence of the type of physician that the patients first seek medical advice from. It appears obvious that general practitioners are not as familiar with EoE and its symptoms as gastroenterologists. But even amongst gastroenterologists the awareness for this multifaceted disease and by this the diagnostics consequences can differ broadly. Unfortunately, our database neither includes the type of physician at first medical attendance nor (in case of gastroenterologists) information regarding the education or location of practice (e.g. specialty center vs. rural practice). Future studies should try to implement these factors in order to implement tailored educational programs.

Our study has several limitations and strengths. One limitation is its retrospective design and the confinement to one single country. Additionally, we were not able to dissect the patient-related delay from the physician-related one. Also, the exact timepoint of symptom manifestation could only be estimated to a certain year in many cases. Strengths of this study are that the analysis was carried out using large number of EoE that were recruited over a long time-period.

With a north-south diameter of 220 kilometer and a west-east diameter of 350 kilometers, respectively, Switzerland is geographically a small country located in the middle of Europe

and has currently a population of approximately 8.8 million inhabitants. There exists a tight network of medical services with 52.3 hospitals per 1 million inhabitants and 4.5 active physicians per 1000 inhabitants. Family doctors, specialists as well as hospitals are therefore easily accessible. The national gastroenterology service is provided by around 430 board-certified gastroenterologists (240 in a private practice, 190 in hospitals). Of note, in Switzerland health insurance is mandatory by law for all inhabitants independent of their socio-economic status. Ninety percent of the costs for medical services are covered by the insurances. We don't know the proportion of referred in the SEED. However, considering a pooled prevalence of 34/100,000 (4), around 3000 people in Switzerland should be affected by EoE and with 1380 patients included, the SEED is a representative cross-section of Swiss EoE-patients, allowing the conclusion that the DD remains high (DD in 1/3 of patients >10 years) in Switzerland. Improving awareness through educational events especially for patients and parents, but also for primary physicians with special focus on the young generation, sending all patients with solid-food dysphagia regardless of their age for endoscopy, and adapting protocols to obtain several biopsies separate in the distal and proximal esophagus in all patients with dysphagia are steps needed to be taken to shorten DD in Switzerland.

Figure legends

Figure 1: Distribution of patients grouped by 10-year intervals at age at diagnosis (a) and age at symptom onset (b).

Figure 2: Diagnostic delay visualized over the entire observational period from 1989 to 2021 (a) and according to milestone publications (b). The red line represents the overall median DD of 4 years.

Figure 3: Diagnostic delay according to age at diagnosis visualized in 10-year intervals. Figure 3b represents the same values as 3a further divided into women (red) and men (green).

Figure 4: Diagnostic Delay according to age at symptom onset grouped in 5-year intervals and further visualized according to gender (red = women, green = men).

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Table 1: Cox Proportional Hazards: Diagnostic delay by patients characteristics/variables and years

univariable	HR	95% confidence interval		p value
		lower limit: 2.5%	upper limit: 97.5%	
age at diagnosis	0.99	0.98	0.99	< 0.001
gender (m/w)	0.96	0.84	1.10	0.593
years	0.99	0.98	1.01	0.387
bolus impaction (y/n)	0.76	0.67	0.86	< 0.001
atopic disease (y/n)	0.78	0.68	0.89	< 0.001
age*atopic disease	-	-	-	-

multivariable	HR	95% confidence interval		p value
		lower limit: 2.5%	upper limit: 97.5%	
age at diagnosis	0.99	0.98	0.99	0.014
gender (m/w)	1.01	0.88	1.15	0.920
years	0.99	0.98	1.01	0.555
bolus impaction (y/n)	0.76	0.67	0.86	< 0.001
atopic disease (y/n)	0.95	0.64	1.40	0.787
age*atopic disease	0.99	0.99	1.00	0.204

Abbreviations: HR = hazard ration; m = male; f = female; y = yes; n = no