# Prevalence of Eosinophilic Esophagitis in Adolescents With Esophageal Atresia

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**ABSTRACT**

**Background and Objective:** Eosinophilic esophagitis (EoE) is an increasingly recognized childhood disease. Esophageal atresia (EA) is the most frequent congenital malformation of the esophagus. Recently, cases of EoE occurring in patients with EA have been reported, although the exact prevalence of EoE in EA remains unknown. The aim is to investigate the prevalence of EoE among EA in adolescents and to describe these patients' characteristics.

**Methods:** Systematic upper gastrointestinal endoscopies with multistage esophageal biopsies were prospectively performed in 63 adolescents with EA. A standardized form was used to collect clinical and endoscopic data. Diagnosis of EoE was made as ≥15 intraepithelial eosinophils/high power field, whatever the response on proton pump inhibitors therapy.

**Results:** Six patients (9.5%) presented an EoE (17–100 eosinophils/high power field). An atopic condition was reported more frequently in the eosinophil ≥15 group than in patients with no EoE (66% vs 16%; $P = 0.014$). Except for chest pain, symptoms and endoscopic features were similar in patients with EoE and patients with no EoE.

**Conclusion:** In our series of 63 patients born with EA, mainly distal tracheoesophageal fistula, the prevalence of EoE is increased, and therefore should be considered in adolescents with EA.

**Key Words:** eosinophilic esophagitis, esophageal atresia, prevalence

(*JPGN* 2019;69: 52–56)

**What Is Known**

- The esophageal atresia is the most frequent congenital malformation of the esophagus.
- Eosinophils infiltration of the esophageal mucosa has been reported in patients with esophageal atresia.

**What Is New**

- The prevalence of eosinophilic esophagitis is high in adolescents with esophageal atresia undergoing systematic upper gastrointestinal endoscopy.

Eosinophilic esophagitis (EoE) is a rare disease with a prevalence among children in developed countries ranging from 0.89 to 4/10,000 (1). But EoE is the most prevalent cause of chronic esophagitis after gastroesophageal reflux disease (GERD) and the leading cause of dysphagia in children and adolescents (2). Since 2007, EoE is defined as a primary clinicopathologic disorder of the esophagus, characterized by the association of upper gastrointestinal symptoms with esophageal mucosa containing ≥15 eosinophils per 1 high power field (HPF) with objective 40 in 1 or more biopsy specimens (1–4).

The pathogenesis of EoE is unclear, although it is generally considered as an allergic disease. The presenting symptoms of EoE include feeding difficulties, dysphagia, food impaction, heartburn, and chest pain (1,3–5). Typical endoscopic features of EoE are white exudates, crêpe-paper mucosa, linear furrows, and/or diffuse esophageal narrowing, whereas a normal-appearing mucosa has been reported in 20% to 30% of patients, especially in children (5,6). Endoscopic features alone do not permit to achieve EoE diagnosis.

Esophageal atresia (EA) is the most frequent congenital malformation of the esophagus (1/2500 to 4500 children), repaired soon after birth (7–9). Despite improvements in the prognosis of this malformation to <10% mortality during the last 3 decades (10,11), a high rate of digestive morbidity is observed in these patients (12). Patients with EA have frequently GERD with gastrointestinal symptoms that are resistant to proton pump inhibitors (PPIs), and are managed by fundoplication in 40% of children (12,13). On the contrary, dysmotility and anastomotic stenosis are common and most patients present long-term digestive symptoms (14,15). Thus, the diagnosis of EoE is more challenging in patients with EA who have commonly gastrointestinal symptoms. Recently, cases of EoE occurring in patients with EA have been reported (16–19) and a retrospective Australian series of 103 children with EA suggested a high rate (17%) of EoE in EA (20).

To investigate the possible association between EA and EoE, we studied the prevalence of EoE in a multicenter, prospective series of 63 adolescents with a history of EA.

## METHODS

### Study Design and Patients

This study was a noninterventional, multicenter prospective study, running from June 2007 to August 2015. Most patients were recruited from an international study of Barrett's esophagus in

Received July 12, 2018; accepted December 1, 2018.

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The authors report no conflicts of interest.



DOI: 10.1097/MPG.0000000000002261

patients with EA, which included patients from 20 centers that participated in the French-speaking Group of Gastroenterology Hepatology, and Nutrition (21). In our study, the patients came from 2 French centers (University Hospitals of Lille and Strasbourg) with the highest number of cases in the study of Barrett esophagus in patients with EA allowing a centralized review of each biopsy by the same pathologists. The inclusion criteria were all patients aged 15 to 20 years with medical history of EA, even if they were asymptomatic. Patients treated with esophageal replacement (coloplasty or gastric transposition) were excluded. From June 2007 to August 2015, the patients were prospectively recruited from a study of Barrett esophagus in patients with EA (21). The patients came from 2 French centers (University Hospitals of Lille and Strasbourg) with the highest number of cases allowing a centralized review of each biopsy by the same pathologist. The study was approved by the ethics committee (CPP North West) and declared to the National Data Protection Authority (CNIL) and the French Consultative Committee for Information Management in Biomedical Research (CCTIRS). All patients and their parents signed informed consent. Upper gastrointestinal endoscopy under general anesthesia was performed in all enrolled patients, irrespective of their presenting symptoms, according to ESPGHAN-NASPGHAN guidelines (15). Esophageal biopsies were taken according to a standardized protocol at least 3 levels: 4 quadrant biopsy specimens from 1 and 3 cm above the Z-line and 4 quadrant biopsy specimens from the anastomotic level. Biopsies of any macroscopic lesion were also collected during endoscopy. At least 12 biopsies per patient were available for analysis.

Following recent international consensus on EoE diagnosis of EoE was made when 1 or more biopsy specimens displaying $\geq$15 intraepithelial eosinophils/HPF, whatever their response on PPI therapy (2).

## Clinical and Endoscopic Variables

We prospectively collected clinical and endoscopic data for each patient using a standardized form, including type of atresia according to the Ladd classification, history of GERD, recent symptoms (dysphagia and reflux symptoms), current treatment of GERD (antiacids, PPI, or prokinetic agents), and endoscopic findings (normal esophagus, inflammation, ulcerations, strictures, hiatal hernia, and any other notable features including white exudates, crêpe-paper mucosa, linear furrows, rings, and diffuse esophageal narrowing). Coexisting allergy diseases (asthma, eczema, documented food allergy) were retrospectively collected from electronic medical records. An eosinophils infiltrate of esophagus, in the childhood before study inclusion, was searched on previous biopsies.

## Histopathological Data

Histopathology was independently assessed on hematoxylin and eosin-stained sections by junior and senior pathologists E.L. and E.L., both of whom reviewed all cases on a multihead microscope to reach a consensus in problematic cases. The area containing the highest density of eosinophils (hotspot) was first selected on whole slide, at low magnification (objective 10). Then the number of intraepithelial eosinophils was counted in 1 "hotspot" field at a magnification 400 (objective 40; field of 0.196 $mm^2$). The activation of eosinophils and local tissue damage were assessed according to the following criteria.

1. Presence of eosinophil superficial layering defined as the preferential superficial distribution of eosinophilic inflammation in the upper third to half of the epithelium (3,22).
2. Presence of microabscesses defined as a cluster of $\geq$4 eosinophils (3,22,23).
3. Degranulation of eosinophils (3,22,24).
4. Intercellular edema (3,22,24).
5. Presence of hyperplasia of the basal zone (>20% of total epithelial thickness on correctly oriented sections) (3,23).
6. Presence of papillary elongation to more than two-thirds of the epithelial height (3,22).
7. Lamina propria fibrosis, graded as absent, minimal, moderate, and severe (3,22,25).

## Statistical Analysis

Statistical analyses were carried out using Prism version 7.0 (GraphPad Prism Software Inc., San Diego, California). Clinical endoscopic and histological data from the 2 patient groups, biopsies with $\geq$15 intraepithelial eosinophils/HPF (EoE) and biopsies with <15 intraepithelial eosinophils/HPF (no EoE), were compared. Qualitative variables were statistically evaluated using the Fisher test.

# RESULTS

A total of 63 patients with a history of EA were included, 6 of them (9.5%) presenting an EoE. Table 1 shows data from the 6 patients with EoE compared with the 57 patients with no EoE (<15 intraepithelial eosinophils/HPF).

The mean age was 16 years in patients with EoE and in patients with no EoE, with a male predominance. A frequent history of GERD and previous dilatations were observed in both groups (NS). All patients with EoE and 51 patients with no EoE had EA with distal tracheoesophageal fistula (TEF). Five patients with no EoE had isolated EA and 1 patient with no EoE had EA with distal and proximal TEF. No patient had EA with proximal TEF. In the limit of the small numbers of patients with EA presenting EoE in our series, a history of allergy was reported more frequently in the EoE group (4 patients, 66%) than in the no EoE group (9 patients, 16%) ($P = 0.014$). Three patients with EoE had food allergy. One patient with EoE had asthma with a positive skin prick test for latex and dust mites. One patient with EoE had allergic rhinoconjunctivitis. In the childhood, 1 EoE patient had an endoscopy with biopsies, 17 no EoE patients had an endoscopy with biopsies and 8 no EoE patients had only endoscopy without biopsy. Overall, 1 patient in the no EoE group had an eosinophil infiltrate (20 eosinophils/HPF) on esophageal biopsies performed 4 years before without PPI therapy. When she entered in our study no EoE was found and she was on PPI.

At the time of endoscopy, 83% of the patients with EoE and 51% of patients with no EoE presented with frequent dysphagia (not significant, NS). Food impaction was found in 66% of patients with EoE and in 44% of patients with no EoE (NS). The dysphagia resulted in feeding difficulties for 50% of the patients with EoE, versus 39% in the no EoE patients (NS). Reflux symptoms were present in 83% of patients with EoE and in 46% of patients with no EoE (NS). In the limit of the small numbers of patients with EA presenting with EoE in our series, retrosternal chest pain was more common in patients with EoE (4 patients, 66%) than in patients with no EoE (6 patients, 10%) ($P = 0.005$). Only 1 patient with EoE and 14 patients with no EoE were free of symptoms.

The season (winter/fall vs summer/spring), when was performed endoscopies, was not different between EoE and no EoE patients. Four patients with EoE and 48 patients with no EoE had a normal esophageal mucosa at endoscopy. Two patients with EoE had esophagitis with erythema and/or ulceration. In the no EoE group, erythema was noted in 7% of patients (4 patients) and ulceration in 9% of patients (5 patients). Only 1 patient, in the

TABLE 1. Demographic, clinical, endoscopic, and histological data in the 6 patients with EoE ≥ 15 (eosinophilic esophagitis group) compared with the 57 patients with EoE <15 (no eosinophilic esophagitis group)

| | Patients with EoE ≥15 (n = 6) | Patients with EoE <15 (n = 57) | *P* value Fisher test |
|---|---|---|---|
| Sex | | | |
| Male | 4 (66%) | 31 (54%) | NS |
| EA with distal TEF | 6 (100%) | 51 (89%) | NS |
| History of allergy | 4 (66%) | 9 (16%) | 0.014 |
| Food allergy | 3 (50%) | 5 (9%) | NS |
| Asthma | 1 (17%) | 4 (7%) | NS |
| Eczema | 0 | 2 (3%) | NS |
| Rhinitis | 1 (17%) | 0 | NS |
| History of GERD | 4 (66%) | 50/53 (94%) | NS |
| History of previous dilatations | 2 (34%) | 30 (53%) | NS |
| Patient on PPI at time of biopsy | 3 (50%) | 11 (19%) | NS |
| Presenting symptoms | | | |
| Dysphagia | 5 (83%) | 29 (51%) | NS |
| Food impaction | 4 (66%) | 25 (44%) | NS |
| Feeding difficulties | 3 (50%) | 22 (39%) | NS |
| Retrosternal chest pain | 4 (66%) | 6 (10%) | 0.005 |
| Regurgitation | 0 | 7/55 (13%) | NS |
| Pyrosis | 4 (66%) | 20/56 (36%) | NS |
| Endoscopy | | | |
| Normal | 4 (66%) | 48 (84%) | NS |
| Stricture | 0 | 1 (2%) | NS |
| Erythema | 2 (34%) | 4 (7%) | NS |
| Ulceration | 1 (17%) | 5 (9%) | NS |
| Hiatal hernia | 2 (34%) | 3 (5%) | NS |
| Histology: activation of Eo | | | |
| Eo superficial layering | 4 (66%) | 0 | 0.0003 |
| Microabscesses | 4 (66%) | 0 | 0.0003 |
| Degranulated Eo | 5 (83%) | 0 | <0.0001 |
| Histology: local tissue damage | | | |
| Intercellular edema | 6 (100%) | 47 (82%) | NS |
| Basal zone hyperplasia | 1 (17%) | 6 (10%) | NS |
| Papillary elongation | 4 (66%) | 12 (21%) | 0.03 |
| Lamina propria fibrosis | 5 (83%) | 31/51 (60%) | NS |

EA = esophageal atresia; Eo = eosinophils; EoE = eosinophilic esophagitis; GERD = gastroesophageal reflux disease; NS = not significant; PPI = proton pump inhibitor; TEF = tracheoesophageal fistula.

no EoE group, had a fibrous stricture at the site of anastomosis. The characteristic endoscopic findings of EoE, such as white exudates, crêpe-paper mucosa, linear furrows, and/or diffuse esophageal narrowing were not observed in any of the patients in these 2 groups.

Eleven patients with no EoE were on PPI at the time of biopsy. Among 6 patients with EoE, 3 patients were on PPI at the time of biopsy (100, 70, and 30 eosinophils/HPF). The 3 others patients with EoE were not treated with PPI at the time of biopsy: 1 patient demonstrated an improvement of eosinophils infiltration after a high dose of PPI (50 eosinophils/HPF before PPI vs 6 eosinophils/HPF after PPI); the 2 other patients did not benefit from a second endoscopy on PPI (17 and 80 eosinophils/HPF). Superficial distribution of eosinophils, microabscesses, and degranulation was exclusively observed in the biopsies of patients with EoE. The distribution of eosinophils was superficial in 4 patients with EoE. Microabscesses were observed in the biopsies of 4 patients with EoE and eosinophil degranulation in 5 patients with EoE.

Intercellular edema and lamina propria fibrosis were frequently observed, while basal zone hyperplasia was uncommon in both groups without any significant difference. Four (66%) patients in the EoE group had papillary elongation versus 12 (21%) in the no EoE group ($P = 0.03$).

## DISCUSSION

Our study is the first to study the prevalence of EoE in adolescents with EA. Indeed, our study includes all adolescents (whatever their occurrence of symptoms) followed in our EA clinics, who had, based on the recent international consensus on EA (15), a systematic endoscopy screening at the time of transition to adulthood. A single previous retrospective series investigated the prevalence of EoE in children with EA (average age of 1.5 years) and found 18 children (17%) with proven EoE among 103 children (20). Differences between the prevalence rate we observed here and the other could be explained by 3 reasons. Firstly, in our series some patients no EoE were on PPI at the time of the biopsy. We cannot exclude (as we can prove in 1 patient who had a previous endoscopy while not on PPI which demonstrated EoE) that some of those patients could have PPI-responsive esophageal eosinophilia resulting in an underestimation of the prevalence rate of EoE in EA. Secondly, GERD is more frequent in 10 first years of life in patients

with EA and could favor EoE in early childhood. Thirdly, 3 no EoE patients with asthma were treated by nebulized corticosteroids which could decrease eosinophils infiltrate in esophageal biopsies. On the contrary, the prevalence of EA in the EoE population is currently unknown in the literature (2).

Our prospective series confirms that the prevalence of EoE is >100-fold higher in EA than in the general population (0.89–4/10,000 persons) (1). Several hypotheses may explain this finding. First, the high prevalence of GERD, which is a common complication of EA surgery, exposes the esophagus to acid peptic injury that may impair the mucosal barrier function and expose mucosa to allergens (26). Second, congenital and/or postsurgical esophageal dysmotility (27) could lead to increased contact time between food and the esophageal mucosa. This phenomenon would lead to chronic irritation and increased mucosal permeability to allergens with an influx of eosinophilic and mast cells (28). Our series highlights a clinical association between EoE and EA. Dysmotility, peptic injury, and allergens are all together implicated in the physiopathology of EoE in patients with EA. Nevertheless, allergy could be the main specific factor as it was not constant in all patients but was more frequent in the EoE group than in the no EoE group, in the limit of the small number of patients included in our series. Further studies are needed to decipher the precise role of genetic, peptic injury, dysmotility, and allergens exposure in the physiopathology of EoE in the context of EA. Finally, the prevalence of EoE in the general population may be underestimated. Indeed, patients treated for EA are frequently scoped in specialized centers in which EoE is well known and an adequate number of biopsies are performed (29).

At time of endoscopy, 76% of 63 patients had symptoms and 82% of 63 patients had a normal endoscopy. Except for chest pain, the presenting symptoms and endoscopic features were similar in eosinophils ≥15 patients to those with no EoE. Because of persistent GERD, dysmotility, and other possible digestive complication, EA patients still present frequent digestive symptoms even during adolescence (30). In our series, except chest pain clinical symptoms do not aid in the screening of EoE in patients with EA.

An atopic condition (food allergy, asthma, or rhinitis) was significantly more frequent in eosinophils ≥15 patients than in those with no EoE, which is in line with the current physiopathogenic hypothesis of EoE being an exaggerated local inflammatory reaction following contact with trophallergens or pneumallergens (2,31). Despite a relative low number of patients with EoE studied here, our results could suggest a history of allergy in a patient with EA, especially when presenting with chest pain, should prompt endoscopy with esophageal biopsies to look for EoE. Whether treatment of EoE in patients with EA could improve clinical symptoms or prevent complications remains to be elucidated.

## CONCLUSIONS

Our study of 63 children born with EA, mainly distal TEF, shows the increased prevalence of EoE and therefore the importance of considering EoE in these adolescents. It also highlights the interest of multistage esophageal biopsies even with a normal appearance of esophageal mucosa at the time of endoscopy.

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