Research paper

Management of eosinophilic esophagitis in children according to atopic status: A retrospective cohort in northeast of France

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ARTICLE INFO

Article history:
Received 3 September 2019
Received in revised form 22 December 2019
Accepted 16 February 2020
Available online 16 March 2020

Keywords:
Eosinophilic esophagitis
Children
Atopy
Remission
Sensitization

ABSTRACT

Introduction: Most children with eosinophilic esophagitis (EoE) are atopic, but the impact of atopy on the remission and development of EoE is still unclear. The aim of our study was to determine the impact of atopy on remission of EoE and to describe allergy tests and the choice of treatment for a cohort of EoE children in France.

Methods: All children diagnosed with EoE between January 2013 and June 2018 in the five pediatric centers in the northeast of France were included. Children were divided into two groups according to personal atopic disorders. Histological remission was defined on the basis of an eosinophilic count below 15 eosinophils per high-power field.

Results: Among the 49 children included, 38 (78%) were atopic. Allergy tests were performed for 45 children (92%). Rates of sensitization were similar in both groups: 64% had food sensitization and 64% had Aeroallergen sensitization. The most commonly attempted first-line therapy was with proton pump inhibitors (63%), followed by swallowed topical steroids (STS) (18%). First-line therapy was not associated with atopic status (P = 0.88). Atopic children had a nonsignificant tendency for a higher remission rate after STS (55% vs. 0%, P = 0.24) and a higher global remission rate (54% vs. 33%, P = 0.18) compared with non-atopic children.

Conclusion: Allergy testing is relevant in the majority of children with EoE whether or not they have atopic disorders. Atopy seems to be associated with better response to STS. Further studies are needed to determine whether atopic status determines histological response.

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1. Introduction

Eosinophilic esophagitis (EoE) is an emerging disease in pediatrics, with a significant increase in its incidence and prevalence over the past 10 years. In children, the prevalence of EoE is estimated to be 111.9 cases per 100,000 inhabitants [1]. EoE is characterized by a chronic inflammation of the esophagus, which can lead to long-term sequelae of fibrosis and strictures and decreased quality of life. The diagnostic criteria for EoE were updated in 2018 by international consensus [2]. EoE is defined by symptoms of esophageal dysmotility associated with an eosinophilic infiltration into the esophageal epithelium (> 15 eosinophils per high-power field [eos/hpf]), after a comprehensive assessment of non-EoE disorders that could cause or potentially contribute to esophageal eosinophilia. Management of EoE includes three possible treatments: proton pump inhibitors (PPI), swallowed topical steroids (STS), or elimination diet (ED). No comparative study has been performed to define the treatment to be adopted according to patient characteristics. Therefore, all three treatments can be considered first-line therapies [3,4].

The association between EoE and atopic disorders is now well-established [5]. In a cohort of 449 patients with EoE, 77.5% had at
least one atopic comorbidity [6]. The relationship between EoE and atopy seems to be bi-directional, with each condition increasing the risk for the subsequent diagnosis of the other. Hill et al. suggested that EoE is a late manifestation of the atopic march, with a T-helper 2 (Th2) predominant mechanism [7]. Food remains the most common trigger and ED can achieve remission of EoE for some patients, with variable efficacy (45.5–90.8%) [8]. In addition, aeroallergens play an important role in the natural course of EoE by modulating EoE disease activity. Seasonal exacerbation and development of esophageal eosinophilia were described in murine models exposed to intranasal aeroallergens [9–11]. Moreover, environmental allergen sensitization may decrease the response to therapy [12].

Response to therapy in EoE is heterogeneous, making therapeutic guidelines difficult to establish. In comparison with asthma, some authors suggest the presence of different phenotypes of EoE, and an atopic EoE phenotype was introduced [13,14]. A lower rate of remission in the atopic group than in the non-atopic group was suggested in some studies [15,16], while Elurí et al. suggested that food allergy is an independent predictive factor of complete response (< 1 eos/hpf) to STS in adults (OR, 12.95; 95% CI, 2.20–76.15) [17]. There is a lack of information regarding the impact of atopic history on the natural course and management of EoE, in particular on treatment efficacy and on the benefit of allergic investigations.

The first aim of this study was to compare treatment outcomes in children according to atopic status. The secondary objective was to describe the use of each treatment (choice of first-line therapy, implementation) and the results of allergy tests in our patients.

2. Material and methods

We performed a multicenter retrospective cohort study between November 2018 and January 2019. Data were collected from five pediatric departments of university hospitals in the northeast of France: Besançon, Dijon, Nancy, Reims, and Strasbourg. All children aged from 1 to 18 years and diagnosed with EoE between January 2013 and June 2018 were included. Patients who did not have at least one visit after initiation of treatment were excluded. The diagnosis of EoE was based on the cut-off value of greater than 15 eos/hpf at 0.25 mm² or greater than 60 eos/hpf at 1 mm² in at least one esophageal biopsy specimen during endoscopy without another eosinophilic infiltration in the gastric and duodenal biopsies. Data collection included demographic information, clinical symptoms, personal and family history of atopy, diagnostic procedures, and response to treatments. Since we used anonymous retrospective data and since patients are informed of possibilities to retrospectively use their data in each center, the approval of the Ethics Committee was not needed. The clinical database was declared to the French Data Protection Authority under number 2214777v0.

Patients were divided into two groups: atopic children and non-atopic children. Atopic children were defined by a personal history of allergic diseases (allergic rhinitis, asthma, atopic dermatitis, and/or food allergy). Atopic sensitization was defined by a positive skin prick test (SPT) and/or a positive serum specific immunoglobulin E (sIgE) assay. SPT results were considered positive when the wheal size was equal to or greater than 3 mm from the negative control papule at 15 min, sIgE results were considered positive at levels greater than 0.35 kU/L [18], and atopy patch test (APT) results were considered positive if the cutaneous reaction was greater than or equal to 1+ according to the European Task Force on Atopic Dermatitis. Causative allergens were defined as those whose elimination from the diet improved symptoms and histological features on follow-up endoscopies with recurrence upon re-challenge. We reviewed the effects of therapies on both clinical symptoms and esophageal histology. Primary outcome was histological response to treatment, defined by an eosinophil peak count below 15 eos/hpf on esophageal biopsy. Secondary outcome was global remission to treatment, defined as clinical response (subjective complete improvement of symptoms reported by either children or parents) and/or histological response to treatment.

Demographics and clinical characteristics are described using mean ± standard deviation or median for continuous variables and frequencies and percentages for categorical variables. Atopic and non-atopic groups were compared using non-parametric tests: Fisher’s exact test for categorical variables and the Wilcoxon test for continuous variables. A P value lower than 0.05 was considered statistically significant. All statistical analyses were performed using the SAS 9.4 software.

3. Results

3.1. Study population

A total of 51 patients were diagnosed with EoE in the five pediatric centers between January 2013 and July 2018. Two patients had no follow-up in the designated center after diagnosis and they were excluded. Among the 49 remaining children, the mean age at diagnosis was 10.3 years ± 4.0 (range: 1.1–15.8) with a majority of boys (84%). Patients had a high incidence of atopic disorders (38/49 patients, 78%) including: food allergy (51%), asthma (43%), allergic rhinitis (37%), and atopic dermatitis (26%). Approximately half of the patients (23/49) had at least one first-degree family member with an atopic condition. No children had siblings with a diagnosis of EoE. The most common presenting symptoms were food impaction, dysphagia, abdominal pain, and diet modification (water consumption between each bite, slow meal, food cut into small pieces, etc). In atopic children, there was a tendency to have more cases of family history of atopy, more food impaction, gastro-esophageal reflux and vomiting, and fewer cases of normal endoscopy, but there was no significant difference between atopic and non-atopic children (Table 1).

3.2. Allergy testing

In our cohort, 45 patients (92%) underwent allergy testing: 36 of 38 patients in the atopic group and nine of 11 patients in the non-atopic group.

3.2.1. Type of allergy test

In total, 37 patients (75%) had a sIgE assay to foods or/aeroallergens: cow’s milk (n = 29), hen’s egg (n = 30), wheat (n = 29), peanut (n = 27), treenut (n = 20), soy (n = 21), beef (n = 12), chicken (n = 11), veal (n = 7), house dust mites dermatophagoides pteronyssinus (n = 11), mold alternaria (n = 8), pets (n = 10), birch pollen (n = 16), and grass pollen (n = 13).

A total of 35 patients (71%) underwent SPTs including: cow’s milk (n = 24), hen’s egg (n = 26), wheat (n = 26), peanut (n = 23), treenut (n = 20), soy (n = 20), beef (n = 4), chicken (n = 4), veal (n = 3), cod (n = 21), house dust mites dermatophagoides pteronyssinus and dermatophagoides farinae (n = 17), mold alternaria (n = 15), cockroach (n = 6), pets (n = 19), birch pollen (n = 23), grass pollen (n = 25), ash pollen (n = 11), plantain (n = 14), mugwort (n = 12), and latex (n = 7).

APT was undertaken for 19 patients (39%), including: cow’s milk (n = 18), hen’s egg (n = 17), wheat (n = 14), peanut (n = 6), treenut (n = 4), beef (n = 12), chicken (n = 1), veal (n = 1), and cod (n = 1).
Peripheral blood eosinophil count ($n = 43$, $88\%$) was also performed for a majority of patients, whereas total IgE level was assayed only in one third of the children ($n = 19$, $39\%$).

### 3.2.2. Results of allergy tests

Assays for sIgE were positive for more than three quarters of patients and SPT for more than half in both groups. APT results were positive in $33\%$ and $50\%$ of patients, respectively, with and without an atopic condition. There was no significant difference between the groups (Table 2). Among patients who underwent allergy testing, 29 of 45 ($64\%$) had a sensitization to at least one food allergen and 23 of 36 ($64\%$) to at least one aeroallergen. Patients were sensitized to the following food allergens by at least one of the testing methods: peanut $43\%$, cow’s milk $40\%$, hen’s egg $40\%$, wheat $38\%$, tree nuts $32\%$, soy $30\%$, and cod $14\%$. Other positive test results were found less frequently: chicken, beef, peas, and lupin. Regarding aeroallergens, children were sensitized to grass pollen $68\%$, tree pollen $57\%$, pets $48\%$, house dust mites $38\%$, and mold $22\%$.

### 3.3. Treatments

In our cohort, use of PPI therapy and STS was similar among the groups. A majority of patients received PPI treatment, whether for first-line therapy or during follow-up: 31 ($82\%$) and 9 ($82\%$) patients, respectively, with and without atopic condition. STS were prescribed to 28 ($74\%$) and eight ($73\%$) patients, respectively. By contrast, ED seemed to be used preferentially for patients with atopic conditions: 22 ($58\%$) versus three (27%), but this difference was not significant ($P = 1.0$). When ED was chosen, ED based on allergy testing was used most frequently ($n = 16$). An empiric ED was prescribed for eight patients: four had a six-food ED, two had a four-food ED, and two had a two-food ED; only one patient received elemental ED (Table 3). Unfortunately, no causative food was identified. Two patients underwent other therapies: one had Nissen surgery and one systemic steroid therapy. Esophageal dilatation was performed on four patients because of esophageal stricture (three had atopic conditions). Regarding first-line...
therapy, there was no difference between the groups (P = 0.88). The most commonly attempted first-line therapies in the whole cohort were PPI (60% and 73%) and STS (18% and 18%) for atopic and non-atopic groups, respectively. No patient received an ED in first-line therapy. Combination therapy was used initially for nine patients (Table 4).

3.4. Response to treatment

Only three patients did not have esophageal endoscopy for histological evaluation during the follow-up. After the first-line therapy, 28 patients (57%) underwent histological evaluation, 17 patients (35%) did not undergo histological evaluation but did not achieve clinical remission, and four patients (8%) had clinical remission but did not undergo any histological evaluation. Histological evaluation took place after 64% of initiated treatments or changes in treatment.

Histological remission was achieved at least once during the follow-up by a higher percentage of patients in the atopic group (20/37, 54%) than in the non-atopic group (3/9, 33%), but this was not statistically significant (P = 0.18). About a quarter of patients had histological remission after PPI treatment in monotherapy in both groups. Histological and global remission after STS tended to be more frequent in atopic children: 54% and 64%, respectively, versus 0% and 43% in non-atopic children. Achievement of histological and global remission after ED was similar between the groups (Table 5). Seasonal clinical exacerbation was reported in two patients, and clinical exacerbation after food was reported in four. All of these patients had atopic disorders.

4. Discussion

We describe the management and outcome of our cohort of 49 children with EoE, according to atopic status. First-line therapy was not associated with atopic status. The results of allergy tests were positive in the majority of children in both groups. There is a tendency for atopic patients to have more macroscopic endoscopic anomalies and to have a better chance of remission with STS.

The baseline characteristics of our study population are typical of pediatric EoE patients, and are similar to those reported in the European Retrospective Pediatric Eosinophilic Esophagitis Registry (RetroPEER) [19] and in the study by Vigier et al. [20] regarding age at diagnosis, majority of boys, and prevalence of atopic disorders. There was no difference according to atopic condition, except for an expected trend for higher prevalence of family atopy in the atopic group.

In our cohort, PPI therapy was used as first-line treatment for 60% of atopic children and 73% of non-atopic children. This high rate was explained by previous recommendations on the definition and diagnosis of EoE, including failure of a PPI trial [21–23]. The latest recommendations published in 2018 suggested that PPI therapy is better classified as a treatment for EoE than as a diagnostic criterion and the definition of EoE was modified [2,3]. In our study, we chose to include all patients with esophageal eosinophilia, even if a PPI trial was not undertaken or if the patients were PPI-responsive. However, owing to guideline changes during the period of inclusion, some cases of PPI-resistant EoE may have been considered as peptic esophagitis before 2018 and not listed in local registries as EoE. This could have led to an underestimation of the remission rate with PPI.

Interestingly, we found a very low rate of ED (58% in the atopic group, 27% in the non-atopic group, but 0% in first-line therapy) in comparison with the RetroPEER study (82.2% in total) and the study of Vigier et al. (29.9% in first-line therapy). On the other hand, STS were used more frequently in our cohort (74% in atopic children and 73% in non-atopic children). One explanation might be that ED lasting several months may be less acceptable in everyday life for the child, their pediatrician, and their parents than STS. ED might also be more challenging to implement because it requires easy access to repeated endoscopy. Contrary to guidelines, allergy testing-based ED was preferentially used in our cohort. During the period of inclusion, the first assessments of ED based on allergy testing in children were encouraging [24] and this kind of dietary intervention could be more acceptable for patients. More recently, the step-up empiric ED appeared to be a better strategy, avoiding endoscopic procedures as well as unnecessary food restrictions [25].
Combination therapy as first-line treatment was used for nine patients. Reasons for this choice were not explained. As suggested by Munoz-Persy et al., combination therapy generally adds no benefit but could have a negative impact on the patient’s quality of life and it is more difficult to discern which of the treatments is the most effective [4].

There was a high rate of histological evaluations in our cohort, since clinical remission was not confirmed by histological evaluation in only four patients (8%) after first-line therapy. Endoscopic evaluation was performed after 64% of initial treatments or changes in treatment, which is higher than reported for a previous cohort (43%) [20]. Moreover, a survey of US gastroenterologists on the management of EoE found that only 46.3% of the participants performed endoscopy with biopsy to monitor EoE [26]. This shows that guidelines on the necessity of repeated endoscopies to monitor therapy response are now well-known by the pediatricians in our cohort.

We found a very low rate of histological remission in comparison with the literature. Although our remission rate for PPI therapy was 22%, a meta-analysis of 33 studies comprising 619 patients with EoE treated by PPI (of whom 188 children) reported an efficacy of 50.5% for histological remission.

Our histological remission rate after ED was 41%, whatever type of ED was used. In the meta-analysis of Arias et al. regarding the efficacy of dietary interventions in patients with EoE, elemental ED was effective in 90.8%, six-food ED in 72.1%, and ED based on allergy testing in 45.5% of cases [8]. Our remission rate is therefore consistent with this meta-analysis since a majority of patients treated by ED had an allergy-test-driven ED.

Our remission rate after STS was lower than that in previous studies: 40% versus approximately 60% [3,17]. One reason might be the fact that choice of treatment did not follow a structured study protocol but was left to the discretion of the treating physician. This may have resulted in inadequate treatment dosing or suboptimal steroid formulation. Furthermore, as some patients did not undergo histological evaluation, there may be an underestimation of the histological remission rate. Interestingly, we found a nonsignificant higher remission rate after STS in the atopic group than in the non-atopic group. This fact was already raised by Eluei et al. [17], where responders to STS tended to have more atopy (82% vs. 66%; \( P = 0.08 \)), and by Shoda et al. [27], who analyzed EoE endotypes. In our study, the number of children in each group and each treatment was too small to perform a multivariate analysis and thus we could not determine the factors associated with remission.

There is no consensus on the definition of histological remission and it varies from study to study. The eosinophil count is commonly used, but the threshold can vary from 1 to 20 eos/hpf. Sometimes, remission is defined as a 50% decrease in eosinophil count from baseline. In our cohort, we chose to define histological remission by an eosinophil count lower than 15 eos/hpf. This choice was made because it is the most frequently used definition in Europe [28]. Moreover, for some of the patients (14/49), the exact number of eos/hpf at diagnosis was unknown and the count was quantified as greater than 15 eos/hpf.

The prevalence of asthma, food allergy, allergic rhinitis, and atopic dermatitis in our EoE population was 43%, 51%, 37%, and 26%, respectively. In comparison, Capucilli et al. found that in their systematic review a prevalence rate of 27–80%, 24–68%, 57–70%, and 6–46%, respectively [5]. The low rate of allergic rhinitis in our population might be due to the retrospective nature of our study. Symptoms of allergic rhinitis could have been less investigated by the pediatrician than other atopic disorders and therefore under-reported in medical reports. Our findings regarding the sensitization rates of EoE patients in food and airborne allergens (64% in both groups) were consistent with published reports in the EoE pediatric population [12,19,29].

More interestingly, sensitization rates are similar between atopic children and non-atopic children, and are higher than the rates in children in the general population [30]. This high rate of atopic sensitization, regardless of atopic condition, highlights the importance of allergy testing in children with EoE whether or not they have atopic disorders or a family history of atopy. Although some studies showed encouraging results regarding ED based on allergy testing [24], guidelines do not recommend using allergy tests to establish dietary therapy in EoE patients [3]. We found a higher rate of peanut sensitization (43%) than cow’s milk and hen’s egg sensitization (40%), while the most frequently reported causative allergens in children are cow’s milk, egg, and wheat [4,19,25]. In the RetroPEER study, patients were sensitized mostly to cow’s milk (45.9%), egg (38.4%), peanut (33%), and wheat (26.5%). Peanut sensitization seems to be frequent although it is not reported as a causative allergen in pediatric EoE. By contrast, the role of aeroallergens in the natural course of EoE is prominent (murine models, seasonal variation of symptoms). Therefore, allergy test could be used to explore a patient’s sensitization and help clinicians to establish EoE phenotypes, rather than to identify causative foods. More studies are needed to establish the role of allergy testing in EoE patients.

Owing to the retrospective nature of our study, patient data were limited by the information that individual providers included in the medical folder. Some patients had multiple sequential or concomitant therapies, and patient adherence to treatment was not recorded. The remission rate for each therapy may have been underestimated. As with other studies on EoE management, the inclusion period extended over 5 years during which there were some important modifications in EoE recommendations on management and diagnosis. Furthermore, the low number of children included may have decreased the ability to detect differences in remission between the atopic and non-atopic groups. This may be addressed by compiling a large prospective database of all children diagnosed with EoE in France. Our study was multicentric, with multiple physicians in each center and the choice of treatment plan was based on practitioner experience, preferences, and even changed for the same practitioner over time and according to guidelines. This may be considered a limitation, but it shows the diverse spectrum of EoE management in the “real world” and the need for precise guidelines.

5. Conclusion

Our study describes the management of children with EoE in five French pediatric centers, and highlights the heterogeneity in the choice of treatments and allergy tests. Allergy testing seems to be relevant in a majority of children with EoE, whether or not a history of atopy is present. A prospective study focusing on the benefit of allergy testing, regarding global management and not only ED, would be helpful to clarify whether allergy tests need to be implemented in the management of patients with EoE. Our study highlights that atopy might be associated with STS response. Additional prospective studies are needed to determine whether atopic status determines histological response, in particular after STS therapy.

Disclosure of interest

The authors declare that they have no competing interest.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.
Acknowledgments

We would like to thank M. Abely, D. Sabouraud, J. Rebeuh, M. Chotard-Curien, and A. Comte for giving us the access to the medical data of their patients.

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