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Pediatric Eosinophilic Esophagitis in Slovenia: Data from a retrospective epidemiological study 2005-2012

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Abstract

Objectives: To assess the incidence, characteristics, therapeutic approach and response to therapy of eosinophilic esophagitis (EoE) in pediatric population from Slovenia.

Methods: A retrospective study was conducted on a cohort of children newly diagnosed with EoE, aged 0 to 18 years, residing in Slovenia, in the period between 2005 and 2012. For each child presenting symptoms, family and personal history of allergies, blood, skin and patch allergy tests, endoscopic and histologic findings, types of therapy, and therapeutic success were recorded.

Results: In total, 25 cases of EoE were identified during the study period. The mean annual incidence (per 100,000 children) was 0.8 (95% confidence interval (CI) 0.58-1.16). The incidences of EoE increased from 0.2 (0.01-1.36), 0.3 (0.01-1.38), and 0.3 (0.01-1.40) in the period 2005-2007, respectively, to 1.8 (0.72-3.76), 1.0 (0.28-2.60), and 1.8 (0.72-3.65) in the period 2010-2012, respectively ($p=0.002$). In 9 patients symptomatic and histologic remission was achieved with specific food elimination diet, in 8 with 6-food elimination diet and in 1 with an additional budesonide. In majority of patients budesonide improved only symptoms, but esophageal eosinophilia persisted. Twenty percent of our children had improvement of histology and symptoms of EoE in spite of gradual reintroduction of all food and stopping all medication.

Conclusions: The annual incidence of childhood EoE in Slovenia is comparable with the reports from the developed European countries, and it increased by 6-folds in the last decade.

Key words: eosinophilic esophagitis, epidemiology, children

What is known:

- The incidence of pediatric eosinophilic esophagitis is rising.
- Presenting symptoms depend on children's age.
- Patients may get into symptomatic and histological remission with therapy with specific food-elimination diets or with topical corticosteroids.

What is new

- The incidence of pediatric EoE in Slovenia is comparable to incidences reported in other European studies, but lower than in USA.
- The incidence of pediatric EoE in Slovenia increased six-fold in the period between 2005 and 2012.

Introduction

Eosinophilic esophagitis (EoE) is characterized by upper gastrointestinal symptoms and abnormal eosinophilic infiltration of the esophagus. The most recent published guidelines determined that 15 or more eosinophils per high power field (HPF) in at least one biopsy of esophageal mucosa after adequate proton pump inhibitor (PPI) treatment are necessary to diagnose EoE ^{1,2}.

The main symptoms of EoE depend on the age of a child. In a cohort of children with EoE, Noel et al. described feeding difficulties in small children, vomiting in older children, and dysphagia and food impaction in adolescents³.

Upper endoscopy with biopsies of esophageal mucosa must be performed to make an accurate diagnosis. A variety of endoscopic characteristics have been reported including linear furrows, white plaques and mucosal rings. A grossly normal appearing esophagus can also be seen in children with histologically proven EoE ¹.

Probably, eosinophilic esophagitis have been underdiagnosed in the past. In addition, different criteria for establishing the diagnosis of eosinophilic esophagitis were used, including various peak numbers of eosinophils per HPF. Consequently, the reports regarding EoE epidemiology are difficult to compare. But in general, the incidence of diagnosed EoE is rapidly increasing due to true rise of new patients and higher awareness of the disease⁴. The highest prevalence of the disease is reported from the United States and Australia⁵. EoE can present at any age, but the majority of affected patients have been men in their 20s or 30s⁶. 20% of all EoE patients are diagnosed in childhood⁷. The main objective of this nationwide study was to report the incidence data, symptoms, endoscopic, and histological characteristics, results of allergy tests, as well as the type and the effect of therapeutic interventions in children with EoE in Slovenia diagnosed

between 2005 and 2012. To the best of our knowledge, only five pediatric epidemiological EoE studies from Europe have been published to date; two from England, the other three were from Denmark, Italy and Poland⁸.

Materials and methods

We performed a retrospective chart review of all pediatric patients diagnosed with EoE in Slovenia in years 2005-2012. In Slovenia, all pediatric patients with suspected EoE are referred to a single institution, University Children's Hospital Ljubljana, because this is the only center that perform a complete workout including allergy testing, diet counselling and follow-up of such patients. Despite this fact, we double-checked with our colleagues in regional centers for a possibility that individual patients had not been referred to Ljubljana but had been diagnosed and treated elsewhere, however, we did not find such cases.

The diagnosis of EoE was established according to current diagnostic criteria^{1,2}. All patients with profound esophageal eosinophilia found at the first endoscopy were put on at least eight-week therapy with at least 1mg/kg/day PPIs, and control endoscopy with at least four biopsies taken from the esophagus, two from the proximal and two from the distal part, was performed while the patients were still on PPI therapy. Only patients with persistence of esophageal eosinophilia showing at least 15 eosinophils per high power field (HPF, 400x, size of one HPF was 0.45x0.45 mm) in esophageal biopsy samples taken at endoscopy performed on PPI therapy were included in the study. Patients diagnosed with other diseases, which could be associated with esophageal eosinophilia, such as Crohn's disease, eosinophilic gastroenteritis, or celiac disease, were excluded.

Data from patients who fulfilled diagnostic criteria for EoE included age, gender, presenting symptoms, family and personal history of allergies, endoscopic and histologic findings, total

IgEs, allergen specific IgEs, respiratory allergy tests, results of skin prick and atopy patch testing.

Skin prick tests and food specific IgE blood tests were indicated and evaluated by experienced pediatric allergologist. The concentration of specific IgEs were analysed by Immulite 2000 (Siemens Diagnostics, Germany) or by UniCap 100 (Phadia Laboratory Systems, Sweden). The cut-off value above 0.35 kU/L, although not necessarily representing true sensitization to a specified antigen, was used as orientation for planning specific food elimination diet. At our institution it's possible to perform skin prick tests to as many as 50 food and 30 indoor and outdoor environmental allergen commercial extracts (Allergopharma, Germany or Alyostal Prick-Stallergens, France). The foods tested were individually selected for each patient on the basis of the clinical history and the food intake, but all patients had skin prick tests for cow's milk, hen's egg, peanut, hazelnut, soy, wheat, rice, corn, chicken meat, pork and beef. Histamine 1 mg/mL and saline were used as positive and negative controls. Tests were read after 15 minutes. The results were given in the longest diameter of the wheal in mm. The result of the prick test was considered positive, if it was at least 3 mm or equal/ bigger than the positive control.

Atopy patch tests were performed using commercially available Haye's test chambers (Haye's Service, Netherlands). In each patient milk powder, fresh egg and wheat, corn, rice, soy and barley flour were used for patch testing. In addition, when it was suspected by parents that some food prepared at home could cause EoE symptoms, the exactly prepared dish was made at home and used for patch test. Half teaspoon of powder or flour was mixed with 3 ml saline to make a paste. Chamber filled with cellulose was the negative control. Two patches containing ten 8-mm chambers were applied to the skin of the upper back. In each patient double testing was performed and patches applied to the left and right part of the upper back contained the same

types of food. The patches were removed at 48 hours and evaluated at 72 hours as follows: 1, erythema; 2, erythema and induration; 3, erythema and marked induration/papules; 4, erythematous papules and vesicular eruption. A score of 2 or above was considered positive.

In addition, we reviewed types of therapy: specific elimination diet based on the results of allergologic tests, 6-food elimination diet (without milk, egg, wheat, soya, nuts and seafood), elemental diet and steroids/swallowed budesonide, and their therapeutic success both at diagnosis and during the follow-up period. We defined therapeutic response as resolution of symptoms and decrease of eosinophil count below 15 per HPF.

Ethical considerations

Informed consent was obtained from parents of all the children. The study was conducted in accordance with the Helsinki Declaration and was approved by the National Committee for Medical Ethics.

Statistical methods

Data on the background population for the period between 2005-2012 was provided by the Statistical Office of Slovenia. The registry based data covered the entire Slovenian population aged 0-18 years.

Annual incidence was directly standardized to the study population in Slovenia. The 95% confidence intervals (CI) of the annual incidence were calculated on the assumption that the number of cases followed a Poisson distribution. For clinical characteristics, continuous variables were reported as mean and standard deviation (SD) or median and interquartile range (IQR) and compared using the independent samples t-test, or Mann-Whitney test where appropriate. A p-value of less than 0.05 was considered statistically significant.

All statistical analyses were conducted using R language for statistical computing.

Results

EoE was diagnosed in 25 children from January 2005 to December 2012. The main features are presented in Table 1. There were 23 boys (92%) and 2 girls (8%). Age at presentation ranged from 4 months to 17 years (mean 9.5 years, SD 4.71 years). The median peak number of eosinophils/HPF on histology of the lower esophageal mucosa was 40 (interquartile range (IQR) 30-60), with a range of 17 to 100. Median peak eosinophils/HPF in the upper esophageal mucosa was 40 (IQR 20-50), with a range of 2 to 100.

Annually, between 1 to 7 newly diagnosed children with EoE were detected. The mean annual incidence rate per 100,000 children in the study period was 0.8 (95% CI from 0.51 to 1.16). Annual incidence rates are reported in Table 2. A significant increase in yearly incidence rates was observed in the studied period of 7 years ($p=0.002$).

Presenting symptoms are shown in Table 3. The most common symptoms at the onset of disease were vomiting in 8 out of 25 children (32%), abdominal pain (24%), food impaction (12%), dysphagia (8%), and failure to thrive (8%). No clinical symptoms were found in 12% of pediatric EoE patients. Two patients from this group of asymptomatic patients were diagnosed during PEG insertion and the third patient was scoped because of suspicion for coeliac disease. Food impaction and dysphagia were more common presentations in older children, whereas vomiting, abdominal pain and failure to thrive were detected more frequently in younger children, but none of the observed differences, except for food impaction ($p=0.004$), were statistically significant.

Allergy tests

Food allergies were identified by a combination of specific IgE blood tests, skin allergy prick tests and patch tests (Table 4). Total IgEs were elevated in 10 out of 17 patients. Food specific IgE levels above 0.35 kU/L were detected in 10 out of 25 children for cow milk proteins, in 9 out of 25 patients for peanuts, in 6 out of 25 cases for egg proteins, and in 4 out of 25 patients with EoE for soy proteins. The specific IgEs values were above 0.35 kU/L in one or two cases for wheat, rice, banana, peach, beef, apple, corn, potatoes, carrots, and pear. Specific IgEs for aeroallergens above aforementioned value were identified in 11 out of 15 patients mainly for dust mite, tree and grass pollen. Skin prick tests were positive for rice in three out of 25 children, for eggs, peanuts, corn and potatoes in two, and for cow milk, soy, apple, wheat, carrot and pear in one patient from our study group. Patch tests were performed in 20 out of 25 patients with EoE and were considered positive in 7 patients (4/20 for corn, 1/20 for rice, wheat, milk, soy, egg, potato, mackerel fish).

Overall, we succeed to identify at least one specific food allergen in 19 out of 25 patients, however, in 6 children all allergy tests were negative.

Endoscopic evaluation

Complete endoscopic findings are presented in Table 1. Characteristic EoE endoscopic mucosal appearance was detected in 22 out of 25 children (linear furrows (12/25), white plaques (6/25) and esophageal rings (4/25)). In three patients esophageal mucosa was completely normal. Esophageal linear furrows were the most common finding, but no significant relationship was noted between age of the child and any of the endoscopic features ($p>0.05$).

EoE patients and therapy

All patient received therapy with PPIs for diagnostic purposes. After making the diagnosis in some but not all patients 24-hour pH-monitoring was performed and this therapy was stopped, if the results were normal. In the others, PPI therapy was continued for some time together with other therapeutic modalities (diet, steroids), but stopped sooner or later during follow up in 12 (48%) patients. The doses of PPIs during follow-up were never higher than 40mg/day, being 20mg/day in most occasions.

All children diagnosed with EoE were treated primarily with dietary therapy. Follow-up endoscopy for assessment of therapeutic success was not performed in two patients, because they didn't show up for control examination. In the rest of the study population endoscopies with tissue sampling were repeated whenever therapy for EoE was changed to assess the activity of eosinophilic inflammation in the esophagus. The time frame between the beginning of each change in therapeutic intervention and endoscopic/histology control was at least 2 months.

The therapeutic approach and response to therapy of individual patients is represented in the Table 5. Ten out of 19 patients with suggestive specific allergy tests were in clinical remission with specific allergen elimination diet, nine of them were also in histological remission. From the remaining 9, five got into remission with six-food elimination diet. Six-food elimination diet was also introduced in six patients with completely negative allergy evaluation. Two of these children were lost for follow-up. Three of them are in complete remission and one patient treated with six-food elimination diet is symptom free, but prominent eosinophilic infiltration persists (40 eos/HPF). In four children who didn't respond to specific elimination diet and six-food elimination diet, swallowed budesonid, 1 mg once daily in the evening for children under 10 ys of age, and 2 mg/daily for those above 10 ys of age, was added. In three cases esophageal eosinophilia persisted in spite of combined therapy, however two of these children became

asymptomatic with time on diet and corticosteroid therapy. The third child with resistant EoE had food impaction in spite of diet and corticosteroid therapy.

After achieving symptomatic and histological remission, foods were gradually reintroduced and follow-up endoscopies were performed at least 2 months later, as presented in Table 5. Some patients decided to stay on six or several specific food elimination diet despite possibility that they would probably tolerate some of the eliminated foods to avoid additional endoscopic controls. Five patients from our group gradually tolerated all foods and were off of all medication but remained in complete symptomatic and histologic remission.

Discussion

Data on the incidence and prevalence of the EoE in the pediatric population and especially from Europe are scarce and vary by geographic regions⁸. We hereby report the results of the first population based study of EoE from Slovenia in pediatric population. The mean annual incidence rate for the period between years 2005 and 2012 was 0.8/100,000. Our study demonstrated a 6-fold increase in the incidence of EoE during the period of 2005-2012; the incidence changed from 0.2/100,000 children in the year 2005 to 1.8/100,000 children seven years later ($p=0.002$). An incidence rate of 1.6/100,000 reported from the region of southern Denmark is quite consistent with the findings of our study⁵, whereas EoE incidences detected in children from the USA and Australia are much higher (12/100,000 and 8.9/100,000, respectively)^{3,9}. In agreement with our study, Noel et al. showed a 4-fold increase in the incidence of EoE in children during a four year period³. Prasad et al. reported an increasing incidence of EoE in adults from 0.9/100,000 in the years 1976-1985 to 8.8/100,000 in the years 1996-2006¹⁰. However, contrary to those reports, incidence in Michigan did not consistently increase over a 6-year study period¹¹. In addition, annual rates of EoE disease in children from West Virginia didn't change over a ten years time span¹². It seems that in the United States the

incidence of EoE may have reached a peak and it became similar to the incidence of Crohn's disease in children. Contrary to reports from the United States, the data from our study suggested that the incidence of EoE in children is still rapidly increasing, maybe due to the higher awareness of EoE and changed environmental factors in our country.

The presenting symptoms and age dependency of our children are in agreement with previously published studies^{13,14}. The most common presenting symptoms in older Slovenian children with EoE were dysphagia and food impaction, whereas in younger children vomiting, abdominal pain and failure to thrive predominated. Patients with dysphagia and food impaction were diagnosed quickly, but children who presented with nonspecific symptoms were referred late to our hospital, and it takes up to three years to diagnose the EoE. In addition, EoE can be found accidentally in asymptomatic children who undergo endoscopy for other reasons. It should be noticed that two out of three of our patients with accidentally found EoE had severe neurologic handicap and were therefore probably not asymptomatic but unable to report the symptoms. As all pediatric endoscopists in Slovenia follow the guidelines that biopsy samples should be taken from oesophagus (lower third), stomach and duodenum during each endoscopy for histologic analysis, even when macroscopic appearance of the mucosa is normal, this probably results in relatively high discovery rate of EoE in asymptomatic patients. Our findings therefore support the recommendation that whenever upper endoscopy is performed in a child, biopsies should be taken for histology evaluation.

The most common endoscopic finding in our cohort was linear furrows. This is not in agreement with the findings of adult studies, where esophageal rings are the predominant endoscopic feature¹⁵, and pediatric studies, where patchy white exudates have predominated^{11,16}. It is unclear yet, whether the endoscopic appearance depends on duration of inflammation, age of presentation or genetic background of the patient. It is possible that the esophageal rings that are

commonly found in adult EoE patients develop over longer periods time during which the esophageal inflammation causes tissue remodelling.

Finally, food allergens are clearly associated with EoE¹⁷. EoE is both IgE- and non IgE-mediated (cell-mediated) disorder. Therefore, both tests for the 1st (skin prick tests, specific IgEs) and 4th (skin patch tests) type immune reaction tests were performed in all patients. In 19 patients from our study population, at least one specific allergen was discovered by various allergy tests. Despite the awareness that both positive and negative results of these tests are not very reliable in recognition of the causative allergens, they can be of some value when specific elimination diets are concerned. Specific allergen elimination diet based on allergy test results was successful in 9 patients. The majority of our children responded well to specific elimination diet or 6-food elimination diet. This is in agreement with the conclusions of other studies, where dietary elimination leads to improvement in oesophageal mucosal biopsy specimens in up to 77% of patients¹⁸. Sixteen percent of our patients did not respond to diet, thus swallowed corticosteroids were added. Budesonid improved patient's symptoms, but esophageal eosinophilia persisted, a finding that was also described by Spergel et al. .

Five children (20% of our cohort) had complete symptomatic and histological remission of EoE in spite of gradual reintroduction of all food and stopping all medication, including budesonide and PPIs. The control biopsies revealing the absence of eosinophilic infiltration were performed not earlier than 3 months after cessation of all therapies, while the duration of follow-up for eventual symptom reappearance was substantially longer in the majority of these patients. However, it is worth mentioning that the follow-up period and especially the time frame between stopping all interventions and the last control biopsies were much too short to drive any conclusions from this observation. Regarding data from previous publications, it seems that EoE

is chronic disease that relapse nearly universally after dietary or medical treatment is withdrawn, although the time course may vary for individual patients¹⁸⁻²³

In conclusion, the annual EoE incidence in Slovenian children is rapidly increasing and is comparable to incidences reported from other regions in Europe.

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Table 1. Characteristics of 25 patients diagnosed with EoE

Table 2. Yearly incidence rates and 95% confidence intervals (CI) per 100,000 children in the period 2005-2012

Table 3. Presenting symptoms by age of onset (mean $\pm$ SD (n)).

Table 4. The results of allergy tests in patients with EoE

Table 5. Types of therapy and response to therapy and food reintroduction in 25 patients with EoE

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Table 1. Characteristics of 25 patients diagnosed with EoE

	No. of patients	%
Age (years): Mean (range)	9.5 (0.4-17)	
Gender: Male	23	92
Female	2	8
Family history of allergy	9	36
Atopic disease- all types: Asthma	9	36
Atopic dermatitis	3	12
Rhinitis	1	4
Endoscopic findings: Linear furrows	12	48
White exudates	6	24
Esophageal ring	4	16
Normal	3	12

Table 2. Yearly incidence rates and 95% confidence intervals (CI) per 100,000 children in the period 2005-2012

Year	Incidence rate	95% CI
2005	0.24	0.01 – 1.36
2006	0.25	0.01 – 1.38
2007	0.25	0.01 – 1.40
2008	0.76	0.16 – 2.23
2009	0.25	0.01 – 1.42
2010	1.78	0.72 – 3.67
2011	1.02	0.28 – 2.60
2012	1.77	0.72 – 3.65
Mean Annual incidence rate	0.79	0.51 – 1.16

Table 3. Presenting symptoms by age of onset (mean $\pm$ SD (n)).

Symptoms	Present	Absent	p-value
Vomiting	9.1 $\pm$ 4.73 (8)	9.67 $\pm$ 4.83 (17)	0.809
Abdominal pain	8.32 $\pm$ 4.32 (6)	9.89 $\pm$ 4.87 (19)	0.489
Food impaction	12.67 $\pm$ 0.66 (3)	9.08 $\pm$ 4.86 (22)	0.004 [†]
Dysphagia	11.87 $\pm$ 3.11 (6)	8.76 $\pm$ 4.94 (19)	0.163
Failure to thrive	9.16 $\pm$ 5.89 (2)	9.54 $\pm$ 4.75 (23)	*

[†] p-value from Welsch t-test (Bartlett test for variance equality: p=0.0245)

* test was not performed because of a very small number of events

Table 4. The results of allergy tests in patients with EoE

No.	Total IgE (kU/L)	Spec IgE (kU/L)	Skin prick test	Patch test
1	48	milk 0.7, rice 0.4	neg	neg
2	503	peanuts 1, soy 1, wheat 1.2, rice 1.1, apple 1.7, banana 2.9, peach 2.9, beef 0.5	corn	neg
3	7	milk 2, egg 1.7, peanuts 1.7	neg	neg
4	33	milk 0.6, egg 0.5	neg	neg
5	298	peanuts 0.4, wheat 0.4, beef 0.5,	egg, peanuts	corn
6	?	egg 5.1, peanuts 1.2	rice, egg, soy, corn, wheat	neg
7	95	neg	neg	corn
8	?	neg	neg	?
9	2	neg	neg	soy, milk
10	?	neg	neg	?
11	?	neg	neg	neg
12	?	neg	?	?
13	28	neg	apple, potatoes, milk	potatoes
14	2542	milk 1.6, peanuts 2.1, soy 1	neg	neg
15	1138	milk 1.2, peanuts 2.8	neg	neg
16	28	milk 0.4, egg 4, peanuts 1	neg	?
17	873	milk 0.8, peanuts 0.5, egg 0.9	peanuts	neg
18	?	neg	neg	neg
19	?	milk 1.3, soy 0.6, corn 2	neg	?
20	542	peanuts 0.5	neg	egg
21	?	peanuts 1, soy 2.3, corn 1.1, peach 0.6, banana 1, apple 2, pear 1, carrot 0.8, potatoes 0.7	rice, potatoe, carrot, pear	corn, wheat, rice, mackerel fish
22	385	milk 0.7	neg	neg
23	210	neg	neg	neg
24	51	milk 0.5, egg 1, peanuts 2	neg	neg
25	607	neg	rice	corn

? the test was not performed.

neg the result of the test was negative.

Table 5. Types of therapy and response to therapy and food reintroduction in 25 patients with EoE

No.	T1	E1	T2	E2	T3	E3	T4	E4	T5	E5	T6	E6
1	SED	-	rice	-	milk	-						
2	SED	+	6FED	+	BUD	+						
3	SED	-										
4	SED	-	egg	-	milk	-						
5	SED	+	6FED	-	soy	-	milk	-				
6	SED	+	6FED	-								
7	SED	-										
8	6FED	-										
9	SED	-	soy	-	milk	-						
10	6FED	-	milk	+								
11	6FED	?										
12	6FED	?										
13	SED	+	6FED	-								
14	SED	+	BUD	+								
15	SED	-	milk	-								
16	SED	-	milk	-	egg	-						
17	SED	-	milk	-	egg	+						
18	6FED	-	soy	-	wheat	-	egg	-	milk	+	fish	-
19	SED	+	BUD	-	soy	-	corn	-				
20	SED	+	BUD	+								
21	SED	+	ELEM	-	*	-	&	-	#	-	milk	-
22	SED	-										
23	6FED	+										
24	SED	-										
25	SED	+	6FED	-	wheat	-	fish	-				

T therapy.

E- the control endoscopy with normal histology.

E+ the control histology showed prominent eosinophilic infiltration.

SED specific elimination diet (based on positive specific allergy tests, as presented in Table 4).

6FED six food elimination diet (milk, egg, wheat, soy, peanuts, sea food).

BUD swallowed budesonide (1 mg<10 ys of age, 2 mg>10 ys of age)

ELEM elemental diet

? the follow-up endoscopy was not performed

* rabbit, sprouts

& cauliflower, potatoes

chicken, cabbage