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FOOD-INDUCED IMMEDIATE RESPONSE OF THE ESOPHAGUS (FIRE) IN PEDIATRIC EOSINOPHILIC ESOPHAGITIS

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June 8, 2023

Abstract

Background: Food-induced immediate response of the esophagus (FIRE) is a new phenomenon that has been described in eosinophilic esophagitis (EoE) patients. It is suspected when unpleasant symptoms occur suddenly on contact of the triggering food with the esophageal surface and recur with repeated exposures. It can often be mistaken for pollen-food allergy syndrome (PFAS) and solid food dysphagia. Data on FIRE is limited to one survey study and case reports, and there are no screening studies conducted on either adults or children with EoE. In this study, we aimed to screen children aged [?]7 years old with EoE for FIRE. *Methods:* Demographic data were collected from medical records. A questionnaire about FIRE was applied to all participants. Skin prick tests (SPTs) were done on suspected patients to identify the triggering foods. FIRE is defined as suitable clinical symptoms with suspected food allergen exposure. *Results:* Seventy-eight patients (74.4% male, median age: 13.5 years) were included. Unpleasant and recurrent symptoms distinct from dysphagia with specific foods were reported in %16.7 of the patients, all of whom had concomitant allergic rhinitis (AR). The symptoms described by almost all patients were oropharyngeal itching and tingling (PFAS: 15.3%) excluding only one patient reporting retrosternal narrowing and pressure after specific food consumption (FIRE: 1.2%). *Conclusions:* Although definitive conclusions regarding the true prevalence of FIRE cannot be made, it does not seem to be common as PFAS. However, it deserves questioning particularly in the presence of concurrent AR and/or PFAS in children with EoE.

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SHORT TITLE: FIRE IN PEDIATRIC EOSINOPHILIC ESOPHAGITIS

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ACKNOWLEDGEMENTS

We acknowledge all patients and their parents participating in this study.

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Conclusions: Although definitive conclusions regarding the true prevalence of FIRE cannot be made, it does not seem to be common as PFAS. However, it deserves questioning particularly in the presence of concurrent AR and/or PFAS in children with EoE.

KEY WORDS

Eosinophilic esophagitis (EoE), food-induced immediate response of the esophagus (FIRE), pediatrics, pollen-food allergy syndrome (PFAS)

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease, characterized by eosinophilic inflammation of the esophagus and clinical symptoms associated with esophageal dysfunction.[1,2] It is diagnosed by histopathological evaluation as [?]15 eosinophils per high powered field (hpf) in the presence of recurrent or persistent gastrointestinal symptoms and excluding secondary causes.[1,3] The main gastrointestinal symptoms are solid food dysphagia and food impaction in adolescents and adults.[1] On the other hand, children may present different symptoms such as abdominal pain, nausea, vomiting, food refusal.[2,3]

Recently, a new phenomenon has been described in adult EoE patients called food-induced immediate response of the esophagus (FIRE)[4]. It is suspected in the presence of unpleasant even painful symptoms that occur suddenly on contact of the triggering food with the esophageal surface and recur with repeated exposures to the same food.[4] These symptoms are unrelated to solid food dysphagia and food impaction, which are well described by patients with EoE. In contrast in case of FIRE, patients usually complain about narrowing, choking and pressure in the esophagus and/or retrosternal region immediately after ingestion of the triggering food.[4,5]

However, FIRE can often be mistaken for and coexist with pollen-food allergy syndrome (PFAS), so it is important to differentiate between the two.[4,5] Similar to PFAS, FIRE is often triggered by fresh fruits and vegetables and develops rapidly.[4]Unlike PFAS, symptoms such as itching, tingling, and numbness which typically occur in the oropharyngeal cavity, are not observed in FIRE.[4,6]

So far, FIRE has been reported in eight adult cases[5]and in only one pediatric case[7] and first described in a survey based study on EoE experts and patients.[4] In this study, for the first time, we screened children with EoE aged [?]7 years old for FIRE.

METHODS

Design of the study and participants

The study was conducted at a single referral center for pediatric EoE patients in Turkiye, Children [?]7 years old with a diagnosis of EoE were included. The demographics of the participants were taken from medical

records. A questionnaire consisting of 14 questions on the symptoms and characteristics of FIRE was applied by the same investigator (GK) to the participants or to their parents when appropriate (Supplement 1). The study was approved by the instutional Ethics Committee (2023-731) Informed written consent and/or assent were obtained according to the participant's age.

Definitions

Eosinophilic esophagitis (EoE): The diagnosis of EoE was based on symptoms associated with esophageal dysfunction and the presence of intraepithelial eosinophils in the esophagus ([?]15 eosinophils/hpf), after excluding secondary causes of esophageal eosinophilia.[1,3]

Food-induced immediate response of the esophagus (FIRE) : FIRE is defined as reproducible unpleasant symptoms occuring immediately after intake of certain foods, unrelated to the well-characterized swallowing diffuculties in EoE.[4]

Pollen-food allergy syndrome (PFAS): PFAS was diagnosed in pollen sensitized patients who demonstrated oropharyngeal symptoms (itching/tingling, mild erythema, mild angioedema) triggered with pollen cross-reactive food(s).[6,8]

Statistical analysis

Statistical analysis was performed using the SPSS (Statistical Package for Social Sciences) for Windows 22.0 (SPSS Inc, Chicago, IL). Categorical variables were presented as numbers and percentages. Continuous variables were presented as mean +- standard deviation or median (interquartile range) depending on its distribution.

RESULTS

A total of 98 EoE patients aged [?] 7 years old were screened. Twenty patients were excluded from the study because of lost to follow-up, unreachability, and neurodevelopmental disorder. Finally, seventy-eight patients (74.4% male) with a median age of 13.5 years (IQR:8 years) were included in the study. (Figure 1). Unpleasant and recurrent symptoms that were distinct from dysphagia with certain foods were described in 13 patients (76.9% male). (Figure 1). The median age at the onset of symptoms of these 13 patients was 12.5 years (IQR: 7 years). All of them had concomitant allergic rhinitis (AR) (23.1% perennial, 76.9% seasonal) and two patients had ongoing IgE-mediated food allergy (patient 9: anaphylaxis with tree-nuts, patient 12: anaphylaxis with fish).

The symptoms existed before and after the EoE diagnosis in 10 patients (77%) and three patients (23%), respectively. Almost all patients described oropharyngeal itching and tingling. The most common triggering foods were kiwi and hazelnut, respectively. The median time from food ingestion to symptom onset was five minutes (IQR: 4 minutes), and the median duration of symptom relief was 30 minutes (IQR: 15 minutes) (Table 1).

PFAS was diagnosed in 12 patients, and FIRE in one patient (Figure 1). This patient (patient 10) was a 16-year-old girl who described narrowing and pressure in the retrosternal area after consuming pickled but not fresh cucumber on repeated exposures. She had not experienced a similar complaint before the diagnosis of EoE. The triggering foods of PFAS were different from the ones responsible for anaphylaxis in two patients (patient 9 and patient 12).

DISCUSSION

To date, there is no data available regarding the prevalence of FIRE in both adult and pediatric cases with EoE. All the data we have on FIRE is derived from a survey study conducted on EoE experts and adult EoE patients, along with case reports of eight adults and one pediatric patient with EoE.[4,5,7] Therefore, in our own EoE series, we questioned and investigated the presence of FIRE in cases aged [?]7 years old whom we believed could express their symptoms. In pediatric cases with EoE, the majority of recurrent immediate reactions to foods are associated with PFAS, and FIRE is quite rare.

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In a face to face meeting on May 7th, 2017, pediatric and adult gastroenterologists and allergists, reached a consensus to assess a new phenomenon "food-induced immediate response of the esophagus" (FIRE) from the expert's and patient's perspective. Later, Biedermann et al. reported a survey study in which they used two seperate questionnaries composed of 20 items for physicians and patients, to assess the presence of FIRE in adult EoE patients. In this study, the unpleasant or painful retrosternal symptoms rapidly developing and recurring with the suspected foods or beverages contact with the esophageal surface were defined as FIRE. This definition does not include well-known EoE symptoms related to solid/dry/fibrous food dysphagia and symptoms consistent with gastroesophageal reflux disease.[4] The majority of EoE experts estimated the prevalence of FIRE symptoms in the EoE population between <5% and 20%. On the other hand, the estimated prevalence of FIRE by EoE patients was 39.7%.[4] Additionally, the reported FIRE cases so far have not provided information on whether they conducted a screening to identify these patients and if they did, how many patients were screened.[5,7] In our study, we found FIRE in only one among 78 patients (1.2%). We do not know if our sample size is sufficient to demonstrate the prevalence of FIRE, however it is at least the first screening study conducted on this issue. Certainly, in order to determine the true prevalence of FIRE in EoE which is already known a rare disease, larger number of patients may need to be screened.

The pathogenesis of FIRE is not known yet. However, it is hypothesized to be IgE mediated due to rapid onset of symptoms after food exposure and association with allergic comorbidities in adult cases.[4,5] Skin prick test (SPT) positivity with suspected foods was present in the single pediatric case and in half of the adult cases with FIRE.[5,7] On the other hand diagnostic criteria of FIRE has not been clarified yet. Therefore, it is not clear whether a positive reaction to the suspected food in SPT is absolutely necessary for diagnosis. In this respect, esophageal prick tests in addition to SPT with suspected foods may provide input for immediate esophageal mucosal response both for pathogenesis and diagnosis of FIRE.[9] It is also suggested that a chemical irritation of the inflamed esophageal mucosa may cause symptoms related to FIRE.[4]

In adult patients with EoE, another well-defined IgE-mediated reaction triggered by food is PFAS.[10-12] However, data about the comorbidity of PFAS in children with EoE is limited.[10,13] PFAS has been studied in two retrospective case series of pediatric EoE, with one reporting PFAS in 7 out of 137 patients (5.1%), while the other series did not report PFAS in any of the 372 cases (0%).[10,13] Although it is not a primary aim of the study, we found that PFAS in children with EoE is not rare (15.3%) as previously reported.[10,13] In addition, all of our patients with PFAS and one case with FIRE had comorbid AR. This was a similar finding to adult case series with FIRE.[5] Therefore, we also believe that FIRE should be specifically questioned in EoE cases, particularly those with identified AR and/or PFAS.[5] Despite their rapid onset and frequent co-existence, it is important to differentiate between PFAS and FIRE due to the completely different nature of their symptoms. On the other hand, FIRE symptoms should also be differentiated from well-known solid food dysphagia seen in EoE cases. Generally, EoE patients are more familiar with dysphagia related to solid foods, and they alleviate these symptoms by drinking water, jumping, chest pounding, inducing vomiting, or developing adaptive eating behaviors.[14] These strategies except avoidance do not provide relief for FIRE symptoms and this can be used as a distinguishing question.

The most common food triggers for FIRE are fresh vegetables and fruits like PFAS. Differently, liquids such as wine, beer, and vinegar were defined by both patients and physicians and determined in two of eight adult cases as FIRE triggering foods.[4,5] Because our patient with FIRE was able to consume fresh cucumber without any issues but experiencing symptoms triggered by pickled cucumber on at least three separate occasions, we hypothesized that vinegar could be the triggering food/beverage.

The sample size may be a limitation of the study. Although SPT positivity is not an obligation to diagnose FIRE according to previously reported adult cases, it would be better if our patient consented on the test. On the other hand, being the first screening study of FIRE in children with EoE in a referral center is the strength of our study.

In conclusion, although we can not comment on true prevalence of FIRE, we believe that it is not common as PFAS but deserves to be a routine part of EoE history as other allergic comorbidities especially in the presence of concurrent AR and/or PFAS. Future studies should concentrate on understanding the pathogenesis of

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FIRE and identifying diagnostic criteria.

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Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**1**
Sex	Male	Male	Male	Male	Female	Male	Male	Female	Male	Female	Male	M
Age at symptom onset (years)	15.4	13.5	11.8	12.5	17.9	14.5	9.7	18	8.8	16	7.7	8
AR[++] (SAR[§]/ PAR[¶])	SAR	PAR	SAR	SAR	SAR	SAR	PAR	SAR	SAR	SAR	SAR	S
Symptoms	Itching, tingling	Itching, tingling	Itching, tingling	Itching, tingling	Itching, tingling	Itching, tingling	Itching, tingling	Itching, tingling	Itching, tingling	Narrowing, pressure	Itching, tingling	I t

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Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**1**
Symptom region	Oro-pharyngeal cavity	Oro-pharyngeal cavity	Oro-pharyngeal cavity	Oro-pharyngeal cavity	Oro-pharyngeal cavity	Oro-pharyngeal cavity	Oro-pharyngeal cavity	Oro-pharyngeal cavity	Oro-pharyngeal cavity	Retro-sternal area	Oro-pharyngeal cavity	O p c
Time to onset (minutes)	2	5	1	1	15	5	10	5	5	5	5	5
Duration time (minutes)	10	30	30	30	30	15	30	30	20	30	20	1
Severity¥ (1-10)	2	2	5	5	5	1	3	5	3	2	4	5
Culprit foods	Kiwi	Banana Hazelnut Walnut Pistachio	Hazelnut	Eggplant	Kiwi Orange Tangerine	Persimmon	Eggplant	Kiwi	Pumpkin seed	Pickled cucumber	Kiwi Banana Persimmon Hazelnut	O O c A W A

TABLE 1 Characteristics of children with EoE+ exhibiting immediate, unpleasant, and recurrent symptoms associated with spesific foods

+EoE: Eosinophilic esophagitis; ++AR: Allergic rhinitis; §SAR: Seasonal AR; ¶PAR: Perennial AR; ¥Raiting on a scale from 1-10, with 10 being t

+PFAS: Pollen-food allergy syndrome; ++FIRE: Food-induced immediate response of the esophagus

FIGURE 1 Study population

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