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FOOD ALLERGY IN ADULT PATIENT WITH REFRACTORY GASTRO-ESOPHAGEAL REFLUX DISEASE: CAN FOOD ALLERGY BE A CULPRIT FACTOR IN GERD?

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food allergy, GERD, skin prick test, patch test, elimination diet.

Abstract

Background: Gastroesophageal reflux disease (GERD) is a common gastrointestinal disorder present nowadays. Several studies investigated relationship between GERD and asthma. Few studies discussed the relationship between food allergy and GERD.
Aim of work: was to study the prevalence of food allergy in adults with refractory GERD, determine the most common allergens and investigate the relationship between food allergy and severity of GERD. Secondary outcome included assessment of improvement of symptoms of GERD after food elimination diet.
Methods: 50 adult patients diagnosed as GERD underwent history of allergy, clinical examination, skin prick, patch test for essential food allergens and open food challenge. Biopsies were taken from esophagus to exclude eosinophilic esophagitis (EE).
Results: 36 patients (72%) showed positive skin tests, 11 of them had positive family history of allergy. Twenty four had grade A GERD, 10 had grade B and 2 had grade C. Common allergens were banana, mango and maize. There was no relationship between severity of GERD and food allergy. Thirty five patients improved on elimination diet, 25 without medication and 10 with medication. Only one patient did not improve.
Conclusion: There is a possible link between food allergy and GERD and evaluation of food allergy in GERD should be considered.

Introduction

Gastroesophageal reflux disease (GERD) is a one of the commonest disorders present nowadays and has gained great attention in clinical practice(1)**.**Patients are diagnosed as GERD when they come complaining of discomfort symptoms and complications due to the reflux of stomach contents(2)**.**
GERD has become a health-quality of life burden due to patients' frequent visits to the physician in addition to the rising cost of investigations and therapy(3)**.**

Extra-gastrointestinal manifestations may occur due to aspiration and regurgitation of gastric juice in GERD patients. These may include dental erosions, chronic cough and recurrent pneumonitis(4)**.**
Surprisingly, posterior laryngitis, chronic hoarseness, nocturnal choking, chronic sinusitis, otitis media, idiopathic pulmonary fibrosis and asthma have been recorded to be present in GERD as atypical symptoms(5)**.**

Several studies have demonstrated a link between GERD and allergy. Most of the studies clarified an ultimate relationship between asthma and GERD in one way or another. They showed that asthma and chronic cough enhance acid reflux. Others mentioned that GERD promote airway inflammation(6)**.**
Food allergy is an immune disorder in which symptoms and signs of digestive problems, hives or swollen airway occur when small amount of allergy-causing food is introduced (7)**.**

Few studies discussed the relationship between GERD and food allergy. These studies evaluated this dilemma in children. One study showed the role of serum interleukin 4 (IL-4) and tumor necrosis factor alpha (TNF-α) in pathogenesis of the reflux symptoms in children with primary acid gastro-esophageal reflux (GER) and GER secondary to cow's milk allergy (CMA) (8)**,**while another study found that cow milk(CM) exposure increased the number of weakly acidic reflux episodes(9)**.**To the best of our knowledge, no studies were found to investigate the relationship between GERD and food allergy in adults.

The aim of this work was to study the prevelance of food allergy in adult Egyptian patients with refractory GERD.

Patients and methods:

This cohort study was conducted on **50** adult patients with refractory GERD who attended the gastroenterology and tropical medicine clinics of Ain-Shams University hospitals in Cairo, and referred to the allergy clinic of Ain-Shams University hospitals for completion of work up for diagnosis. An informed consent was taken from all participants prior enrollment of this study which was approved by the Ain Shams Medical Research Ethics Committee. All the studied patients underwent esophagogastroduodenoscopy (OGD) to confirm our diagnosis of GERD after failure of empirical treatment with proton pump inhibitors for 8 weeks(10).GERD was diagnosed according to the Montreal and Los Angelos classification for diagnosis and severity of GERD(2,11).

Obesity, stress, and drugs, other allergic diseases(asthma, allergic rhinitis, atopic dermatitis and allergic conjunctivitis),other gastro-intestinal diseases with reflux symptoms and eosinophilic eosophagitis (EE), which are common causes of GERD, were excluded from this study.

The patients were subjected to the following:

1- Full detailed history, age of onset of GERD, history of food allergy, and clinical examination.
2- GERD questionnaire: The GERD-Health Related Quality of Life Questionnaire (GERD-HRQL) is a validated and well-structured questionnaire that measures changes in typical GERD symptoms such as regurgitation and heartburn in response to surgical or medical treatment(12,13):

Total Score: Calculated by summing the individual scores to questions 1-15.

- Greatest possible score (worst symptoms) = 75
- Lowest possible score (no symptoms) = 0

Heartburn Score: Calculated by summing the individual scores to questions 1-6.

- Worst heartburn symptoms = 30
- No heartburn symptoms = 0
- Scores of ≥ 12 with each individual question not exceeding 2 indicate heartburn elimination.

Regurgitation Score: Calculated by summing the individual scores to questions 10-15.

- Worst regurgitation symptoms = 30
- No regurgitation symptoms = 0
- Scores of ≥ 12 with each individual question not exceeding 2 indicate regurgitation elimination.

3- Upper gastroduodenscopy for GERD grading was done using Pentax FG29W and multiple biopsies from proximal and distal parts of esophagus were taken to exclude oesinophilic esophagitis and to classify GERD degree according to Los Angeles classification.

4-All biopsies taken from different parts of esophagus were fixed in 10% formaline solution not more than 12 hours and processed into paraffin blocks. 4:5 mico-meter tissue thickness sections were cut on glass slides and stained with routine Haematoxin and Eosin staining for histo-pathological examination. The following histopathological features were assessed before presumptive diagnosis reflux esophagitis can be made. Those features included the intraepithelial eosinophilic count, basal cell hyperplasia, extension of lamina propria papillae and intrapapillary blood vessel dilatation. Eosinophilic esophagitis (EE) was diagnosed by presence of more than 15 eosinophils/HPF along with formation of eosinophilic microabscesses and markedly increased epithelial hyperplaasia (14).

5- History for allergy and clinical assessment were conducted. History included previous diagnosis of allergy, atopic manifestations of the disease, history of food allergy or food induced attacks, past history of illnesses, immunizations, history of child being breastfed or on artificial milk, and family history of allergy.

6-Skin prick test: Puncturing the skin was done with a calibrated lancet (1 mm) held vertically, or a hypodermic needle or blood lancet at an angle of 45°, and introducing a drop of diluted allergen. All patients undergoing skin prick testing should also have a positive histamine control and negative diluent (saline) control test included. An itchy wheal should develop at the histamine puncture site within 10 minutes. Test solutions are standardized to give a mean wheal diameter of 6 mm. The maximum or mean diameter of the wheals to various allergens should be read at 15 minutes. A wheal of 3mm or more in diameter was generally considered to represent a positive response (indicating sensitization to the allergen)(15). Common food allergens used in this study included strawberry, nuts, spices, maize, wheat, milk, mango, banana, barley, sesame, garlic, fish, egg and soya beans.

7-Skin patch test: Tiny quantities of materials (allergens) in individual square plastic or round aluminium chambers were applied to the upper back. They were kept in place with special hypoallergenic adhesive tape. The patches remained in place undisturbed for at least 48 hours. Getting the back wet during patch testing, vigorous exercise or stretching should be avoided. At the second appointment, usually 48 hours later, the patches were removed. The back was marked with an indelible black felt tip pen or other suitable marker to identify the test sites, and a preliminary reading was done. These marks must be visible at the third appointment, usually 24–48 hours later (72–96 hours after application)(16). Reactions as erythema, papules and vesicles were considered a positive reaction(17).

8-Oral food challenge test(OFC): Before proceeding with the OFC antihistamines should have been discontinued for >72 h and any other medications for the treatment or prevention of allergic diseases(18). After elimination of the food tested for two weeks, re-evaluation of GERD symptoms was done.

Statistical Methodology:

The data and results were collected and tabled using Microsoft Office Excel 2007. Statistical analysis of the results was done using SPSS v15.0. Tables & graphs were performed using Microsoft Word 2007.
Quantitative variables were expressed as minimum, maximum and mean ± SD.
Qualitative variables were expressed as number and percentage. Chi-square test was used to compare qualitative variables. ANOVA test was used to compare more than two groups as regard quantitative variables. Post-hoc analysis was done to in case the ANOVA test was significant to study the comparison between two groups. P values of ≤ 0.05 and ≤ 0.001 were considered statistically and highly statistically significant, respectively.

Results

The study included 50 Egyptian patients; 56% were females. The mean age of the studied patients was 30.78±7.87 years old(Table 1).

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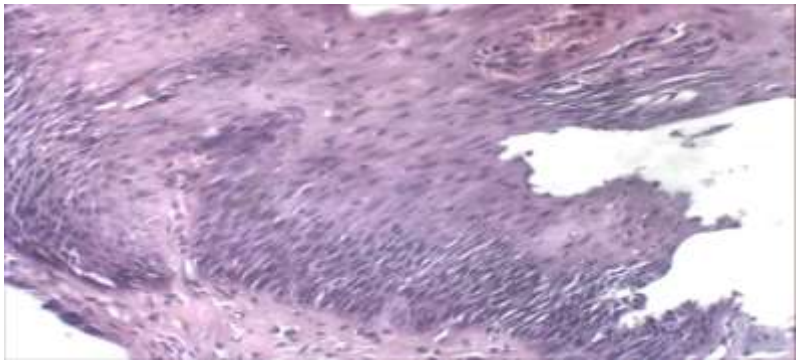
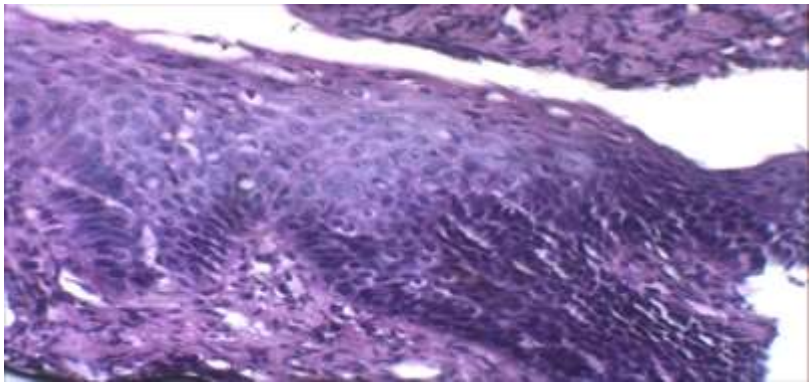
Table 1: Socio-demographic distribution of the studied cases

Gender	Number	%
Male	**22**	**44**
Female	**28**	**56**
Age	**Minimum-maximum**	**Mean± SD**
	18-45	**30.78±7.87**

In all the examined biopsies, the diagnosis of EE is ruled out; the intraepithelial eosinophils were scattered (no evidence of clustering and microabscess formation) and were ranged 0-5/HPF. Basal cell hyperplasia exceeding 15-20% was seen in all cases. Extension of lamina propria papillae into more than two-third of mucosal thickness was seen in 80 % of cases all of which showed capillary ectasia and congested venules. No evidence of specific inflammation was present (fig 1).



A



B

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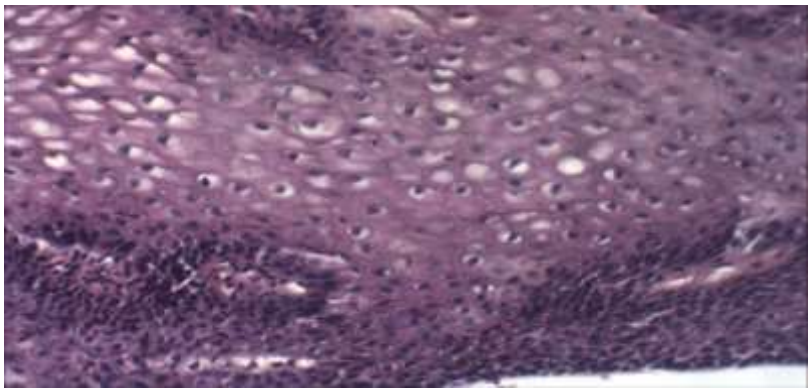

C

Fig 1: Histologic features of reflux esophagitis .(A&B) These biopsies demonstrate non specific changes in form of basal cell hyperplasia and papillary elongation along with scattered neutrophils and lymphocytes(Hematoxylin and eosin x 200).(C) Absence of numerous eosinophilic infiltrate exclude the diagnosis of eosinphilic esophagitis (Hematoxylin and eosin x 400).

Most of the patients (66%) were grade A GERD, 28% were grade B and 6% were grade C. SPT was positive in 70% of the cases. Patch test was done for 15 SPT negative patients and was positive in one case only (6.7%). The prevalence of food allergy according to SPT and patch test was 36/50 (72%) (fig.2 and table 2).

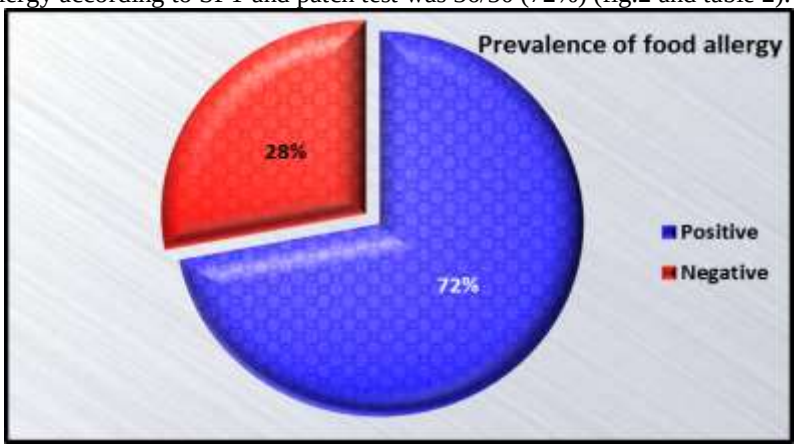

Fig 2:. Prevalence of food allergy in adult patients with refractory GERD

Table 2: Grading of GERD and prevalence of food allergy

	Number	%
GERD		
A	**33**	**66**
B	**14**	**28**
C	**3**	**6**
SPT		
Positive	**35**	**70**
Negative	**15**	**30**
Patch test (n=15)		
Positive	**1**	**6.7**
Negative	**14**	**93.3**

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Common allergens were banana, mango and maize followed by wheat, fish and egg (fig 3).

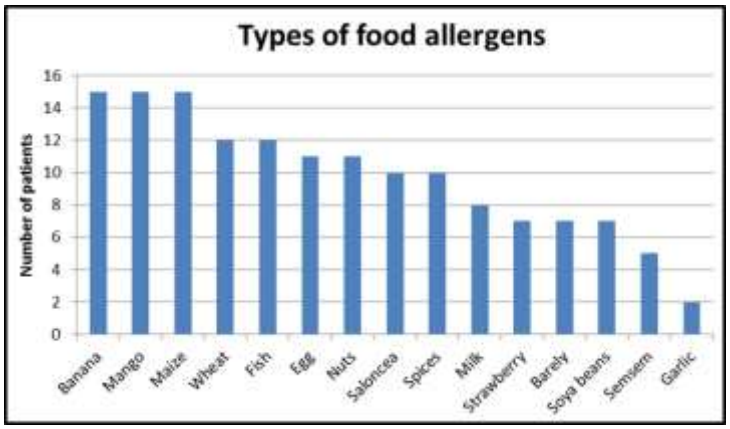

Fig 3: common food allergens with GERD

There was insignificant association between the grade of GERD(severity) and number of patients with food allergy (χ^2=0.5 , p>0.05)(table 3 and fig.4).

Table 3: Relation between grading of GERD and number of patients with food allergy .

	A (n=33)	B (n=14)	C (n=3)	X	p
N (%)	2 (72.7%)	10 (71.4%)	2 (66.7%)	0.5	0.9

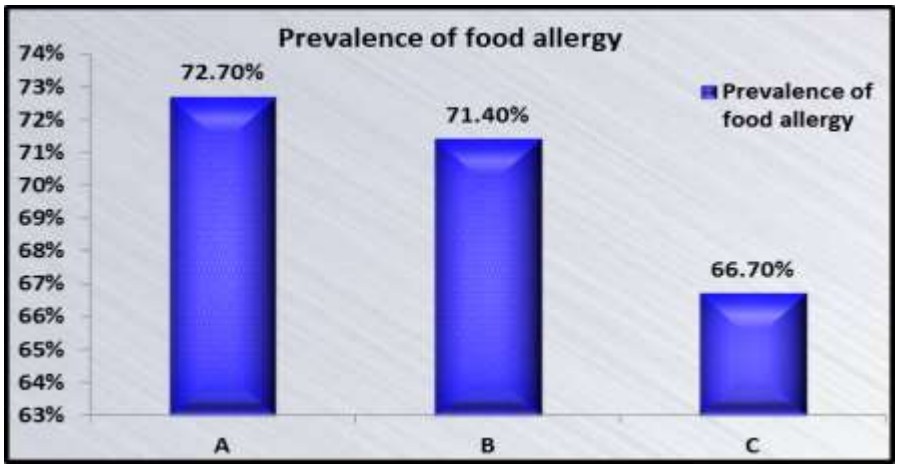

Fig 4:Prevalence of food allergy in different grades of GERD

Out of the 36 cases with food allergy, only one patient (2.8%) didn'timprove, and 35 (97.2%) improved(fig 5); 71.4% improved without medications and 28.6% improved with medications(table 4). There was statistical significant improvement of patients with GERD on diet elimination diet without treatment.

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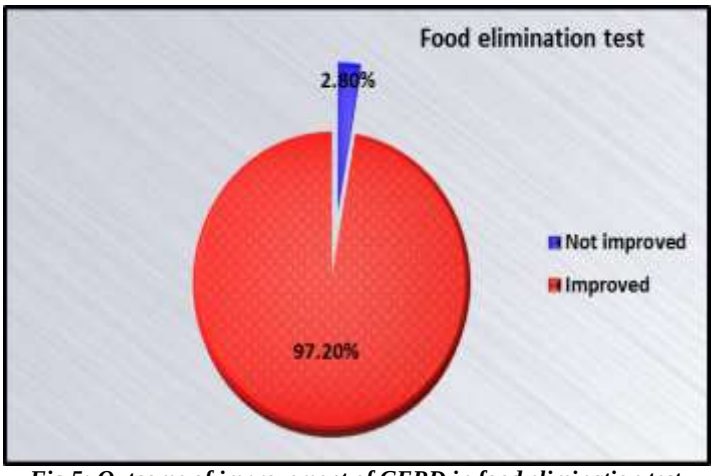

Fig.5: Outcome of improvement of GERD in food elimination test

Table 4: Diet elimination outcome

	Number	%
Not improved	**1**	**2.8**
Improved	**35**	**97.2**
Without medications	**25**	**71.4**
With medications	**10**	**28.6**

Table 5 and fig 6 showed that79.2% of grade A patients and 60% of grade B patients responded to diet elimination without drug. On the other hand, 20.8% of grade A patients, 40% of grade B patients and 50% of grade C patients improved on diet elimination and medication together.

Table 5: Relationship between different grades GERD and response to diet elimination with and without drugs

	A (n=24)	B (n=10)	C (n=2)	X	p
Without drug	**19 (79.2%)**	**6 (60%)**	**0**	**3.8**	**0.1**
With drug	**5 (20.8%)**	**4 (40%)**	**1 (50%)**		

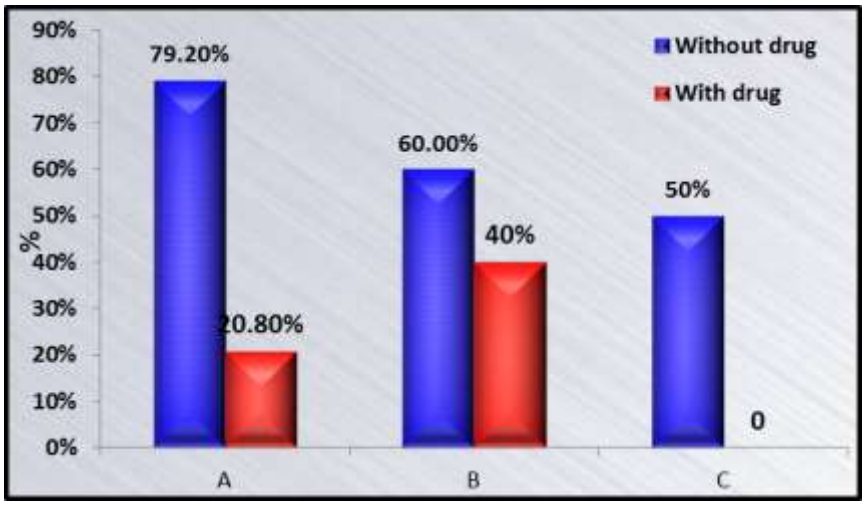

Fig 6: Relationship between GERD and response to diet elimination with and without drugs

Discussion

Gastro-esophageal reflux is a common disorder widely distributed around the world. Typical symptoms include regurgitation and heartburn. Atypical symptoms include laryngitis, chronic cough, asthma, and chest pain(19).

Food allergy presents itself in many forms due to affection of different areas of the body. This includes respiratory, cutaneous, gastrointestinal, and systemic manifestations. As for the gastrointestinal (GI) system, immune-pathophysiology divided the food allergy disorder into three categories; acute onset due to food-specific IgE antibody(e.g.oral allergy syndrome), chronic form of IgE mediated food allergy(e.g.eosiophilic oesophagitis) and T-cell mediated form(e.g. food protein-induced disorders) (20). Standard tests used to identify the culprit food allergens are skin prick testing, atopy patch test (APT) and Immunocap RAST (21).

Because a possible role for food allergy in the etiology of GERD has not, to the best of our knowledge, been investigated in adults, so the aim of this study was to study the prevelance of food allergy in adult patients with GERD of unknown etiology.

Out of 50 patients; 56% were females and 44% were males. Most of the patients were grade A (66%), 28% were grade B and 6% were grade C.

In our study, as regards the tests for food allergy; 35(70%) patients were SPT positive and out of the 15 SPT negative patients, only one patient was patch test positive. This suggests a high prevalence of food allergy among patients with GERD. Among the 36 GERD patients with food allergy, 25(97.2%) patients improved after diet elimination either without medications, while 10 (71.4%) patients improved with medications (28.6%). Only one patient (2.8%) didn't show any improvement on diet elimination. This also signifies a possible association between the presence of GERD and food allergy.

Few studies dealt with this issue in children. In a study on infants with GERD, they found that the prevelance of cow milk allergy in those patients ranged from 16% to 42% (22).

Salvatore and Vandenplas, 2002 demonstrated a possible link between cow milk allergy(CMA) and gastro-esophageal reflux (GER). They stated that there might be a common pathological pathway, on molecular basis, involving neurological, motor and immune pathways. They recommended a thorough allergy history and proper tests to evaluate the condition for possibility of applying cow milk free diet as a first line therapy instead of anti-reflux treatment especially to those resistant to drug therapy(22).
Also Farahmand et al.2011 conducted a study on 81 children with GER and found that 54 of the patients (66.7%) were found to present the signs and symptoms of CMA(23).
Borrelli et al., 2012 conducted their study to assess and compare the pattern of reflux in a selected population of infants with cow's milk (CM) allergy (CMA) and suspected gastro-esophageal reflux disease (GERD). They concluded that in children with CMA and suspected GERD, CM exposure increases the number of weakly acidic reflux episodes. Although their study design and inclusion criteria were different from our study, they reached a conclusion near to ours which related GERD to food allergy(9).

Ramirez-Mayans et al., 2014conducted their study to verify the presence of GER in children with CMA and they found that fourteen of the 47 children (29%) presented with GER, according to the result of the 24-hour intraesophageal measurement and therefore concluded the existence of a relation between the two pathologies(24).
Most common food allergens in adults according to our study were banana, mango and maize, whereas in a study in United States, most common food allergens in atopic adults, regardless of GERD, included shellfish, peanut, tree nuts, fish(25).

Unfortunately we couldn't prove a potential association between presence of food allergy and degree of severity of GERD. Only one study, according to our knowledge, conducted by Janiszewska and Czerwionka-Szaflarsk 2003 ,demonstrated the possibility of a link between them and proved the role of food allergy as intensification factor to symptoms of GERD(26).

They explained that IgE-dependent allergy and coexistent gastro-oesophageal reflux in children and youth mount the intensity of gastro-oesophageal reflux and that oesophageal mucosa is subjected to harmful effects of gastric contents(26).

In an attempt to prove an actual link between food allergy and GERD, patients were put on elimination diet according to the positivity of allergy skin tests. In general, 97.2% of GERD patients improved on diet elimination, 71.4% without needing to use antacid medications as adjuvant treatment. Only 2.8% of patients didn't improve alone on elimination diet and continued complaining of GERD symptoms even when going back to their medications.

Conclusion

In conclusion the present study postulates the possibility of association between food allergy and GERD especially refractory GERD to treatment. Limitation to our study is the lack of control cases to detect significance to percentage of this association and prevelance. Larger scaled studies are recommended, in adults and on molecular basis, to determine an explanation of this association. Further studies are also needed to evaluate the pH changes on introduction of the culprit food allergens. Wide epidemiological survey would be beneficial for better diagnosis and cost effective management.

Conflict of interest

The authors declare that no funding or grant was received for the study, and that they have no conflict of interest, financial or personal relationship related to the study.

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