Allergol Immunopathol (Madr). 2014;42(2):109–114

Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica

www.elsevier.es/ai

ORIGINAL ARTICLE

The relationship between gastro-oesophageal reflux disease and asthma during childhood

C. Özcan[a], M. Erkoçoğlu[a], E. Civelek[a], H. Demirkan[b], C.T. Kırsaçlıoğlu[c], H.T. Tiryaki[b], T. Giniş[a], C.N. Kocabaş[a,*]

[a] *Ankara Children's Hematology Oncology Education and Research Hospital, Department of Pediatric Allergy, Ankara, Turkey*
[b] *Ankara Children's Hematology Oncology Education and Research Hospital, Department of Pediatric Surgery, Ankara, Turkey*
[c] *Ankara Children's Hematology Oncology Education and Research Hospital, Department of Pediatric Gastroenterology, Ankara, Turkey*

Received 7 June 2012; accepted 28 August 2012
Available online 21 December 2012

KEYWORDS
Childhood asthma;
Gastro-oesophageal reflux disease;
Food allergy

Abstract
Background: The relationship between GERD and asthma is complex. It is not yet clear whether GERD is an accompanying finding or a cause of asthma, or even if it is an aggravating factor. The aim of this study was to determine the frequency of asthma and allergic diseases in patients who underwent 24-h pH monitoring for a suspicion of GERD, including a comparison between subjects with and without GERD.
Method: Subjects who were evaluated by 24 h ambulatory intraoesophageal pH monitoring were investigated for the presence of asthma and allergic disorders. All participants were subjected to a skin prick test and a complete blood count and serum levels of specific IgE.
Results: A total of 204 subjects (49.5% male) with a mean age of 7.8 ± 4.3 years were enrolled. A diagnosis of GERD was made in 78 (38.2%) subjects after 24 h pH monitoring. The frequency of asthma in subjects with GERD was 20.5% compared to 25.4% in subjects without GERD ($p = 0.424$). Subjects with GERD presenting with respiratory symptoms have higher incidence of asthma compared to subjects with GERD presenting with gastrointestinal symptoms (35.3% and 5.3% respectively; $p = 0.001$).
Conclusion: Although, patients with and without GERD had comparable frequencies of asthma, our findings suggest that subjects who present with respiratory symptoms suggestive of GERD should also be evaluated for the presence of an underlying asthma.

Introduction

Gastro-oesophageal reflux disease (GERD) typically presents with oesophageal symptoms such as heartburn and regurgitation, although non-oesophageal symptoms like chronic

* Corresponding author.
E-mail address: cankocabas@yahoo.com (C.N. Kocabaş).

0301-0546/$ - see front matter © 2012 SEICAP. Published by Elsevier España, S.L. All rights reserved.
http://dx.doi.org/10.1016/j.aller.2012.08.009

cough, hoarseness and chest pain are not uncommon.[1,2] Furthermore, chronic cough and wheezing can be the sole presenting manifestation of GERD,[3,4] and 24 h oesophageal pH monitoring should be performed in subjects in whom cough is still yet unexplained after a detailed history and physical examination and chest radiograph.[5]

GERD has been shown to play a role in inflammatory diseases of the upper and lower respiratory tract. The relationship between GERD and asthma is particularly complicated. It is not yet clear whether GERD is an accompanying finding or a cause of asthma, or even if it is an aggravating factor.[6] Gastro-oesophageal reflux was identified in asthmatic children even without any gastrointestinal symptoms.[7]

Twenty-four hour pH monitoring is considered the gold standard test for making a diagnosis of GERD.[8] Using this method, different studies have reported a GERD prevalence of between 55–83% in adults and 50–63% in children with asthma.[9–11]

Although numerous studies have evaluated the prevalence GERD in patients with asthma, very few studies have focused on the prevalence of asthma in patients with GERD. In this study, we aimed to evaluate and compare the frequency of asthma and allergic diseases in patients with or without GERD, evaluated by 24-h pH monitoring.

Materials and methods

This study was undertaken in Ankara Children's Health and Diseases Hematology-Oncology Hospital, the third largest tertiary healthy centre in Ankara, with the approval of the local ethics committee and written informed consent was obtained from the participants and from their parents. The study population consisted of children between 6 months to 17 years of age who underwent 24-h ambulatory intra-oesophageal pH monitoring with a suspicion of GERD, between June 2010 and June 2011. Subjects were stratified into two groups based on presenting symptoms (symptoms before pH monitoring); those with respiratory symptoms (cough, wheezing) and gastrointestinal symptoms (nausea, vomiting, acid reflux and abdominal pain) which persisted for at least four weeks. We evaluated all the participants for the presence of allergic disorders, and a family history of physician diagnosed allergic disorders was obtained.

GERD diagnosis

A diagnosis of GERD was made using 24-h ambulatory intra-oesophageal pH monitoring. None of the subjects were on acid suppressive medications before or during the study. This is performed by placing an acid-sensitive probe proximal to the lower oesophageal sphincter which measures and records oesophageal pH over a period of 24 h. Data are then transferred onto a computer and analysed using specific software (MMS, OhmegaR, The Netherlands). A diagnosis of GERD was based on the reflux index, which is the ratio of the time a pH less than 4 was measured, to the total time of pH evaluation. Gastro-oesophageal reflux was defined as a reflux index of more than 10% in infants under two years of age, and more than 5% in children older than two years of age.[12,13] Reflux indices were calculated using a commercial software program (MMS, OhmegaR, The Netherlands).

Allergic evaluation

All participants were evaluated (after pH monitoring) for the presence of asthma and allergic disorders and a detailed family history for allergic disorders was obtained. The diagnosis of asthma was made according to Global Initiative for Asthma guidelines (GINA).[14] Briefly, in subjects who were older than five years asthma diagnosis was made for a history of multiple episodes of wheezing with at least a 12% improvement in forced expiratory volume in one second following bronchodilator therapy, whereas in subjects who were five years old or younger asthma diagnosis was made by history of recurrent respiratory symptoms; a strong family history of asthma in first degree relatives; and/or atopy presenting as atopic dermatitis, food allergy and/or allergic rhinitis. Subjects with an underlying chronic condition other than asthma were excluded from the study. Spirometry was performed (Spirolab 2, Rome, Italy) and analysed in accordance with published recommendations.[15,16] The following variables were obtained from the best of three reproducible forced expiratory manoeuvres: FVC, FEV1 and FEV1/FVC ratio.

A diagnosis of allergic rhinitis was confirmed by a positive skin test or by the presence of specific IgE in subjects whose parents answered in the affirmative to the question ''Since birth, has your child had nasal discharge, nasal congestion, nasal itching or sneezing without the presence of the common cold or a flu-like infection?''. A diagnosis of atopic dermatitis was only accepted if it had previously been made by a physician, with a compatible history.

All subjects underwent skin prick testing for *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Cat and Dog dander*, *Alternaria*, *Cockroach*, *Aspergillus*, *Clodosporium*, *Betulaceae*, *Grass mix*, *Tree mix*, *Artemisia*, *Oleaceae*, *Saliceae*, *Parieteria*, *egg*, *wheat*, *peanut*, *hazelnut*, *milk*, *sesame*, *soya*, *fish*, *histamine*, and *negative controls* (Stallergens, Antony, France). These tests were performed on the volar surface of both forearms, with results recorded after 15 min. Results were considered positive when the mean wheal diameter was at least 3 mm larger than that produced by the control. Blood samples were obtained from all participants for the determination of complete blood counts and serum levels of total IgE as well as specific IgE (Fx5: egg white, milk, fish, wheat, peanut, soybean; Phadiatop: aeroallergens; Pharmacia Diagnostics AB, Uppsala, Sweden).

Subjects with a positive reaction to any of the aeroallergens or food allergens on a skin test, or those who had an elevated specific IgE level of >0.35 kIU/ml were considered to have allergen sensitisation.

Statistical analysis

Statistical analysis was performed using the SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Values were either provided as numbers and percentages, or as mean ± standard deviation, where applicable. Comparisons of the frequency of allergic diseases and other variables between subjects

Table 1 Demographic characteristics of study population.

	No. of patients (%)
Gender (male)	101 (49.5)
Age,[a] *years*	7.8 ± 4.3
Presenting symptoms	
Respiratory	106 (52.0)
Gastrointestinal	98 (48.0)
Asthma	48 (23.5)
Allergic rhinitis	47 (23.0)
Atopic dermatitis	15 (7.4)
History of food allergy	44 (21.6)
Exposure to cigarette smoke	92 (45.1)
Parental history of asthma and/or allergic rhinitis	74 (36.3)
Allergen sensitisation	66 (32.3)
Inhaled allergen	45 (22.1)
Food allergen	32 (15.7)
Serum IgE levels,[a] *U/mL*	70.5 ± 142.0
Eosinophilia,[a] %	2.3 ± 2.4
GERD	78 (38.2)

[a]Values provided as mean ± standard deviation; GERD, gastro-oesophageal reflux disease.

with and without GERD were made using the Chi-square test, Fisher's exact test and student's *t*-test. A *p*-value of $\leq$0.05 was considered indicative of statistical significance.

Results

A total of 204 subjects (49.5% male) with a mean age of 7.8 ± 4.3 years were enrolled in the study, of whom 52% have presented with respiratory symptoms and 48% have presented with gastrointestinal symptoms. Overall, a diagnosis of GERD was established in 78 subjects (38.2%), while 48 subjects (23.5%) were diagnosed with asthma. The demographic and general characteristics of the study population have been summarised in Table 1.

Fifty-nine percent of subjects with GERD were male, compared to 43.7% of subjects without GERD ($p = 0.033$). There was no difference between subjects with GERD and without GERD in terms of mean age, presenting symptoms, exposure to cigarette smoke and history of an allergic disorder (Table 2).

Subjects with GERD presenting with respiratory symptoms had higher incidence of asthma compared to subjects with GERD presented with gastrointestinal symptoms (35.3% and 5.3% respectively; $p = 0.001$) (Table 3).

Forty-eight (23.5%) subjects were diagnosed with asthma. Of the asthmatic subjects 33.3% of them had GERD, whereas 39.7% of non-asthmatic subjects had GERD ($p = 0.424$) Within the asthmatic subjects, GERD was diagnosed in 37.5% (6/16) of subjects with atopic asthma (allergen sensitisation) compared to a GERD rate of 33.3% (10/30) in subjects with non-atopic asthma, a difference that was not statistically significant ($p = 0.777$).

Asthmatic subjects with GERD, 68.8% were male, compared to 37.5% among those without GERD ($p = 0.041$). The association between GERD and asthma was significantly more frequent in males than in females. A history of exposure to cigarette smoke in the home was present in 50% of asthmatic subjects with GERD and in 43.8% of those without GERD. The difference between the groups was not statistically significant ($p = 0.682$).

A history of food allergy presented in 21.6% (44/204) of subjects. Only two of them had continuing symptoms with the suspected foods during the study and one of which had GERD, while the other did not. Eight of the subjects with a history of food allergy had a positive skin test for suspected foods and/or were positive for Fx5 specific IgE. GERD was present in six of the eight subjects, compared to two subjects who did not have GERD ($p = 0.054$).

A total of 15 subjects who had persistent gastrointestinal symptoms (ten of them had negative pH monitoring and five of them had positive pH monitoring and were unresponsive to acid suppression therapy) underwent endoscopic examination. After evaluation of biopsy specimens, eosinophilic oesophagitis was not detected in any of them.

Thirty-two (41%) of the subjects diagnosed with GERD were under the age of five years while the remaining 46 (59%) were aged more than five years. Other than GERD occurring more frequently in males among subjects older than five years, there was no statistically significant difference between subjects with and without GERD in terms of presenting symptom and personal or family history of atopy.

Discussion

In this study, we attempted to determine the frequency of allergic disorders and allergen sensitisation in subjects evaluated for GERD by 24 pH monitoring, while also comparing subjects who had GERD with those who did not. The frequency of GERD in our study population was 38.2%. Among all participants, a diagnosis of asthma was present in 23.5% of subjects whereas 32.3% of subjects had allergen sensitisation. There was no difference between subjects with and without GERD in terms of frequency of allergic disorders including asthma and allergen sensitisation.

Very few studies have evaluated the prevalence of asthma in GERD subjects, with conflicting results. In a population-based study, it was reported that the presence of GERD was not associated with an increased risk of developing asthma.[2] However, in another study based on the use of ICD codes, the reported prevalence of asthma in children with GERD was 13.2% compared to a prevalence of 6.8% in healthy controls.[17] Tsai et al. also managed to demonstrate a 1.97-fold increased risk of developing asthma in subjects diagnosed with GERD using endoscopy and 24-h pH monitoring.[18]

In our study, a diagnosis of GERD was made using 24 h pH monitoring, which is widely considered to be the gold standard. We did not observe a statistically significant difference in the frequency of asthma in subjects with and without GERD.

According to studies from Turkey, the prevalence of physician-diagnosed asthma is between 6.9 and 10.7%.[19,20] On the other hand, we managed to establish a much higher asthma prevalence of 23.5%, which could be attributed to the fact that all participants in this study were symptomatic and that asthma and GERD may mimic each other, especially in children.

Table 2 Comparison of patients with and without GERD.

	With GERD $n=78$ (%)	Without GERD $n=126$ (%)	p-Value
Gender (male)	46 (59.0)	55 (43.7)	0.033
Age,[a] *years*	7.6 ± 4.4	8.0 ± 4.3	0.582
Presenting symptoms			
Respiratory	40 (51.3)	66 (52.4)	0.879
Gastrointestinal	38 (48.7)	60 (47.6)	0.879
Asthma	16 (20.5)	32 (25.4)	0.424
Allergic rhinitis	18 (23.1)	29 (23.0)	0.992
Atopic dermatitis	8 (10.3)	7 (5.6)	0.211
History of food allergy	20 (25.6)	24 (19.0)	0.266
Exposure to cigarette smoke	35 (44.9)	57 (45.2)	0.959
Parental history of asthma and/or allergic rhinitis	29 (37.7)	45 (35.7)	0.780
Allergen sensitisation	23 (30.3)	43 (35.8)	0.421
Inhaled allergen	17 (24.6)	28 (25.0)	0.956
Food allergen	14 (20.9)	18 (16.4)	0.447
Serum IgE levels,[a] *U/mL* ($n=204$)	69.6 ± 119.1	62.6 ± 144.5	0.949
Eosinophilia,[a] *%* ($n=204$)	2.1 ± 1.8	2.4 ± 2.7	0.492
FEV1,[a] *%*[b]	92.9 ± 14.4	92.4 ± 14.6	0.864
FEV1/FVC, %[b]	94.4 ± 12.7	99.1 ± 10.7	0.052

[a]Values provided as mean ± standard deviation.
[a] Performed by 41 patients with GERD and 78 patients without GERD. FEV1, forced expiratory volume in one second; FVC, forced vital capacity; GERD, gastro-oesophageal reflux disease.

In a study by Gronstein et al. on subjects who were evaluated by pH monitoring, investigators observed that mild GERD was associated with respiratory symptoms.[21] However, we could not demonstrate a difference between subjects with and without GERD in terms of presenting symptoms. We also found that subjects with GERD presented with respiratory symptoms have a higher incidence of asthma compared to subjects with GERD presented with gastrointestinal symptoms, which supports the idea that GERD is likely to play a causal role in chronic cough and possibly asthma.[22]

Most of the previous studies have reported a higher frequency of GERD in males,[18] although in some, there was no particular gender predilection.[23] Very few studies even reported on a higher prevalence of GERD in females.[24] In our study, GERD was more prevalent among males. The reasons behind this particular gender predilection remain elusive.

Table 3 Comparison of patients who presented with respiratory symptoms and with gastrointestinal symptoms.

	Respiratory symptoms $n=106$ (%)	Gastrointestinal symptoms $n=98$ (%)	p-Value
Gender (male)	55 (51.9)	46 (46.9)	0.480
Age,[a] *years*	6.9 ± 4.0	8.9 ± 4.5	0.001
Asthma	32 (30.2)	16 (16.3)	0.020
Allergic rhinitis	24 (22.6)	23 (23.5)	0.888
Atopic dermatitis	10 (9.4)	5 (5.1)	0.236
History of food allergy	21 (19.8)	23 (23.5)	0.526
Exposure to cigarette smoke	41 (38.7)	51 (52.0)	0.055
Parental history of asthma and/or allergic rhinitis	42 (39.6)	32 (33.0)	0.327
Allergen sensitisation	33 (33.0)	33 (34.4)	0.839
Inhaled allergen	22 (24.4)	23 (25.3)	0.897
Food allergen	13 (15.1)	19 (20.9)	0.319
Serum IgE levels,[a] *U/mL* ($n=204$)	78.3 ± 176.6	62.6 ± 95.6	0.451
Eosinophilia,[a] *%* ($n=204$)	2.3 ± 2.6	2.2 ± 2.1	0.843
FEV1,[a] *%*[b]	92.1 ± 14.2	93.0 ± 14.8	0.738
FEV1/FVC, %[b]	96.3 ± 11.9	98.6 ± 11.2	0.286
GERD	40 (37.7)	38 (38.8)	0.879

[a]Values provided as mean ± standard deviation.
[b] Performed by 56 patients with respiratory symptoms and 63 patients with gastrointestinal symptoms; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; GERD, gastro-oesophageal reflux disease.

Yüksel et al. reported that subjects with non-atopic asthma had more common GERD than subjects with atopic asthma.[25] But similar to a recent study,[26] we did not observe a statistically significant difference in the frequency of GERD among asthma subjects with and without a history of atopy.

Several studies report on a high prevalence of food sensitisation in subjects with GERD.[27,28] Although the subjects in our study with and without GERD have similar food sensitisation, in subjects with food allergy history accompanying GERD had higher food sensitisation than subjects without GERD, but it was not statistically significant. In conclusion, all of the subjects enrolled in the study underwent 24-h pH monitoring with a suspicion of GERD, and although we did not observe a significant difference between subjects with and without GERD in terms of prevalence of asthma and atopy, the frequency of these conditions was still higher than that of the general population. Our findings suggest that subjects who present with respiratory symptoms suggestive of GERD should also be evaluated for the presence of an underlying asthma.

Ethical disclosures

Protection of human subjects and animals in research. We declare that the procedures followed were in accordance with the regulations of the responsible Clinical Research Ethics Committee and in accordance with those of the World Medical Association and the Helsinki Declaration.

Patients' data protection. We declare that they have followed the protocols of their work centre on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing to participate in that study.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients mentioned in the article. The author for correspondence is in possession of this document.

Conflict of interest

All of the authors have no conflicts of interest in the manuscript.

References

1. Jaspersen D, Kulig M, Labenz J, Leodolter A, Lind T, Meyer-Sabellek W, et al. Prevalence of extra-oesophageal manifestations in gastro-oesophageal reflux disease: an analysis based on the ProGERD Study. Aliment Pharmacol Ther. 2003;17:1515–20.
2. Ruigomez A, Rodriguez LA, Wallander MA, Johansson S, Thomas M, Price D. Gastroesophageal reflux disease and asthma: a longitudinal study in UK general practice. Chest. 2005;128:85–93.
3. Irwin RS, French CL, Curley FJ, Zawacki JK, Bennett FM. Chronic cough due to gastroesophageal reflux. Clinical, diagnostic, and pathogenetic aspects. Chest. 1993;104:1511–7.
4. Sheikh S, Stephen T, Howell L, Eid N. Gastroesophageal reflux in infants with wheezing. Pediatr Pulmonol. 1999;28:181–6.
5. Harding SM, Richter JE. The role of gastroesophageal reflux in chronic cough and asthma. Chest. 1997;111:1389–402.
6. Khoshoo V, Le T, Haydel Jr RM, Landry L, Nelson C. Role of gastroesophageal reflux in older children with persistent asthma. Chest. 2003;123:1008–13.
7. Holbrook JT, Wise RA, Gold BD, Blake K, Brown ED, Castro M, et al. Lansoprazole for children with poorly controlled asthma: a randomized controlled trial. JAMA. 2012;307:373–81.
8. Rudolph CD, Mazur LJ, Liptak GS, Baker RD, Boyle JT, Colletti RB, et al. Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: recommendations of the North American Society for Pediatric Gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr. 2001;32 Suppl. 2:S1–31.
9. Buts JP, Barudi C, Moulin D, Claus D, Cornu G, Otte JB. Prevalence and treatment of silent gastro-oesophageal reflux in children with recurrent respiratory disorders. Eur J Pediatr. 1986;145:396–400.
10. Andze GO, Brandt ML, St Vil D, Bensoussan AL, Blanchard H. Diagnosis and treatment of gastroesophageal reflux in 500 children with respiratory symptoms: the value of pH monitoring. J Pediatr Surg. 1991;26:295–9.
11. Gustafsson PM, Kjellman NI, Tibbling L. Bronchial asthma and acid reflux into the distal and proximal oesophagus. Arch Dis Child. 1990;65:1255–8.
12. Vandenplas Y, Goyvaerts H, Helven R, Sacre L. Gastroesophageal reflux, as measured by 24-hour pH monitoring, in 509 healthy infants screened for risk of sudden infant death syndrome. Pediatrics. 1991;88:834–40.
13. Sondheimer JM, Haase GM. Simultaneous pH recordings from multiple esophageal sites in children with and without distal gastroesophageal reflux. J Pediatr Gastroenterol Nutr. 1988;7:46–51.
14. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J. 2008;31:143–78.
15. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26:319–38.
16. Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, et al. General considerations for lung function testing. Eur Respir J. 2005;26:153–61.
17. El-Serag HB, Gilger M, Kuebeler M, Rabeneck L. Extraesophageal associations of gastroesophageal reflux disease in children without neurologic defects. Gastroenterology. 2001;121:1294–9.
18. Tsai MC, Lin HL, Lin CC, Lin HC, Chen YH, Pfeiffer S. Increased risk of concurrent asthma among patients with gastroesophageal reflux disease: a nationwide population-based study. Eur J Gastroenterol Hepatol. 2010;22:1169–73.
19. Saraclar Y, Kuyucu S, Tuncer A, Sekerel B, Sackesen C, Kocabas C. Prevalence of asthmatic phenotypes and bronchial hyperresponsiveness in Turkish schoolchildren: an International Study of Asthma and Allergies in Childhood (ISAAC) phase 2 study. Ann Allergy Asthma Immunol. 2003;91:477–84.
20. Civelek E, Cakir B, Boz AB, Yuksel H, Orhan F, Uner A, et al. Extent and burden of allergic diseases in elementary schoolchildren: a national multicenter study. J Investig Allergol Clin Immunol. 2010;20:280–8.
21. Gorenstein A, Levine A, Boaz M, Mandelberg A, Serour F. Severity of acid gastroesophageal reflux assessed by pH metry: is it associated with respiratory disease? Pediatr Pulmonol. 2003;36:330–4.
22. Havemann BD, Henderson CA, El-Serag HB. The association between gastro-oesophageal reflux disease and asthma: a systematic review. Gut. 2007;56:1654–64.
23. Nilsson M, Johnsen R, Ye W, Hveem K, Lagergren J. Lifestyle related risk factors in the aetiology of gastro-oesophageal reflux. Gut. 2004;53:1730–5.
24. Louis E, DeLooze D, Deprez P, Hiele M, Urbain D, Pelckmans P, et al. Heartburn in Belgium: prevalence, impact on daily

life, and utilization of medical resources. Eur J Gastroenterol Hepatol. 2002;14:279–84.
25. Yüksel H, Yilmaz O, Kirmaz C, Aydoğdu S, Kasirga E. Frequency of gastroesophageal reflux disease in nonatopic children with asthma-like airway disease. Respir Med. 2006;100:393–8.
26. Kang SK, Kim JK, Ahn SH, Oh JE, Kim JH, Lim DH, et al. Relationship between silent gastroesophageal reflux and food sensitization in infants and young children with recurrent wheezing. J Korean Med Sci. 2010;25:425–8.
27. Nielsen RG, Bindslev-Jensen C, Kruse-Andersen S, Husby S. Severe gastroesophageal reflux disease and cow milk hypersensitivity in infants and children: disease association and evaluation of a new challenge procedure. J Pediatr Gastroenterol Nutr. 2004;39:383–91.
28. Meer S, Groothuis JR, Harbeck R, Liu S, Leung DY. The potential role of gastroesophageal reflux in the pathogenesis of food-induced wheezing. Pediatr Allergy Immunol. 1996;7: 167–70.