Preliminary Report

The Study of Allergic Skin Test in Patients with Globus Pharyngeus: A Preliminary Report

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Background: *Globus pharyngeus is the lump sensation in the throat associated with various conditions including somatoform disorder and gastroesophageal reflux disease. However, many patients with unrelated causes were found to respond to anti-allergic treatment.*
Objective: *Determine the results of allergic skin test in globus pharyngeus patients who had unidentified causes.*
Material and Method: *Fifty-four globus pharyngeus patients were enrolled and referred for complete physical examination, screening psychological status, videostroboscopy, and reflux finding score assessment. All patients including 38 controlled subjects underwent skin prick test and/or intradermal test. The globus patients who had positive test were recommended to have anti allergic treatment. Barium swallowing study, ambulatory double-probe pH monitoring, or plain film cervical spine was done in patients with negative skin tests and in non-response to medication.*
Results: *There was statistically significant difference of positive skin test results between globus and the control group (77.8% vs. 28.6% OR = 13.12, p < 0.001). In positive skin test-globus group, globus symptom was improved in 64.3% after allergic treatment, which 85.2% had moderate and excellent improvement. In patients with negative skin test and non-response group show various conditions including gastroesophageal reflux disease (18.52%), abnormal esophageal manometry (40.74%), and myofascial pain syndrome (3.71%).*
Conclusion: *Due to high prevalence of positive skin test in globus pharyngeus patients, this symptom should be considered as one of the atypical allergic manifestations.*

Keywords: *Conversion disorder, Gastroesophageal reflux, Skin tests*

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Globus phryngeus, or sensation of the lump in the throat, is a common problem that comprises 3% to 4% of all new referrals in otolaryngology clinics[1,2]. It occurred one or more times in 45% of apparently healthy people[3]. Globus pharyngeus had been thought to be an anxiety state, however, in later studies, patient with globus sensation were found to be psychically healthy. Those patients had some evidence of esophageal disorders[4-6]. Many cases in the literature were found to have different causes such as cervical osteophytes[6,7], hyperplastic pharynx, posterior cricoid web[1,8], lingual tonsil hypertrophy[9,10], temporomandibular joint dysfunction[11], hyperviscoelasticity of epipharyngeal mucous[12], esopharyngeal structure and motor disorder[13-15]. Most of them were reported by the case series or in the small sample sizes.

Recently, gastroesophageal reflux disease (GERD) is one of the most studied in the correlation with the globus symptom. However, nowadays, these studies still have conflicting results[16-20], especially in

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Asian countries, which have lower prevalence of GERD than Western countries[21,22]. In clinical practice for globus patients, if the physical examinations are negative for laryngopharyngeal reflux diseases, the empirical treatment of anti-reflux regimens are often started. However, oftenly, they do not give symptomatic relief. On the other hand, many patients who have globus symptoms unrelated to any causes respond well to anti-allergic treatments. These are very interesting in clinical observations.

According to Mill[8] who first studied the correlation between globus and rhinosinusitis in seven cases, all of the patients had abnormal sinus x-ray. The explanation was it might be due to the mucous drip in to the posterior pharynx. This posterior nasal drip could occurr in both sinusitis and allergic patients. Presently, there is no well-controlled studies in the literature to identify the relationship of the globus symptoms and the allergic disease.

Therefore, the aims of the present study were to determine the prevalence of allergic skin test in patients with globus pharyngeus and to describe the natural history of this symptom.

Material and Method

A non-randomized controlled study was conducted between July 2005 and June 2006 at the otolaryngology clinic, Phramongkutklao hospital, Thailand. The study was approved by the Institutional Review Broad and the Ethical committee of Royal Thai Army Medical Department. There were two study groups, the controlled group and the globus pharyngeus group. The controlled group consisted of 38 healthy volunteers who were aged more than 18 years old. They had no globus symptoms, no typical allergic symptoms and all had normal oropharynx, larynx, and pharynx examinations. The volunteers were recruited during annual physical examinations at the out-patient clinic. All of them had skin tests performed. In the globus pharyngeus group, the consecutive cases of patients with "lump in the throat" complaints without true dysphagia or organic diseases were enrolled in the present study. After initial assessment, all patients underwent complete ENT examination, videostroboscopy, reflux finding score (RFS) assessment[23], and psychological screening using General Health Questionnaire (GHQ12)[24], Thai version[25]. Inclusion criteria included age more than 18 years old, no typical allergic symptoms (e.g itching, sneezing, rhinorrhea, or asthma). All also had no abnormality on examination of the oropharynx, larynx, and pharynx and should stop the antihistamine, ketotifen, and steroid drugs at least 1 week before being enrolled in the study. Exclusion criteria included patients with classic allergic symptoms, classic gastritis or gastroesophageal reflux symptoms (e.g regurgitation heartburn), and with reflux finding score (RFS) > 7[23], which suggested laryngopharyngeal reflux condition, patients with severe systemic diseases, who received β-blocker, or monoamine oxidase inhibitor, those who had obvious psychic disorders e.g anxiety, depression and somatoform disorder, patients with history of anaphylaxis to common allergen, dermographism condition, and patients who smoked or had alcoholic habits.

Reflux finding scores

In the globus pharyngeus group, the video-stroboscope were performed and reviewed. The "Reflux Finding Score (RFS)[23]" were scored by a blind experienced otolaryngologist to find the laryngopharyngeal reflux (LPR) condition as the etiology of globus symptoms. The patients who had RFS > 7 had a high possibility of having LPR[23] and were excluded from the present study.

Allergy testing

Skin prick test

The presence of common 30 standardized aeroallergens (pollens, weed trees, dander, house dust, mites, mold and miscellaneous) were assessed through a screening skin- prick test (GREER laboratories, Inc). Skin prick test was performed with 1 drop of standardized aeroallergens placed on both volar sites of upper extremities and scratched with a lancet needle. Positive skin prick test was recorded when there was wheal and flare response, and wheal diameter more than 5 mm after 15 minutes. Negative control was done with 1 drop of 50% glycerol + 50% coca's, positive control was done with 1 drop of histamine hydrochloride (1 mg/ml).

Intradermal test

For the patients with negative skin prick test, intradermal skin test were performed. Injection 0.01 ml of standardized aeroallergens (GREER laboratories, Inc) on the shoulder area with number 27 gauze needles, slope 45 degree to plane and 2 cm apart from each aeroallergen and negative skin test was performed with Sterile Diluent's For Allergen Extracts Normal Saline With Serum Albumin (GREER laboratories, Inc). Positive skin test was recorded when there was wheal and flare response more than 5 mms after 15 minutes.

Empirical treatment of the allergy

All the positive skin test globus patients then underwent allergic medication therapies to determine the correlation of the positive tests and the globus symptoms. At the initial of the present study and at 1 month after treatment, the visual analogue score (VAS) were evaluated the improvement of the symptoms by the subjects. The positive outcomes were defined when the improvement was more than 30 mm of the VAS scales.

Ambulatory pH monitoring

In cases of the positive skin test patients who did not improve globus symptoms after allergic treatments, the 24 hr-pH-monitoring was performed with esophageal manometry. The double antimony electrodes were used (Jebsen & Jessen Model pH 406 Denmark). The distal electrode was positioned at 5 cm proximal to the upper border of LES and the proximal one was positioned at 2 cm above the UES.

If the outcome measurements for the Esophageal probe were Demeester score > 14.72[26], it was determined to be a positive result. For the pharyngeal probe, the results were positive when percent time pH < 4 more than 0.02% in upright, more than 0% in supine position, or over all > 0.1% or reflux episode more than three[27].

Other investigations

The plain film cervical spine and barium swallowing studies were performed if necessary in the patients who were suspected to have osteophytes or esophageal mass or who did not respond to the therapies. The results were summarized in frequency table and flow chart in term of number and percent.

Results

Sixty-six globus patients were identified and 12 subjects were excluded because they had one or more of the exclusion criteria. Finally, 54consecutive globus patients were enrolled in the present study. These comprised of 36 females (66.7%) and 18 males (33.3%). Mean ages were 44.7 $\pm$ 12.3 years old. Mean duration of symptom was 5 months. Most of them were married and were housewife (Table 1). Forty (74%) patients had intermittent symptoms while 11 (20.4%) had continuous ones.

Forty-nine (91%) of the globus patients had other associated symptoms such as throat clearing (78.4%) and intermittent cough and mild difficulty in swallowing (27.5%). Most patients had globus sensation at about midline of the neck but they could not point the exact level.

Allergic skin test

Of 54 globus patients, 42 (77.8%) had positive skin test while eight (28.6%) of the 28 controlled subjects had positive results (Fig. 1), which were statistically significantly different (OR = 13.12, p < 0.001). In addition, seven patients (16.6%) of the skin test positive group developed classic allergic symptoms after the beginning of the present study during the 1-year follow-up period (range 2-8 months, mean 3.7 months).

Empirical treatment & Visual analogue scale

Twenty-seven (64.3%) of the positive skin test globus patients had significant improvement (increased VAS > 30 mm) after allergy therapies. In this group, 85.2% had moderate and excellent outcomes (> 55 mm and > 75 mm, respectively) after 1 month of empirical therapies (Fig. 1).

The rest of the positive test group and the negative test group had other special investigations performed as follow.

Table 1. Demographic data of the globus and controlled subjects

Characteristics	Number (%)	
	Globus patients (n = 54)	Controlled patients (n = 38)
Age (year)		
< 21	1 (1.9%)	3 (7.9%)
21-30	7 (13.0%)	4 (10.5%)
31-40	11 (20.3%)	11 (28.9%)
41-50	20 (37.0%)	11 (28.9%)
> 50	15 (27.8%)	9 (23.7%)
Sex		
Female	36 (66.7%)	25 (65.8%)
Male	18 (33.3%)	13 (34.2%)
Marrital status		
Married	32 (59.3%)	24 (63.2%)
Single	17 (31.5%)	12 (31.6%)
Window	4 (7.3%)	2 (5.3%)
Divorced	1 (1.9%)	0
Occupation		
House wife	19 (35.2%)	13 (34.2%)
Labor	14 (25.9%)	9 (23.7%)
Officer	10 (18.5%)	7 (18.4%)
Private	7 (13.0%)	5 (13.2%)
Student	2 (3.7%)	3 (7.9%)
Agriculture	2 (3.7%)	1 (2.6%)

Ambulatory pH monitoring

All 15 of non-improvement-positive test group and 12 of the negative skin test group (total n = 27) had been performed 24 hr-pH monitoring. Five (18.5%) had positive pH-study (3 had typical LPR and 2 patients had borderline results) (Fig. 1). All of them responded well with GERD therapy regimen.

Esophageal manometry

Of those 27 patients with positive skin test who did not respond to allergic therapy and those who had negative skin test, 11 (40.7%) patients had positive findings on esophageal manometry (4 high UES resting pressure, 5 low amplitude peristalsis contraction, and 2 high amplitude peristalsis contraction) (Fig. 1).

Other investigations

The 13 barium swallowing studies and four cervical spine films all had negative results. There was one patient (3.7%) diagnosed as myofascial pain syndrome at the neck muscle and his globus symptom disappeared after local injection of 10% xylocain.

There were 37.03% (10/27) in the negative skin test group and non-response positive skin test group who had negative results in all investigations (Fig. 1) and received supportive therapies, which had gradual response.

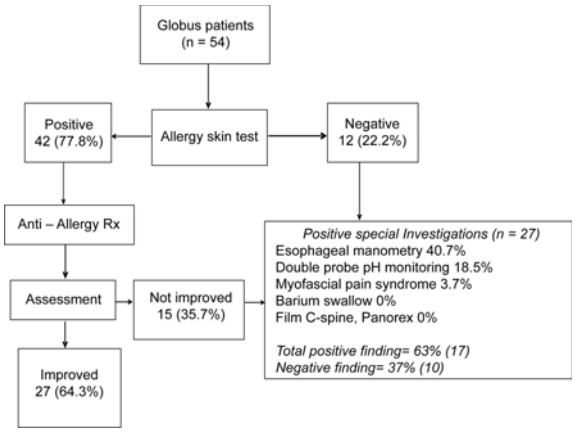

Fig. 1 Flow chart showing the results of the study

Discussion

Characteristic data of the globus patients in the present study were comparable with the study of Malcomson[1], Moloy[2], Batch[28] and Timon[29], which the globus patients had the average age of onset = 44.7 years (Batch 45.2 years, Timon 43 years). The point level of the globus sensation could not be identified in most patients. Most associated symptom was throat clearing, which was the same as Timon's study[29]. Onset of symptoms was gradual in 74%, which contrasted to 56% of Timon's study. There were two interesting findings regarding the associated diseases among patients that had not been reported before. One globus patients had associated weight loss, which esophageal manometry showed low amplitude contraction of esophageal body. Another globus patient had myofascial pain syndrome but his symptom disappeared after xylocain injection.

In the present study, 77.8% of the globus patients had skin test reactivity to common allergen, which was higher than 21.05% of the control group. These findings suggested the potential association between globus symptom and the positive skin test. A placebo-randomized controlled trial of the allergy treatments should be considered in further study.

The authors excluded the patients who were suspected to have laryngopharyngeal reflux (RFS > 7) from the present study because the authors were concerned only with globus patients with unidentified causes. Ambulatory pH tests were performed only in patients with a negative skin test and positive skin test who did not respond to allergic medications. Therefore, the prevalence of GERD in globus patients could not be obtained from the present study. The reasons the authors did not perform pH test in all globus patients were it was an invasive procedure and up to date, its sensitivity was relatively controversial. In these groups, 18.5% had positive double-probe pH test. This prevalence of reflux was lower than previously reported[17-19,30].

In general, the skin prick test is a gold standard in diagnosis of allergy. In cases of negative skin tests, intradermal tests have been used to confirm the diagnosis. Diagnosis of allergic diseases depend on a patient's history, physical examination and positive skin tests. Positive test results without typical allergic signs and symptoms may be due to previous sensitization with aeroallergens. Furthermore, in some patients, the presence of irritants or non-specific mast cell secretagogues may explain positive responses with concentrated extracts, especially when intradermal route is used. Using prick puncture test, positive skin tests probably detect the presence of specific IgE antibodies to environmental allergens, although their presence may not always coincide with clinically significant allergic disease[31]. However, the presence of positive skin tests in asymptomatic subjects may predict the

onset of allergic symptoms. According to Haggy's study[32], asymptomatic patients with positive skin test had a more significant incidence of allergic rhinitis (32%) and asthma (6%) than asymptomatic patients with negative skin test after 7 years follow up. As in the present study, seven patients (16.6%) with globus symptom and positive skin test developed typical allergic symptoms within 1 year.

From these findings, globus may be one of the early or may be atypical manifestation of allergic symptoms. The mechanism of how allergy can cause globus sensation may be due to posterior nasal drip stagnation in the pharynx or hypopharynx, allergy induces laryngitis[33,34] and allergy induces hyper-viscoelasticity of pharyngeal mucous secretion[12].

Globus pharyngeus symptom may be associated with the silent allergic reaction or positive allergic skin tests. This symptom may be one of the atypical manifestations of the allergy. The placebo-randomized controlled trials are needed to confirm the hypothesis.

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References

1. Malcomson KG. Globus hystericus vel pharyngis (a recommaissance of proximal vagal modalities). J Laryngol Otol 1968; 82: 219-30.
2. Moloy PJ, Charter R. The globus symptom. Incidence, therapeutic response, and age and sex relationships. Arch Otolaryngol 1982; 108: 740-4.
3. Thompson WG, Heaton KW. Heartburn and globus in apparently healthy people. Can Med Assoc J 1982; 126: 46-8.
4. Lehtinen V, Puhakka H. A psychosomatic approach to the globus hystericus syndrome. Acta Psychiatr Scand 1976; 53: 21-8.
5. Deary IJ, Wilson JA, Mitchell L, Marshall T. Covert psychiatric disturbance in patients with globus pharyngis. Br J Med Psychol 1989;62 (Pt 4): 381-9.
6. Maran A, Jacobson I. Cervical osteophytes presenting with pharyngeal symptoms. Laryngoscope 1971; 81: 412-7.
7. Counter RT. Globus hystericus and cervical osteophytes. J R Nav Med Serv 1977; 63: 81-4.
8. Malcomson KG. Radiological findings in globus hystericus. Br J Radiol 1966; 39: 583-6.
9. Tremble GE. Hypertrophied lingual tonsils. Laryngoscope 1957; 67: 785-95.
10. Tremble GE. The clinical significance of a lump in the throat. AMA Arch Otolaryngol 1959; 70: 157-65.
11. Puhakka HJ, Kirveskari P. Globus hystericus: globus syndrome? J Laryngol Otol 1988; 102: 231-4.
12. Shiomi Y, Shiomi Y, Oda N, Hosoda S. Hyper-viscoelasticity of epipharyngeal mucus may induce globus pharyngis. Ann Otol Rhinol Laryngol 2002; 111: 1116-9.
13. Watson WC, Sullivan SN. Hypertonicity of the cricopharyngeal sphincter: A cause of globus sensation. Lancet 1974; 2: 1417-9.
14. Linsell JC, Anggiansah A, Owen WJ. Manometric findings in patients with the globus sensation [abstract]. Gut 1987; 28: A1378.
15. Flores TC, Cross FS, Jones RD. Abnormal esophageal manometry in globus hystericus. Ann Otol Rhinol Laryngol 1981; 90: 383-6.
16. Woo P, Noordzij P, Ross JA. Association of esophageal reflux and globus symptom: comparison of laryngoscopy and 24-hour pH manometry. Otolaryngol Head Neck Surg 1996; 115: 502-7.
17. Hill J, Stuart RC, Fung HK, Ng EK, Cheung FM, Chung CS, et al. Gastroesophageal reflux, motility disorders, and psychological profiles in the etiology of globus pharyngis. Laryngoscope 1997; 107: 1373-7.
18. Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. Laryngoscope 1991; 101 (4 Pt 2 Suppl 53): 1-78.
19. Smit CF, van Leeuwen JA, Mathus-Vliegen LM, Devriese PP, Semin A, Tan J, et al. Gastropharyngeal and gastroesophageal reflux in globus and hoarseness. Arch Otolaryngol Head Neck Surg 2000; 126: 827-30.
20. Pearlman NW, Stiegmann GV, Teter A. Primary upper aerodigestive tract manifestations of gastroesophageal reflux. Am J Gastroenterol 1988; 83: 22-5.
21. Goh KL, Chang CS, Fock KM, Ke M, Park HJ, Lam SK. Gastro-oesophageal reflux disease in Asia. J Gastroenterol Hepatol 2000; 15: 230-8.
22. Cho YS, Choi MG, Jeong JJ, Chung WC, Lee IS, Kim SW, et al. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study

in Asan-si, Korea. Am J Gastroenterol 2005; 100: 747-53.
23. Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (RFS). Laryngoscope 2001; 111: 1313-7.
24. Goldberg DP. The detection of psychiatric illness by questionaire. Maudsley monograph No 21. London: Oxford University Press; 1972.
25. Nilchaikovit T, Sukying C, Silpakit C. Reliability and validity of the Thai version of the General Health Questionaire. J Psychiatr Assoc Thai 1996; 41: 2-17.
26. Richter JE, DeMeester TR,Wu WC. Normal 24-hour esophageal pH value: influence of age and gender. Gastroenterology 1990; 98: A122.
27. Smit CF, Tan J, Devriese PP, Mathus-Vliegen LM, Brandsen M, Schouwenburg PF. Ambulatory pH measurements at the upper esophageal sphincter. Laryngoscope 1998; 108: 299-302.
28. Batch AJ. Globus pharyngeus: (Part II), Discussion. J Laryngol Otol 1988; 102: 227-30.
29. Timon C, O'Dwyer T, Cagney D, Walsh M. Globus pharyngeus: long-term follow-up and prognostic factors. Ann Otol Rhinol Laryngol 1991; 100: 351-4.
30. Wilson JA, Pryde A, Piris J, Allan PL, Macintyre CC, Maran AG, et al. Pharyngoesophageal dysmotility in globus sensation. Arch Otolaryngol Head Neck Surg 1989; 115: 1086-90.
31. Demoly P, Michel FB, Bousquet J. In vivo methods for study of allergy: skin test, technique, and interpretation. In: Adkinson NF, Yunginger JW, Busse WW, Bochner BS, Holgate ST, Simons FE, editors. Middleton's allergy principles & practice. 6th ed. Philadelphia: Mosby; 2003: 631-43.
32. Hagy GW, Settipane GA. Risk factors for developing asthma and allergic rhinitis. A 7-year follow-up study of college students. J Allergy Clin Immunol 1976; 58: 330-6.
33. Dixon HS. Allergy and laryngeal disease. Otolaryngol Clin North Am 1992; 25: 239-50.
34. Jackson-Menaldi CA, Dzul AI, Holland RW. Allergies and vocal fold edema: a preliminary report. J Voice 1999; 13: 113-22.

การศึกษาภาวะภูมิแพ้ด้วยการทดสอบทางผิวหนังในผู้ป่วยที่มีภาวะกลืนจุก

ปริยนันทน์ จารุจินดา, อธิก แสงอาภาวิริยะ, สุริยะ จักพาก, สุวิน สมเงิน, ไข่มุกด์ เพ็ชรศรีกุล

ภาวะกลืนจุกเป็นภาวะความรู้สึกมีก้อนในลำคอ เกิดได้จากหลาย ๆ สาเหตุเช่น ภาวะทางจิตเวช ภาวะกรดไหลย้อนเป็นต้น อย่างไรก็ดีพบว่ามีผู้ป่วยจำนวนหนึ่งที่ตอบสนองต่อการรักษาด้วยยาลดอาการภูมิแพ้ แต่ในปัจจุบันยังไม่มีการศึกษาถึงความสัมพันธ์ดังกล่าว จุดประสงค์ของการศึกษานี้เพื่อดูความสัมพันธ์ของการทดสอบภูมิแพ้ทางผิวหนังกับภาวะกลืนจุกที่หาสาเหตุอื่นไม่ได้ โดยผู้ป่วยอาการกลืนจุก 54 คน ได้รับการตรวจร่างกายอย่างละเอียด ทำแบบทดสอบทางจิตเวช (GHQ 12) ตรวจกล้องบริเวณลำคอ และประเมินคะแนนภาวะกรดไหลย้อน ผู้ป่วยกลุ่มควบคุมมี 38 คนเป็นผู้มีสุขภาพดี ไม่มีอาการกลืนจุกหรือภูมิแพ้ ทั้ง 2 กลุ่มได้รับการทดสอบภูมิแพ้ทางผิวหนัง ผู้ที่ให้ผลบวกจะได้รับการรักษาด้วยยาต้านภูมิแพ้และประเมินผลใน 1 เดือน ผู้ที่ให้ผลลบหรือผู้มีผลทดสอบบวกแต่ไม่ตอบสนองต่อยา จะได้รับการตรวจพิเศษเพิ่มเติม ผลการศึกษาพบว่ากลุ่มผู้ป่วยภาวะกลืนจุกมีผลทดสอบทางผิวหนังเป็นบวกสูงกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ (77.8% เทียบกับ 28.6%, OR = 13.12, p < 0.001) กลุ่มที่ให้ผลบวกพบว่า 64.3% ตอบสนองต่อยาต้านภูมิแพ้ได้ดี โดยกลุ่มนี้ 85.2% ตอบสนองในเกณฑ์ดีมาก กลุ่มที่ให้ผลทดสอบเป็นลบ และในกลุ่มที่ไม่ตอบสนองต่อยาภูมิแพ้ พบมีภาวะอื่นร่วมด้วย เช่น ภาวะกรดไหลย้อน 18.52%, การบีบตัวของหลอดอาหารผิดปกติ 40.74% และภาวะกล้ามเนื้อคอเกร็งเฉพาะที่ 3.71% จากการที่พบอุบัติการณ์ผลทดสอบภูมิแพ้ทางผิวหนังเป็นบวกในอัตราค่อนข้างสูง จึงควรคำนึงว่าภาวะกลืนจุกอาจเป็น อาการแสดงหนึ่งของผู้ป่วยภูมิแพ้ที่ไม่มีอาการภูมิแพ้ด้านอื่นที่ชัดเจน