

## ORIGINAL ARTICLE

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# Sensitization to Food Additives in Patients with Allergy: A Study Based on Skin Test and Open Oral Challenge

Mozhgan Moghtaderi,<sup>1,2</sup> Zinatosadat Hejrati<sup>3</sup>, Zahra Dehghani<sup>3</sup>,  
Faranak Dehghani<sup>3</sup>, and Niloofar Kolahi<sup>3</sup>

<sup>1</sup> Allergy Clinic of Ali-Asghar Hospital, Allergy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

<sup>2</sup> Allergy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

<sup>3</sup> Department of Pediatrics, College of Medicine, Islamic Azad University,  
Kazerun Branch, Kazerun, Iran

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## ABSTRACT

There has been a great increase in the consumption of various food additives in recent years. The purpose of this study was to identify the incidence of sensitization to food additives by using skin prick test in patients with allergy and to determine the concordance rate between positive skin tests and oral challenge in hypersensitivity to additives.

This cross-sectional study included 125 (female 71, male 54) patients aged 2-76 years with allergy and 100 healthy individuals. Skin tests were performed in both patient and control groups with 25 fresh food additives.

Among patients with allergy, 22.4% showed positive skin test at least to one of the applied materials. Skin test was negative to all tested food additives in control group. Oral food challenge was done in 28 patients with positive skin test, in whom 9 patients showed reaction to culprit (Concordance rate=32.1%).

The present study suggested that about one-third of allergic patients with positive reaction to food additives showed positive oral challenge; it may be considered the potential utility of skin test to identify the role of food additives in patients with allergy.

**Keywords:** Allergy; Food additives; Skin test

## INTRODUCTION

Food additives are different substances which are added to food products during processing or storage for certain technical functions.<sup>1,2</sup> The most common additives include antioxidants,

colors, emulsifiers, gelling agents, stabilizers, sweeteners, thickeners and preservatives, although many of them serve more than function.<sup>3,4</sup> There have been the significant risks of food additives ranging from behavior disturbances in children to asthma and anaphylaxis.<sup>5-7</sup>

The prevalence of adverse reaction to food additives was estimated to be 0.01- 0.2% in general population and 2% to 7% in patients with atopy<sup>8,9</sup> but the exact incidence has not been identified yet. The problem in

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**Corresponding Author:** Mozhgan Moghtaderi; MD;  
Allergy Clinic of Ali-Asghar Hospital, Allergy Research Center,  
Shiraz University of Medical Sciences, Shiraz, Iran. Tel/Fax: (+98  
71) 3235 1575, E-mail: moghtadery@sums.ac.ir

## Sensitization to Food Additives

investigating the incidence of sensitization to food additives comes back to the large numbers of additives under suspicious, vague patient's subjective symptom as well as the absence of simple and standardized diagnostic tests.

Skin prick test (SPT) is one of the most informative and simple diagnostic methods for detecting IgE-mediated sensitization to allergens. There is a minor role for skin testing in food and food-additives sensitization because the enzymatic degradation of food proteins during preparing commercial extracts and also implicating only a small number of IgE mediated reaction in patients with hypersensitivity to food additives.<sup>10-12</sup> Oral challenge testing with food additives preceded by a trial of an additive-free diet is the definitive procedure for detecting the offending agent.<sup>13</sup>

There are wide variations in the prevalence of sensitization to food additives in different countries because of dissimilarities in using processed foods among people. However, few studies evaluated sensitization to food additives in patients with allergy in this area. This study was designed to identify allergy to food additives in patients with allergy comparing to control. The present study also aimed to explore the concordance between sensitization to food additives by SPT and food challenge.

### MATERIALS AND METHODS

This cross-sectional study involved patients with allergic rhinitis (AR), asthma and chronic urticaria referred to an allergy clinic at Ali-Asghar Hospital affiliated to Shiraz University of Medical Sciences, Iran between February and September 2015. The diagnosis of AR was based on ARIA,<sup>14</sup> asthma according to GINA<sup>15</sup> and chronic urticaria was defined as unidentified urticaria lesions for longer than 6 weeks, with supervision of an allergy subspecialist. Patients who were being treated with systemic corticosteroids, angiotensin-converting-enzyme inhibitors or beta blockers and pregnant women as well as those with positive dermatographism were excluded from the study. Patients were excluded if they had physical urticaria or cutaneous vasculitis.

One hundred unrelated healthy individuals with no personal or family history of asthma and other atopic diseases were selected as the control group and matched for ethnicity and geographic area of residence. After approval of the study protocol by the Ethics Committee of our university, informed consent for food

additive skin test and challenge was obtained from each participant in both groups. Demographic information about age, gender, type of allergic disease and duration of disease was recorded.

A questionnaire was used to obtain information from patients about their allergic reactions including tingling and burning sensation in the mouth, respiratory symptoms and rhinitis within a few minutes after the ingestion of certain food. Certain foods were cream cheese, hamburger, meat, sausage, and soda pop which had processed with our culprit food additives.

SPT were performed on the forearms with calcium chloride, carrageenan, citric acid, cola color, cola flavor, colorless extract, flavor of butter, gluten, isolated soy protein, lemon extract, lipase, monosodium glutamate, microcrystalline cellulose (MCC), natamycin, nitrate, orange extract, paprika, phosphate, rennet, shani extract, sodium benzoate, sodium lactate, sodium metabisulphite, stabilizer 407 and trisodium citrate. These food additives obtained from factories in Shahrak Sanati of Shiraz, Iran and were prepared in a concentration of 100 mg/mL with normal saline according to the concentration as described by Park HW et al.<sup>11</sup> Food additives were pricked with a sterile lancet on patients' forearm. In order to avoid false-positive result, the drops were placed at least 2 cm apart from each other. Histamine (10 mg/mL) and saline were used as positive and negative controls, respectively. The results of the skin tests were examined after 15 min and considered positive when the wheal was  $\geq 5$  mm in diameter than the negative control. Topical corticosteroids were stopped one day before the skin test. Individuals were requested not to take any type of antihistamine medication for five days prior to the SPT.

After performing SPT, in patients and control groups with positive test to at least one food additives, open oral food challenge (OOFC) was performed in the clinic under the supervision of an allergist. The initial challenge procedure consisted of single-blind challenge using a placebo control (100 cc dextrose water 5%) and if there were no symptoms after 1 hour, then, OOFC was performed. Doses of food additives were determined by considering maximum amount of food additive that can be consumed in a 24-hour period in one's diet according to National Library of Medicine Database, therefore, a solution of food additive 100 mg/100 cc dextrose water 5% for all additives was prepared except for MSG with higher dose 2500 mg/100 cc. Patients' symptoms were recorded each 30

minutes and they were instructed to record any reactions occurring up to 24 hours after open challenge and call the allergist.

### Statistical Analysis

All data was analyzed by SPSS version 18 software. Descriptive statistics, Chi-square and T test were used to examine and compare the relationship between the characteristics of the sample.  $p$  value < 0.05 was considered as significant.

## RESULTS

One hundred and twenty-five patients (female 71, male 54) in the age range of 2 to 76 years old (mean age  $24.4 \pm 17.53$  years) with AR, asthma, chronic urticaria were included in this study. Out of them, 28 (22.4%) patients showed a positive skin test to at least one of the applied food additive allergens. One hundred individuals were included in the control group. Participants in this group were sex-matched ( $p=0.06$ ) but not age-matched ( $p=0.001$ ) with the patients with allergy. None of individuals in control group showed sensitization to SPT.

SPT was negative to natamycin, sodium benzoate, citric acid, lemon extract, stabilizer 407 and sodium lactate in all our patients. Reactive SPT to carrageenan, colorless extract, trisodium citrate, flavor of butter, cola color, orange extract, colorless extract, shani extract, sodium metabisulfite, MCC and monosodium glutamate was found each in one patient. Sensitization to trisodium citrate was detected in two patients to phosphate, and paprika and isolated soy protein each in three patients. Sensitization to nitrate, calcium chloride, gluten and lipase was detected each in four patients.

The most frequent sensitization was to cola flavor in five patients. Four patients showed sensitization to more than one additive allergen. Demographic characteristics and reactivity to food additives in patients with various types of allergy and control group are presented in Table 1.

**Table 1. Demographic characteristics and reactivity to food additives in patients with allergy and control**

Characteristics	
Allergic rhinitis	
Number (%)	50(40%)
Sex(F/M)	27/23
Mean age (year) $\pm$ SD	18.26 $\pm$ 11.35
Mean duration of disease (year) $\pm$ SD	6.31 $\pm$ 4.94
Positive skin test (%)	12(24%)
Positive skin test and open challenge (%)	3(6%)
Asthma	
Number (%)	52(41.6%)
Sex(F/M)	25/27
Mean age (year) $\pm$ SD	29.21 $\pm$ 22.05
Mean duration of disease (year) $\pm$ SD	7.04 $\pm$ 6.54
Positive skin test (%)	13(25%)
Positive skin test and open challenge (%)	4(7.7%)
Chronic urticaria	
Number (%)	23(18.4%)
Sex(F/M)	19/4
Mean age (year) $\pm$ SD	27 $\pm$ 13.06
Mean duration of disease (year) $\pm$ SD	3.88 $\pm$ 6.16
Positive skin test (%)	3(13%)
Positive skin test and open challenge (%)	2(8.6%)
Control	
Number	100
Sex (F/M)	69/31
Mean age (year) $\pm$ SD	31.58 $\pm$ 9.29
Positive skin test	0

**Table 2. Patients with positive skin test and oral challenge to food additives**

Patient number	Sex	Age (years)	Diagnosis	Positive skin test and open challenge	Symptoms after challenge
1	M	43	Asthma	Isolated soy protein Trisodium citrate Flavour of butter	Dyspnea Dyspnea Dyspnea& flushing
2	F	45	Asthma	Isolated soy protein	Urticaria
3	F	35	Chronic urticaria	Lipase	Dyspnea
4	F	46	Asthma	Cola color	Dyspnea
5	F	38	Allergic rhinitis	Colorless extract	Urticaria
6	M	10	Asthma	Sodium metabisulfite	Cough& dyspnea
7	F	15	Asthma	Isolated soy protein Gluten	Urticaria Cough& dyspnea
8	F	35	Chronic urticaria	Lipase	Dyspnea
9	M	38	Allergic rhinitis	Colorless extract	tingling and burning sensation in the mouth

## Sensitization to Food Additives

Nine out of 28 patients with positive SPT to food additives showed intolerance to culprit food additive by open challenge. Table 2 shows patients' characteristics with positive skin test and oral challenge to food additives, two patients reacted to more than one food additives.

Eight patients had a history of allergy to the certain foods while none of them were found positive reactivity to applied food additives.

### DISCUSSION

The selection of the standard test for discriminating hypersensitivity to food additives is still under investigation. Despite the issues which are disagreement with the use of SPT for food additives,<sup>16,17</sup> we found positive SPT to food additives in 22.4% of patients with allergy. Park et al. showed reactive SPT to food additives in 3.7% of patients with allergy,<sup>11</sup> this lower result could be related to fewer types of food additives (7 vs. 26 in our study). It is also possible that false positive SPT occur to additives due to irritation; therefore, control SPT was conducted on non-allergic individuals in this study.

The most frequent sensitization was to cola flavor in our study. Numerous flavoring substances are allowed for use in foods and each of them contains hundreds of various chemical compounds. These chemical compounds are often mixture of small molecular-weight substances that are not likely allergen.<sup>18,19</sup> Although there are a few reports of IgE-mediated allergic reactions to flavoring agents,<sup>19,20</sup> it appears some chemicals in flavoring agents could possibly act as haptens to elicit an IgE-mediated response.

Positive SPT to nitrates, calcium chloride, gluten and lipase were the same in this report (each 3.2%). Nitrates are used as curing agents in meat products. One study has described anaphylactic reaction to nitrate in a 22-year-old man which was confirmed by double blind placebo challenge.<sup>21</sup>

Calcium chloride is the most common food additives in our diet; it has many applications in the food industry where it is used either as food additive or as food processing agent. The main applications for calcium chloride in food industry are: cheese making, firming agent in canned vegetables and beer breweries.<sup>22</sup> Although this study showed sensitization to calcium chloride by SPT, there is currently no evidence to

suggest it induces allergic reactions in the amounts found in food and drinks.

Gluten is the protein found in wheat, barley, oat and rye. It is used extensively in packaged and processed foods as fillers, dusters, and emulsifiers. Many people are aware that avoiding gluten means avoiding bread, pasta and cereal, but we often forget about the gluten in soy sauce, marinades, dry nuts, cosmetics, and skin care products.<sup>23,24</sup> The increased incidence of gluten intolerance probably is the result of gluten being used as food additive, not just a grain source.

The most studies emphasize on the role of food additives in chronic urticaria.<sup>16, 25</sup> Among our patients with atopy the rate of sensitization to food additives was more in patients with asthma followed by allergic rhinitis and chronic urticaria.

Oral challenge testing with additives, preferably preceded by a trial of an additive-free diet, is the definitive procedure for detecting the offending agent.<sup>12</sup> In clinical practice, open and single blinded food challenge is frequently used. This study showed 9 out of 125 patients with allergy (7.2%) developed reactions after oral challenging with food additives. In a survey of 1483 Dutch adults, 3 persons (0.2%) reacted to food additives by double-blind placebo-controlled food challenge.<sup>26</sup> In a British study that started with questionnaire in 18,582 individuals and mixed-additive challenge conducted at home, the researchers estimated prevalence of adverse reactions to food additives 0.01% to 0.2%.<sup>27</sup> In addition to using more food additives in this study, high difference can also be related to selection of patients who are allergic.

Concordance rate between SPT and open challenge to food additives was 32.1% in present study that little is currently known about this relation.

Symptoms due to sensitization to food additives are usually less severe than those induced by food allergy;<sup>26</sup> therefore diagnostic approaches as reporting symptoms is difficult. None of our patients with history of reaction to food additives showed positive reactivity to applied food additives.

Hypersensitivity reactions appeared in skin and respiratory systems in our patients after challenging. Hannuksela M, et al. report that the most important skin symptoms caused by food additives are urticaria, angioneurotic edema, and contact urticaria.<sup>28</sup>

Our study was limited primarily by the lack of oral challenge in all patients with allergy and control group. This may lead to less precise estimation of

hypersensitivity to food additives. This could have been due to practical trouble in performing challenge with various kinds of food additives in all studied individuals. Furthermore, we cannot also precede trial of an additive-free diet in patients who showed positive oral challenge to additives.

In conclusion, about one- third of allergic patients with positive reaction to food additives showed positive oral challenge; it may be considered the potential utility of skin test to identify the role of food additives in patients with allergy.

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