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Follow-Up of the Wheat Allergy in Children; Consequences and Outgrowing the Allergy

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ABSTRACT

Allergy to wheat is a common food allergy. In spite of this fact, there is not enough literature regarding the features and outgrowing of this allergy. The objective of this study was to evaluate the manifestations of this allergy and to follow the patients to evaluate whether outgrowing allergy happens again and when it occurs.

Eight wheat allergic patients diagnosed between 2000 and 2001 were re-evaluated together with 13 other new cases of wheat allergy referred to the Immunology and Allergy Pediatric Department from June 2004 to March 2006. For all cases, the demographic data along with a complete history regarding allergy to wheat and other types of allergy were collected in questionnaires. The specific IgE measurements (*in vivo* and *in vitro*) and oral food challenge (in the absence of a relevant history related to allergy to wheat) were performed.

Severe anaphylaxis was seen after wheat ingestion in more than 90% of the patients. Oral tolerance to wheat developed in three patients (37.5%) out of 8 known previous cases who had been followed for eight years, the mean age of oral tolerance to wheat was 68 ± 6.36 (range; 36 months to 108 months).

Clinical reactions in our wheat-allergic patients were more severe than those reported before. These patients were at risk for developing chronic allergic symptoms such as asthma. We also found that oral tolerance to wheat was happening in a minority of our patients.

Keywords: Anaphylaxis; IgE mediated hypersensitivity; Oral tolerance; Wheat allergy

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INTRODUCTION

Food allergy is among the most common allergic problems with a 6% to 8% incidence in the western countries.^{1,2} The most important foods causing food

allergy include milk, egg, peanut, nuts, soy, fish and wheat.^{3,4}

Food allergy to wheat must be differentiated from bakers' asthma (a pulmonary allergy to the protein present in wheat flour) and celiac disease (a non-IgE mediated food allergy to wheat and gliadin based cereals).⁵

Allergy to wheat is a very serious problem. Firstly, wheat is the most common cereal planted and is widely used by human beings.^{6,7} It is one of the most important sources of protein and accounts for 70% of the protein usage worldwide.⁸ Secondly, wheat enters the human diet very early (approximately at 5 months of age) and allergy to it is even possible in a breast-fed infant. Thirdly, most of the children allergic to wheat suffer from moderate to severe atopic dermatitis which, together with allergy to other types of foods including milk and egg, results to very severe allergic reactions like anaphylaxis.⁹ Allergy to wheat has less been evaluated in comparison to allergy to milk.¹⁰ IgE-related reaction to wheat flour has been defined as bakers' asthma quite early in the 20th century.¹¹ Manifestations of allergic reaction to wheat may be immediate or delayed according to the time of onset or mild to life-threatening depending on the severity of the reactions. Typical signs and symptoms of acute allergic reaction to wheat include oropharyngeal symptoms, urticaria, angioedema, deteriorating atopic dermatitis, rhinitis, asthma, gastrointestinal symptoms and anaphylaxis in the extreme.^{12,13}

Delayed reactions of food allergy to wheat in children including erythema, itching, eczema and gastrointestinal reactions have been determined a few hours after oral ingestion of wheat by Scandinavian researchers.^{14,15} Although it has been defined in the reports that allergy to wheat rarely results in classic signs and symptoms of IgE-mediated food allergy in adults, some reports of genuine allergy to wheat have also been mentioned.^{9,11}

Prognosis of allergy to wheat and determination of food tolerance to this allergic substance have not been evaluated as thoroughly as cow milk. This study was performed as a follow up of the previous study on the children allergic to wheat by Pourpak et al (2000-2001)¹⁶ and aims to evaluate more patients allergic to this cereal and follow the previous patients to evaluate wheat tolerance in them. This project was approved by research center of Asthma, Allergy and Immunology of Tehran University of Medical Sciences.

PATIENTS, MATERIALS AND METHODS

All patients referred to the Immunology and Allergy Department of children Medical Center hospital from 2004 to 2006 diagnosed with wheat allergy were evaluated. In addition, patients evaluated between 2000 and 2001 in whom the diagnosis of allergy to wheat had been confirmed were included. A previously designed questionnaire which included demographic data of the patients (age, sex, clinical symptoms, and the relationship and interval between the symptoms and ingestion of wheat) was filled out for each patient. After taking an informed consent, the patients were enrolled in the study.

Diagnosis of allergy to wheat was made if the patients had a clinical history consistent with an IgE-mediated allergic reaction on wheat ingestion or by open food challenge test. If the clinical symptoms were not convincing and wheat IgE test result was positive, Jones et al. reported that up to 10 gr of wheat flour (about 1.2 g of protein) was needed to induce symptoms in children suspected of wheat allergy on the basis of positive prick tests.¹⁷ It is advisable to begin with a starting dose below the expected _threshold dose.¹⁸ Therefore we started with 100 mg of wheat flour into bread or Haleem (a dish consisting of meat and wheat) in open food challenge test. The progressive increment was by using logarithmic mean (100 mg, 300 mg, 1 gr, 3gr, 10gr)¹⁸ every 15-30 minutes in the absence of allergic reactions, until the final dose (10gr).

All patients followed regarding the acute reactions of anaphylaxis, urticaria, vomiting, and wheezing. If any of these reactions developed, the test was confirmed as positive and the patient underwent treatment with intramuscular epinephrine, if necessary, diphenhydramine, and also a 6-hour period of observation of the symptoms and vital signs.^{18,19}

To confirm an IgE-mediated reaction to wheat, the skin prick test in addition to serum specific IgE test was performed in all patients. If delayed symptoms such as atopic dermatitis developed, two weeks of cereal deprivation was attempted. The patient then underwent a complete clinical examination, the challenge test in the hospital, and afterwards a one-week cereal-included diet was attempted at home again. If the eczematous reactions exacerbated during the one-week period, the wheat challenge test was considered positive and particular skin prick tests and serum specific IgE level with regard to wheat were evaluated. Another aim of

this study was to evaluate whether the patients had outgrown their allergy to wheat or not.

Prick Test

This test was performed in the volar surface of the forearm using the commercial extract of the wheat kernel and also other cereals including rye, oat and barley all provided by AllergoPharma, Germany. Histamine chloride (10mg/mL) and 0.9% sodium chloride were used as positive and negative controls, respectively. Positive skin reaction was defined as a wheal with a minimum diameter of 3 millimeters more than the negative control within 15 minutes of the test.

In each serum sample, the levels of total and specific IgE against wheat protein were determined using the ELISA method. This test was performed using the commercial laboratory materials from AllergoPharma, Germany. The positive reaction graded from 0 to 5+. A total of 21 patients were evaluated in the study.

RESULTS

Eight previous patients were re-evaluated using the prick or ELISA tests and a history was taken about the recent convincing allergic symptoms due to accidental or intentional ingestion of wheat, in the absence of which the wheat challenge test would be performed. In 13 new patients, the diagnosis was confirmed using the prick test or evaluation of the serum level of specific IgE along with a convincing history of food allergy to wheat or the positive oral challenge test to wheat. Seven patients who were diagnosed having wheat allergy (33.3%) were girls and 14 (66.7%) were boys. The mean age of the patients was 62.8 ± 47 (range: 7 months to 168 months). The mean age of initiation of the clinical manifestations was 5.35 ± 1.1 months (range: 3 months to 8 months). All patients had some degree of anaphylaxis regarding the results given by Hugh A Sampson (Table 1). A total of 14 (66.6%), five (23.8%), one (4.7%) and one (4.7%) patient had anaphylaxis grade 4, 3, 2 and 1, respectively. Nineteen patients (90.5%) had dermatologic allergic reactions including urticaria, flushing, and itching after ingestion of wheat. Ten patients (47.6%) showed gastrointestinal symptoms including nausea, vomiting and diarrhea after wheat ingestion.

Table 1. Distribution of the frequency of acute and chronic clinical symptoms in patients with allergy to wheat (n=21)

Clinical Symptom	N(%)
<i>Acute</i>	
– Skin	19 (90.5)
– Digestive	10 (47.6)
– Respiratory	18 (85.7)
<i>Chronic</i>	
– Asthma	11 (52.4)
– Eczema	5 (23.8)

Furthermore, 18 patients (85.7%) experienced respiratory problems including wheezing, cough, and dyspnea (Table 1). Chronic symptoms of allergy including asthma and atopic dermatitis were present in 11 (52.4%) and five (23.8%) patients, respectively (Table 1).

History of allergic symptoms including urticaria, asthma, and/or rhinitis was negative in the parents of 15 patients (71.4%). Allergy was detected in both parents of four children (19%) and in one of the parents in two of the cases (9.5%). In nine of the cases (42%) the wheat prick test was 1+, exactly the same number as the 2+ prick test result (nine cases, 42%), compared to the 3+ test result in only one patient (4%).

Specific IgE (using ELISA method) was negative in four cases; in two (9.5%), three (14.3%), seven (33.3%), and three (14.3%) cases, this test was reported as 1+, 2+, 3+ and 4+, respectively. Serum specific IgE was not performed in two patients. (Figure 1)

The rye prick test result was negative in one patient. In four (22.2%), nine (50%), and four (22.2%) patients this test results were 1+, 2+ and 3+, respectively (totally 17 patients had a positive test results). In three patients, those test was not performed. The barley prick test results was negative in seven patients (38.8%); it was 1+ in 10 (55.6%) and 2+ in one (5.6%) patient.

The rice prick test results was negative in five cases (27.8%) and positive in 13 of the patients, of which 10 (55.6%) were 1+ and three (16.6%) were 2+. The corn prick test results was negative in four children (22.2%) compared to two groups of seven patients (33.8%), each having a 1+ and 2+ test result. The skin prick test results for oat showed negative in four (22.2%), 1+ in eight (44.8%), and 2+ in six (33.2%) of the children. Our results showed a significant relationship between the frequency of allergy in female patients and allergy in their parents ($p=0.0001$). Moreover, a significant relationship was detected between the

positive ELISA test and the female gender which may show a more severe reaction in the girls ($p<0.007$). A significant relationship was found between the chronic symptoms including asthma and eczema, and the degree of the positive ELISA test towards wheat; the more positive the ELISA test, the more severe the chronic symptoms ($p<0.0001$).

We also found that 8 out of 21 patients (44.4%) had positive skin prick test results towards other food allergens; three to eggs, one to soya, three to milk and one to nuts. Eight of the patients were followed for at least 6 years, three of whom had gained oral tolerance to wheat (37.5%). The mean age of occurrence of oral tolerance to wheat was 68 ± 6.36 (range: 36 months to 108 months).

DISCUSSION

Wheat is a very common protein source that is used widely and allergy to it can cause nutritional and

emotional problems for the children and their families.

It is commonly believed that allergic reaction to wheat is rarely severe.²¹ Some studies have shown that the most common clinical symptoms in children are atopic dermatitis with or without respiratory symptoms or digestive problems. Food-exercise induced anaphylaxis, anaphylactic shock, angioedema, the irritable bowel syndrome, eosinophilic esophagitis and few cases of ulcerative colitis or wheat induced headache are the symptoms described in adults.^{10,11,21,22} In other studies, it has been stated that allergy to wheat is more prevalent in children and infants than realized, but its signs and symptoms are usually manifested in patients as atopic dermatitis and are often mild.²³

However, Skripak et al found a frequently severe allergic reaction to wheat, with 45% of unintentional exposures resulting in anaphylaxis,²⁴ anaphylaxis was also a common manifestation of wheat allergy in our study.

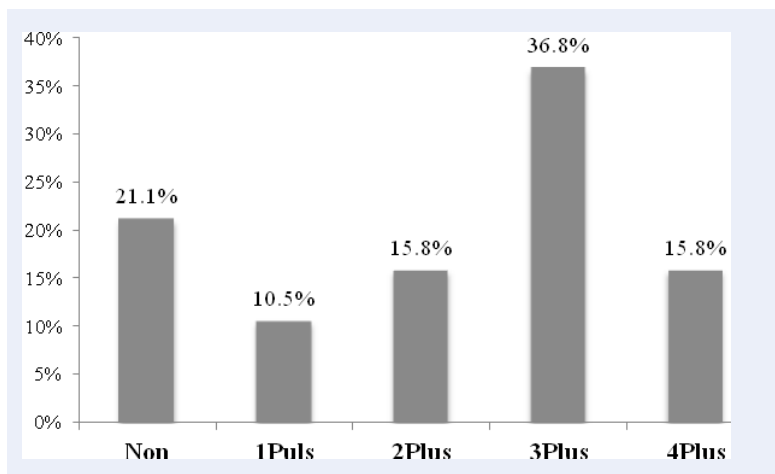


Figure 1. Distribution of the frequency of specific IgE (ELISA method) positivity rate to wheat allergens in patients with allergy to wheat

Table 2. Distribution of the frequency of skin prick test positivity rate to other cereals in wheat allergic patients (n=21)

Grading		Rice	Rye	Barley	Oat	Corn
Severity		n(%)	n(%)	n(%)	n(%)	n(%)
-	-	5 (27.8)	1 (5.6)	7 (38.8)	4 (22.2)	4 (22.2)
-	+	10 (55.6)	4 (22.2)	10 (55.6)	8 (44.4)	7 (38.8)
-	++	3 (16.6)	9 (50)	1 (5.6)	6 (33.2)	7 (38.8)
-	+++	0	4(22.2)	0	0	0

Follow-up of Wheat Allergy

As mentioned in the results, all our 21 patients showed different degrees of anaphylaxis within 15 to 30 minutes after ingestion of wheat. Even more than 90% of our patients experienced 3rd to 4th grade anaphylaxis signs and symptoms after the oral ingestion of wheat. More than 68% of the patients had positive wheat ELISA test results (2+ or more) which may show the severity of allergy in these patients.

As in the previous study reported by Pourpak et al¹⁶, in the current study we also noticed that the allergic clinical manifestations to wheat were very severe, which was not the case in other studies. The difference may firstly be related to the fact that our center is a referral hospital, and we have had to deal with more severe types of diseases. Secondly, it may be possible that the chronic or mild symptoms of wheat allergy are not taken serious enough or never diagnosed. Specific genetic backgrounds or different nutritional habits may also play role in this regard. To reach an accurate conclusion, a multi-center study is needed. We also found a strong association between allergy to wheat and asthma in our population, so that, more than 52.4% of patients had symptoms of asthma. There was also a positive relation between the rate of positive ELISA test results to wheat and between asthma and eczema in these patients, which might indicate the fact that the occurrence of chronic symptoms may be related to the severity of the disease. There are some reports of asthma associated with food allergy.^{25,26} However, the high rate of asthma associated with allergy to wheat in our studied population, may be related to a certain extent, to the fact that wheat is a member of grass family responsible for a large number of respiratory allergies⁸ and may also give us an idea that allergy to wheat may intrigue asthma and respiratory diseases in the future in the patients.

As stated in the results, similar to other allergic diseases, wheat allergy was more prevalent in the boys (almost twice as much as the girls). The early appearance of allergic manifestation to wheat coincided with the onset of complementary food which was often when the child was less than 6 months old. On the one other hand, this may show the necessity of starting complementary food after 6 months of age, but on the other hand, there are growing studies claiming that delaying initial exposure to cereal grains until after 6 months may increase the risk of developing wheat allergy and their results do not support delaying

introduction of cereal grains for protection against food allergy.²⁷ Rye was the most common cereal with a high degree of positive skin prick reaction but to draw any conclusion regarding the prevalence of simultaneous real rye allergy in patients with allergy to wheat, a higher population of patients and also an oral challenge test to rye may be necessary. Pourpak et al reported that, in spite of having positive specific IgE in Prick and ELISA test to rice and corn, their patients could tolerate these cereals by open food challenges²⁸ and proposed these cereals as the best cereal substitutes for wheat in patients with wheat allergy. This was also true in our newly diagnosed wheat-allergic patients. It is also claimed in the literature that most of the patients with allergy to wheat naturally tolerate gluten-free cereals, i.e. maize and rice and also oats, even though cross allergy between wheat and these cereals has been described²⁴. Additionally, 44.4% of our cases had positive skin prick test results to other foods which may again be indicative of the importance of allergy to wheat, being highly followed by allergy to other main foods. We detected a significant relationship between the female gender and the history of allergy in their parents and also a significant relationship between the female gender and the rate of positive ELISA test results, which might illustrate the severity of wheat allergy in the female gender.

Despite the high prevalence of wheat allergy, affecting 0.4% to 1% of children, relatively little is known about its natural history.²⁹ It has been stated in the previous studies that alimentary food allergy can be transient and may disappear with a few years of avoidance of culprit food and also with the increase of age.²² It was mentioned earlier that the possibility of acquisition of tolerance to food allergens varies widely by the food.³⁰⁻³³ In the cases of milk and egg allergy the prognosis was considered good. It is believed that only approximately 20% of children with peanut and tree nut allergy resolved by adulthood and regarding wheat allergy the prognosis was thought to be uncertain. The natural course of only a small number of patients with wheat allergy has been reported in the literature, and in these studies one-fourth to one-third of patients became tolerant in a 1- to 2-year period^{34,35}. In another study, Moneret-Vautrin et al reported at 2 years of age as the mean age for developing oral tolerance in wheat allergic patients³⁶ It is claimed that over the past two decades, food allergies have become both more prevalent and longer lasting.²⁴ In a large cohort study

reported by Keet et al, half of children with wheat allergy outgrew their allergy by 6 1/2 years of age (School age); and by 4 years of age, 29% had become tolerant; and by the age of 10 years, 62% had become tolerant. Thirty-five percent remained allergic during their teenage years.²⁹ In the present study, eight previously referred patients were evaluated with the age range of 96 months to 144 months. Oral tolerance occurred only in three patients (37.5%). Although our sample size was small, we observed that the minority of the patients (37.5%) outgrew wheat allergy. These results are in concordance with recently published studies in this regard and comparing other studies. We also noticed a more prolonged clinical course until outgrowing wheat allergy in our patients, as their age was between 8 to 12 years old at the time of the study. Our limitation in the study was the small size of the patients who were followed. For resolving wheat allergy, we propose that a multi-center study with more numerous wheat allergic patients to follow in a longer duration of time would be needed to draw a definite conclusion regarding the development of oral tolerance.

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