



# Oral Wheat Immunotherapy in a Patient with Anaphylaxis Despite Negative Sensitization Tests

Mahsa Rekabi<sup>1</sup>, Saba Arshi<sup>2</sup>, Sepideh Darougar<sup>1\*</sup>, Vahab Rekabi<sup>3</sup>, Mohammad Nabavi<sup>2</sup>, Morteza Fallahpour<sup>2</sup>, Mohammad Hassan Bemanian<sup>2</sup> and Abolfazl Rajabi<sup>4</sup>

<sup>1</sup>Pediatric Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>2</sup>Department of Allergy, Hazrate Rasoul Hospital, Iran University of Medical Sciences, Tehran, Iran

<sup>3</sup>Department of Molecular Pathology and Cytogenetics, Islamic Azad University of Medical Sciences, Tehran, Iran

<sup>4</sup>Department of Radiology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

\*Corresponding author: Pediatric Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran. Tel: +98-2127123000, Email: sepidehdarougar@yahoo.com.

Received 2018 August 14; Accepted 2018 October 21.

## Abstract

**Introduction:** Wheat allergy can develop at any stage of life. The aim of this report was to demonstrate that skin testing and specific IgE have poor specificities and sensitivities for wheat allergy.

**Case Presentation:** A 37-year-old female presented symptoms that were initiated immediately after consumption of bread and biscuits. She was well until two months prior to her recent admission. Her skin prick test, RIDA assay, and patch test for wheat showed negative results despite a history of two episodes of anaphylaxis. She underwent an oral food challenge, which confirmed wheat allergy. A desensitization procedure was recommended for her. At the end of the immunotherapy process, she had normal intake of wheat without any symptoms.

**Conclusions:** Negative sIgE and SPT results do not rule out clinical food allergy. Oral food challenges are still the cornerstone of diagnosis of food allergy.

**Keywords:** Wheat, Food Allergy, Desensitization, Oral Food Challenge, Oral Immunotherapy

## 1. Introduction

Food allergy is a general health problem in children and adults all over the world, affecting 5% of adults and if IgE-mediated, it is associated with a high risk of fatal anaphylaxis (1). Wheat is a widely consumed grain and it is estimated that almost a half of calories consumed by humans worldwide come from cereals, particularly wheat (2). Wheat has a high nutritional value and palatability (3). Gluten is a mixture of seed storage proteins found in wheat, which may trigger all kinds of gluten-related disorders (4). Gluten-related disorders, such as wheat allergy and celiac disease, are immune-mediated conditions, while non-celiac gluten sensitivity occurs as symptomatic adverse reactions, in which neither allergic nor autoimmune mechanisms are involved (5). Wheat allergy is known as an uncommon cause of food allergy in adults, particularly when addressing IgE-mediated mechanisms (6). However, wheat allergy can develop at any stage of life. Some people can eat bread for years without any ill effects and then suddenly one day develop symptoms of wheat al-

lergy due to a gradual build-up of wheat antibodies over time, which, by reaching a critical level, could develop into respiratory, gastrointestinal and skin reactions.

The aim of this report was to demonstrate that although skin testing and specific IgE are routinely used to identify sensitization to food, they have poor specificities and sensitivities for wheat allergy. Therefore, oral food challenge still acts as the gold standard for identification of real wheat allergy.

## 2. Case Presentation

A 37-year-old female was presented to the researchers' allergy clinic for symptoms that were apparently initiated immediately after consumption of bread and biscuits. She had an unremarkable medical history with normal developmental milestones during childhood. She was otherwise normal without any history of infantile gastrointestinal reflux or colitis, atopic dermatitis, allergic rhinitis, weight loss or chronic diarrhea during childhood, except

for a state of drowsiness and a sense of itching, which occurred following consumption of bread and biscuits. However, these objective symptoms were overlooked and she did not seek medical attention at that time.

She was well until two months prior to her recent admission at the age of 37 when she experienced itching, flushing, hypotension, arthralgia, and dizziness after eating bread and biscuits. Surprisingly, these symptoms were more prominent during winter and they were severe enough to be initiated even by opening of the biscuit box, without eating a piece. There was no similar history in other family members and her siblings. Her first anaphylactic episode manifested with generalized body itching, headache, breathing difficulty, hypotension (70/55 mmHg), and vomiting 20 minutes after eating a biscuit. She recovered completely from this anaphylactic episode yet continued to have two more attacks following bread consumption before presenting to the allergy clinic.

The patient underwent a thorough screening for infectious, hepatic, and metabolic disorders. Table 1 illustrates the results of some of the assays performed for the patient.

Celiac disease was excluded due to normal serology (Table 1). Her skin prick test was negative, showing no sensitivity, particularly to wheat and grass. The RIDA assay and patch test for wheat were also negative. Her pulmonary function test was normal. Nasal smear revealed no eosinophilia. Furthermore, C1q, anti-C1q, anti-LKM, and immune profile, including serum complement levels, were all normal.

Because of the existing discrepancy between history and test results, it was decided to perform an oral food challenge. The purpose of the challenge was simply to prove that the patient is allergic to wheat, despite her negative test results. The challenge was performed after taking a formal consent in a semi-intensive care unit with all necessary resuscitation equipment. The patient had an intravenous access established. Wheat and rice flour (as placebo) were prepared. The patient did not show any symptoms while receiving rice flour, yet during the administration of wheat, she developed erythematous skin rash (hives), hypotension, and abdominal pain. Therefore, the challenge was stopped and treatment for anaphylactic reaction was initiated. A desensitization procedure was recommended.

Oral immunotherapy was commenced with a starting dose of 0.01 mg of wheat protein, according to the OIT protocol shown in Table 2. During six months of desensitization, she had two episodes of anaphylaxis with signs and symptoms, including angioedema, flushing, hypotension, pruritic erythematous skin, arthralgia, and musculoskeletal complaints. At the end of the immunotherapy process, which lasted six months, she had normal intake of wheat without any symptoms. Then, a second challenge procedure

Table 1. Results of the Laboratory Tests

Test	Result	Reference Value
WBC, cell/micL	5.93	P = 56, L = 35, Mo = 7, E = 2
Hg, g/dL	14.3	
Platelet	315000	
FBS, mg/dL	88	70 - 110
BUN, mg/dL	16	5 - 23
Creatinine, mg/dL	0.8	0.6 - 1.2
Cholesterol, mg/dL	268	150 - 200
Triglyceride, mg/dL	132	30 - 200
AST, IU/L	18	Up to 40
ALT, IU/L	16	Up to 40
T3, ng/dL	105	60 - 220
T4, mcg/dL	7.5	4.5 - 12.5
TSH, micIU/mL	1.4	0.4 - 6.1
Prolactin, micIU/mL	149	30 - 819
Anti Endomysial Ab (IgG)	Negative titer	Up to 1/10
Anti Endomysial Ab (IgA)	Negative titer	Up to 1/10
Anti Gliadin Ab (IgA), U/mL	35	Up to 12
Anti Gliadin Ab (IgG), U/mL	1.2	Up to 12
Anti tissue transglutaminase, U/mL	3	< 12
IgA (serum), mg/dL	104.7	71 - 360
HBsAb, mIU/mL	505	≥ 10
Helicobacter (IgG), Au	31.2	< 20
Helicobacter (IgA), Au	38.9	< 20

was performed with all kinds of flour available in the market to assess tolerance induction. At this point, the patient tolerated all types of bread without any signs and symptoms.

### 3. Discussion

Wheat allergy is more common in children and according to the American College of Asthma, Allergy and Immunology, about 65% of children outgrow the allergy by the time they reach adolescence. The prevalence of wheat allergy is about 0.5%, worldwide (7). While the symptoms of wheat allergy are usually mild, in some cases it may become severe, although wheat has never been reported as the cause of fatal anaphylaxis (8). According to a study performed by Scibilia et al. wheat is an important food allergen in adults and should not be overlooked in this age group (6).

**Table 2.** Oral Desensitization Protocol Used for the Patient

Day	Dilution	1st Dose/Day	Last Dose	Final Dose	Solution, mg/cc
<b>First Phase: 0.02 g/mL (Semolina)</b>					
1-18	0.01 mg/cc	1 mL	10 mL	0.3 mg	10/1000
19-30	0.1 mg/cc	3 mL	10 mL	3 mg	100/1000
31-39	1 mg/cc	3 mL	10 mL	30 mg	1000/1000
40-48	2 mg/cc	6 mL	10 mL	60 mg	2000/1000
49-57	4 mg/cc	15 mL	10 mL	120 mg	4000/1000
58-120	4.5 mg/cc	25 mL	75 mL	1000 mg	4500/1000
Day	First Dose	Last Dose	Final Dose		
<b>Second Phase: 1-1.4, g (Pasta)</b>					
121-144	2 pastas	15 pastas twice a day	42 g		
145-200	15 pastas twice a day	100 pastas a day	70 g		

The diagnosis of wheat allergy is based on patient’s clinical history, detection of wheat-specific IgE, and on the results of food elimination diets and oral challenges (8). Once the patient is suspected to suffer from wheat allergy, the diagnosis should be confirmed by demonstration of wheat specific-IgE.

The clinical case presented in the current report showed negative skin prick test and RIDA, despite two episodes of anaphylactic reactions following ingestion of wheat. According to the literature, it is believed that wheat extract IgE testing has a low specificity (2) with a poor predicting value (1). Again, freshly made solution with wheat flour, which was prepared and used for skin test did not contain insoluble major wheat allergens, such as prolamins. In recent studies, component resolved diagnosis (CRD) has gained interest (1). Considering the role of major wheat allergens, which are relevant for inducing food allergy in Japanese and Swedish studies, Tri a 19, correlated better with OFC-proven IgE-mediated wheat allergy. However, this test was not approved by other studies. This test is not available in Iran. Less difficult blood tests, including Basophil Activation test are also not available in Iran. Since oral food challenge is a far more accurate test, it was performed to confirm a true allergic event. Furthermore, the efficient wheat oral immunotherapy protocol used for this patient with a history of multiple episodes of anaphylaxis following consumption of wheat products, demonstrates real food allergy, despite negative in vitro and in vivo tests.

### 3.1. Conclusion

This case confirms the difficulty in diagnosis of wheat allergy. Negative sIgE and SPT results do not rule out clinical food allergy. Also, the size of the skin prick test and the levels of specific IgE are not useful neither in diagnosis of wheat allergy nor in evaluation of wheat tolerance.

Despite the risk of severe allergic reactions with oral food challenges, they are still the cornerstone of diagnosis of food allergy and other tests should be considered as additional tools to aid in the diagnosis of food allergy.

### Footnotes

**Conflict of Interests:** None declared.

**Ethical Committee:** This research was confirmed by the Iranian Registry of Clinical Trials with registration reference of IRCT2013102015076N1. The study protocol was approved by the Ethics Committee of Iran University of Medical Sciences, Tehran, Iran. The dietary protocol was started after an informed written consent was obtained from the patient.

**Funding/Support:** There was no significant financial support for this work that could have influenced its outcome.

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