

THE EFFECT OF WHEAT ALLERGY ON THE COURSE OF ATOPIC ECZEMA IN PATIENTS OVER 14 YEARS OF AGE

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Summary: Few studies concerning the importance of wheat allergy affecting the course of atopic eczema in adolescents and adult patients exist. Aim: The evaluation if wheat allergy can deteriorate the course of atopic eczema. Follow-up of patients with confirmed food allergy to wheat. Method: Altogether 179 persons suffering from atopic eczema were included in the study: 51 men and 128 women entered the study with an average age of 26.2 (s.d. 9.5 years) Dermatological and allergological examinations were performed, including skin prick tests, atopy patch tests, and specific serum IgE for wheat, open exposure test and double-blind, placebo-controlled food challenge test with wheat flour. Results: Wheat allergy affecting the courses of atopic eczema was confirmed in eight patients (4.5%) out of 179 patients enrolled in this study by double-blind, placebo controlled food challenge test. The course of atopic eczema showed a positive trend in patients with confirmed food allergy at 3, 6, 9, 12 month follow-up (statistical evaluation with paired t-test) after the elimination of wheat flour. Conclusion: Wheat allergy may play an important role in the worsening of atopic eczema (acting as a triggering exacerbating factor) only in a minority of adolescents and adult patients (4.5% in our study). The diagnostic methods (skin prick test, specific IgE, atopy patch test, history) cannot be used as separated tests for the determination of food allergy to wheat in patients with atopic eczema. Open exposure tests and double-blind, placebo-controlled food challenge should be used for the confirmation of wheat allergy affecting the course of atopic eczema.

Key words: Atopic eczema; Wheat allergy; Specific IgE; Atopy patch tests; Skin prick tests; Challenge tests; Double-blind, placebo-controlled food challenge test

Introduction

Wheat allergy, which usually begins in early childhood, is outgrown by 3–5 years of age in most cases, as happens with egg and milk. The majority of wheat-allergic children concomitantly suffer from moderate-to-severe atopic eczema and sensitization to other foods such as milk and eggs (1, 2, 3, 4). In adults, food allergy to ingested wheat seems to be infrequent and especially described as an anaphylactic reaction for the most part induced by exercise (food-dependent, exercise-induced anaphylaxis – FDEIA, (3, 5, 6). In some cases, IgE-mediated allergy to wheat may lead to worsening of atopic eczema or gastrointestinal symptoms (7, 8). Adult – onset wheat allergies show a wide range of onset ages, up to the seventh decade, and are believed to mostly persist (9, 10). In the last couple of years, a few studies (11, 12, 13) regarding wheat allergy in patients sensitized through other routes than gastrointestinal tract have been reported (occupational asthma (so-called baker’s asthma) and rhinitis or contact urticaria).

Up to now, studies dealing with wheat allergy in adult patients suffering from atopic eczema are rare and the significance of food allergy regarding the course of atopic eczema

in adolescents and adult patients may be underestimated (14). A problem in the most published clinical evaluations of food allergy in patients suffering from atopic eczema is that eczema which usually worsens on the day after the oral food challenge or even later was not scored systematically before and the day after oral food challenges (15). The role of food allergens for eczematous reactions in atopic eczema with a diagnostic algorithm for the elucidation of such late reactions to foods was given in the position paper of the EAACI – European Academy of Allergy and Clinical Immunology (16).

Diagnosis of food allergy is based on personal history, measurement of specific IgE (serum specific IgE level – sIgE, skin prick tests – SPT), atopy patch tests (APT), challenge tests (open exposure test – OET, double-blind, placebo-controlled food challenge test – DBPCFC). DBPCFC always remains the golden standard in diagnosis of food allergy (17).

The aim of the study is the assessment of wheat allergy in patients over 14 years of age who are suffering from atopic eczema. In particular, we want to evaluate whether food allergy to wheat can deteriorate the course of atopic eczema. Our other aim is to follow-up patients with confirmed food

allergy to wheat by assessing the severity of atopic eczema during the 12 months following the elimination of a food allergen.

Methods

Patients over 14 years of age suffering from atopic eczema who were examined at the Department of Dermatology and Venereology, Faculty Hospital and Medical Faculty of Charles University, Hradec Králové, Czech Republic from January 2005 to September 2009 were included in the study.

The diagnosis of atopic eczema was made according to the Hanifin-Rajka criteria (18).

All patients included gave informed consent with the study and our study was approved by the appropriate ethics committee.

Personal history

The detailed personal history of possible food allergy was taken in all included patients.

The patients answered if they suffered from immediate or late food adverse reactions affecting the skin (itching, rash, urticaria, worsening of atopic eczema), affecting the gastrointestinal tract, or respiratory tract. The history of food-dependent, exercise – induced anaphylaxis (FDEIA), occupational asthma and rhinitis. Contact urticaria was also evaluated.

Examinations

Diagnostic work-up of food allergy to wheat in intervals with milder symptoms of atopic eczema (evaluated with SCORAD – Scoring Index of Atopic Dermatitis) was performed.

After the discontinuation of antihistamines and topical steroids for at least 5 days and systemic steroid therapy and phototherapy for at least two months, skin prick tests, atopy patch tests, and challenge tests (OET, DBPCFC) were performed. The serum level of the specific IgE to wheat flour was examined. The patient was allowed to treat himself with a low potency topical corticosteroid. No other anti-inflammatory substances were applied, nor was UV-therapy.

Skin prick test

Commercial food extracts Alyostal (Stallergens, France) with wheat was used for skin prick tests. SPTs were placed on the volar side of the forearm according to the extent of atopic eczema. SPTs were carried out by a standardized method using lancets with a 1 mm tip. The results were read after 15 minutes and were assessed by comparison with the wheal induced by histamine (10 mg/ml) and with negative control. A wheal with a diameter greater than 3 mm in comparison with a negative control was scored as positive.

Specific IgE

The serum level of the specific IgE to wheat was measured by CAP – (system FEIA – Fluorescent Enzymate Immune Assay – Pharmacia Diagnostics, Uppsala, Sweden). A level of specific IgE higher than 0.35 U/ml was assessed as positive.

Atopy patch tests

Atopy patch tests were performed on non-lesional, non-abraded, untreated skin of the back during remission.

A technique similar to conventional patch tests was used for atopy patch testing – CURATEST F strip (Lohmann & Rauscher International GmbH & Co. KG D-56579, Rengsdorf, Germany) with 12 mm cup size. Wheat powder was dissolved in distilled water (1 g/10 ml). Grading of positive APT reactions was similar to the criteria used in conventional contact allergy patch testing with the modifications of the European Task Force on Atopic Dermatitis (EFTAD) (19).

The diagnostic hypoallergenic diet

The diagnostic hypoallergenic diet was introduced following the patient's informed consent. We recommended the following foods to the patient over a period of four weeks: gluten free foods, potatoes, rice, meat – beef, pork, vegetable, and fruits only after thermal modification (because of cross reaction with pollen allergy). Parsley, celery, and seasoning were forbidden due to the fact that cross-reactive pollen allergens are not destroyed after thermal modification. The patients were allowed to drink only drinking water, mineral water, or black tea.

Patients recorded in special tables the symptoms of atopic eczema (the extent of skin involved, itching, and sleep disorder) and other potential health problems. The severity of atopic eczema was evaluated by the SCORAD system at the beginning of the study and then at the end of the specific hypoallergenic diet before the open exposure test and during the open exposure test up to 48 hours after the challenge.

When it was impossible to avoid steroids, the patient was allowed to treat himself with a low potency topical corticosteroid. No other anti-inflammatory substances, antihistamines, or UV-therapy were applied.

Open exposure test

Consecutively open exposure tests (OET) were performed after the elimination diet. This test was performed in intervals without symptoms or during a consistent period with regard to atopic eczema. The patient was allowed to treat himself with a low potency topical corticosteroid. It was recommended to make the oral provocation under the same conditions which the patient had during the diet. This diet was not recommended during pollen season in patients

suffering from pollen allergy and these patients were thus put on this diet in another season out of the year.

The OET with wheat was performed with wheat flour in the form of pasta (one dose = 200 g of pasta prepared from wheat flour and water given during 60 minutes in incremental dosages in intervals of 10 minutes) 3 times – at 8.00 a.m., 6.00 p.m., and 8.00 a.m. the next day.

The food challenge results were scored as positive if one or more of the following objective and subjective clinical reactions were noted: itching, rash, urticaria, angioedema, vomiting, wheezing, abdominal pain, diarrhea, pruritus, or worsening of atopic eczema (evaluated with SCORAD). Early reactions were defined as clinical symptoms within 2 hours after the ingestion of the dose in OET and late symptoms if occurring after more than 2 hours.

If the test with wheat flour was negative, the patient introduced wheat flour in the diet regimen. The severity of atopic eczema was evaluated during the average daily intake of wheat flour over a period of 3 months.

Double-blind, placebo-controlled food challenge (DBPCFC)

In the case the physician or the patient recording worsening of the atopic eczema or some other reactions during the open exposure test with wheat, the patient continued in the elimination of wheat. During the intervals with mild symptoms of atopic eczema the diagnosis of wheat allergy was defined with a higher precision by a double-blind, placebo-controlled food challenge. This test was performed with the use of lyophilised food and placebo (glucose) in gelatine capsules. Lyophilized wheat flour was blinded in opaque capsules. One capsule contained 250 mg of dried wheat flour. Three doses of capsules (31 capsules are in one dose) were administered at 8.00 a.m., 6.00 p.m., and 8.00 a.m. the next day. The first dose of DBPCFC was administered on an empty stomach under the supervision of a medical doctor: 1, 2, 4, 8, and 16 capsules with 15 minutes intervals (= altogether 31 capsules gradually administered during one dose). The second and third doses were served in a home setting. Early (two hours after the first dose) and later reactions were observed.

The diagnosis of food allergy was confirmed if a challenge with food was positive and negative with the placebo. The patient continued with the elimination diet if DBPCFC was positive. If the test result was negative, a tolerance to the food in diet was proved.

Scoring of atopic eczema

Severity of eczema was scored in agreement with SCORAD score, with assessment of topography items (affected skin area), intensity criteria (extent of erythema, oedema, crusts, excoriations, lichenification, xerosis), and subjective parameters (extent of itch and loss of sleep). The severity of atopic eczema was evaluated with SCORAD as mild if up

to 20 points, as moderate from 20 to 50 points, as severe if over 50 points.

The severity of atopic eczema was evaluated by the SCORAD at the beginning of the study before the specific hypoallergenic diet in all included patients (SCORAD I) and at the end of this diet in all included patients (SCORAD II). In patients with food allergy confirmed by DBPCFC, the severity of atopic eczema was evaluated in 3, 6, 9, and 12 months after elimination of wheat from the diet.

Statistics

Our study was evaluated statistically. Fisher´s exact test was used for the evaluation of the importance of the diagnostic method in diagnostic work-up of food allergy with regard to the results of DBPCFC with wheat flour.

The difference in SCORAD in patients with confirmed food allergy at 3, 6, 9, and 12-months follow-up was evaluated with a paired t-test.

Results

Altogether 179 persons suffering from atopic eczema were included in the study: 51 men and 128 women entered the study with an average age of 26.2 (s.d. 9.5 years), with a mean SCORAD of 32.9 points, s.d. 14.1 (max. 79.5 points, min. 12.5 points) at the beginning of the study.

All 179 patients were subjected to SPTs, APTs, sIgE and to OET with wheat flour. DBPCFC with wheat flour was done in patients with positive results in OET with wheat flour.

Our results were processed according the recommendation of the Standards for Reporting of Diagnostic Accuracy (STARD) initiative (20).

Tab. 1: shows the results of examinations with wheat flour in the diagnostic work-up of food allergy in comparison with the confirmed food allergy in open exposure tests and DBPCFC.

Examination	Result of the examination (no of patients out of 179)		No of patients with confirmed food allergy in OET (DBPCFC)
	Positive	Negative	
Atopy patch test	Positive	8	0, in 1 patient contact urticaria
	Negative	171	8
Skin prick test	Positive	20	2
	Negative	159	6
Specific serum IgE	Positive	8	5
	Negative	171	3
Open exposure test	Positive	16	8
	Negative	163	0
Personal history	Positive	8	4
	Negative	171	4

Personal history

Suspected food allergy to wheat was recorded in 8 patients as a possible cause of the worsening of atopic eczema, but only in four of them was it confirmed in OET and DBPCFC. On the other hand, the food allergy to wheat was confirmed in another 4 patients without the suspicion of this allergy.

Specific IgE, skin prick tests

Eight patients expressed specific IgE to wheat flour. DBPCFC confirmed allergy to wheat in five of them. Positive SPT reactions to wheat flour were recorded in 20 patients. DBPCFC confirmed the food allergy to wheat in two of them.

Atopy patch tests

Atopy patch tests were recorded as positive to wheat in eight patients, but food allergy in OET was not confirmed in these patients.

Open exposure test

The open exposure test was performed in 179 patients. A positive reaction in OET was recorded in 16 patients.

Double-blind, placebo-controlled food challenge (DBPCFC)

From 16 positive OET to wheat flour, the DBPCFC confirmed allergy to wheat flour in 5 patients. One man interrupted the DBPCFC, although food allergy is very probable. In another 2 women the DBPCFC was not done because of confirmed celiac disease and because of severe reaction in OET. Altogether, the wheat allergy was confirmed in 8 patients. In six patients the wheat allergy was contradicted. In one case the DBPCFC was not done because of pregnancy and in one patient there was an intolerance of gelatine capsules.

Evaluation of the severity of atopic eczema in patients with confirmed food allergy to wheat

Patients with confirmed food allergy in DBPCFC in 3, 6, 9, and 12 months after elimination of wheat flour from their diet were systematically scored and the severity of atopic eczema was evaluated in each of these periods and compared to the SCORAD before the diet. In all these patients a decrease in SCORAD was recorded and the difference in SCORAD was statistically significant in each of these periods.

In patients with negative reactions in open exposure test and in DBPCFC, the severity of atopic eczema was evaluated after introducing wheat flour into meals over a period of

3 months. No other reactions to wheat flour were observed in these patients.

The statistical evaluation of personal history, APT, SPT and sIgE for wheat flour

No relation was found between personal history and the positive outcome of DBPCFC, p-value = 0.159.

A relation between the results of specific IgE and DBPCFC was confirmed, p-value = 0.0027, but this result is considered as exploratory because of the small number of patients with positive results to wheat flour in DBPCFC.

No relation was found between the results in SPT and the positive outcome of DBPCFC, p-value = 0.371.

No relation was found between the results in atopy patch test and the positive outcome of DBPCFC, p-value = 1.

The statistical evaluation of SCORAD

The severity of atopic eczema in patients with confirmed food allergy at 3, 6, 9, and 12-months follow-up was evaluated with a paired t-test and the decrease in SCORAD is statistically significant in each of these periods (p-value = 0.018).

Discussion

Wheat ingestion can elicit typical IgE-mediated reactions of early onset, including urticaria, angioedema, bronchial obstruction, nausea and abdominal pain, or systemic anaphylaxis in severe cases. Delayed hypersensitivity symptoms appear about 24 hours after wheat ingestion and include gastrointestinal symptoms and exacerbation of atopic eczema (21, 22). Retrospective analyses by Niggemann and Breuer have shown that the patient's history of food related eczema does not have a high diagnostic importance (23, 24, 25). Sometimes foods induce clinical symptoms while being tolerated on other occasions. Physical exercise is one of the best-known augmentation factors. Other augmentation factors are drugs, alcohol, warm baths, hormonal factors, or stress (25). In our study, suspicion of food allergy to wheat in the history was recorded in eight patients as a possible cause of the worsening of atopic eczema, but food allergy in OET was confirmed only in four of them.

For IgE-mediated disorders, skin prick tests provide a rapid means to detect sensitization. However, a positive test response does not necessarily prove that the food is causal. Negative SPT responses usually confirm the absence of IgE-mediated allergic reactivity. A positive SPT response might be considered confirmatory when combined with a recent and clear history of a food-induced allergic reaction to the tested food (26, 27, 28). Serum tests to determine food-specific IgE antibodies (CAP System) provide another modality to evaluate IgE-mediated food allergy. Undetectable serum food-specific IgE levels might be associated with clinical reactions for 10 to 25% (26). As the diagnostic ac-

curacies of wheat SPTs and in-vitro IgE assays have been shown unsatisfactory (29, 30), the diagnosis of immediate wheat allergy is currently based almost exclusively on the results of oral food challenges. In our study, eight patients expressed specific IgE to wheat flour, DBPCFC confirmed allergy to wheat in five of them. Positive SPT reactions to wheat flour were recorded in 20 patients, although DBPCFC confirmed the food allergy to wheat only in two of them.

A number of investigators have examined the use of the atopy patch test in addition to skin prick tests for the diagnosis of non-IgE-mediated food allergy primarily in patients with atopic eczema and allergic eosinophilic esophagitis. Isolauri and Turjanmaa found a very good association between positive patch test results and late reaction to food allergen in children with atopic eczema (31). Recently, the prevalence and agreement with clinical history and specific IgE of positive APT reaction was investigated in 314 patients with atopic eczema in remission at 12 European centers (19). The authors stress that the clinical relevance of positive APT reactions is still to be proven by standardized provocation and avoidance tests and may also depend on the APT model.

The results of DBPCFC and OET in our study confirmed that food allergy to wheat in adult patients deteriorates the course of atopic eczema in 4.5% of patients. In this provocation test, early clinical responses are those reactions observed within 2 hours of the last administered dose. Late-phase reactions are those occurring between 2 and 48 hours. Generally, food challenges can cause three different patterns of clinical reactions to foods in patients with atopic eczema: 1. Noneczematous reactions/immediate-type reactions, the clinical symptoms of which include cutaneous symptoms such as pruritus, urticaria and rashes and/or noncutaneous gastrointestinal or respiratory symptoms or even anaphylaxis; 2. Isolated eczematous reactions/late reactions, e.g. flare-up after hours or even days; 3. A combination of noneczematous and eczematous reactions. In some previous publications, the eczematous reactions were defined as late (i.e. by time) or delayed (i.e. by mechanism) reactions (32). In order to distinguish eczematous responses clearly from early cutaneous reactions, the suspected food should be given over a period of 2 days. This provocation scheme was recommended for the detection of 'true' eczematous late-phase reactions by the German Society of Allergology and Clinical Immunology (33).

In the study of Scibilia (34), the number of subjects with a history of wheat allergy who have a genuine allergy by double-blind, placebo-controlled food challenge was shown. Thirty-seven double-blind, placebo-controlled wheat challenges were performed on 27 patients. A total of 13 out of 27 (48%) patients had a positive result. Specific IgE was more sensitive than skin test for wheat; however, specificity and predictive values were low for both tests. Thus, these tests should not be used to validate the diagnosis of wheat allergy. Similar results were obtained in our study as well.

Our study was analyzed statistically. It is concluded a pilot study. We confirmed that in the diagnosis of food al-

lergy affecting the course of atopic eczema DBPCFC is the most important examination.

Conclusion

Wheat allergy may play an important role in the worsening of atopic eczema (acting as a triggering exacerbating factor) only in a minority of adolescents and adult patients (4.5% in our study). This study shows that the diagnostic methods (skin prick tests, specific IgE, atopy patch tests, history) cannot be used as separated tests for the determination of food allergy in patients with atopic eczema. DBPCFC may help to prevent unnecessary restrictive diets that are not based on a proper diagnosis and may lead to malnutrition and additional stress on patients suffering from atopic eczema.

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Received: 25/04/2011

Accepted in revised form: 01/11/2011

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