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Original article

Wheat allergy: diagnostic accuracy of skin prick and patch tests and specific IgE

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Background: Food allergy makes an important contribution to the pathogenesis of atopic eczema in infants. However, clinical data on cereal allergy are scanty. The objective was to study the relevance of patch testing, skin prick tests, and the concentration of wheat-specific IgE antibodies (CAP RAST) in correlation with oral wheat challenge in infants with suspected wheat allergy. In particular, we aimed to determine whether the patch test could increase the diagnostic accuracy in detecting wheat allergy.

Methods: The study material comprised 39 infants under the age of 2 years. Of these patients, 36 were suffering from atopic eczema and three had only gastrointestinal symptoms. The patients were subjected to a double-blind, placebo-controlled or open wheat challenge. Wheat-specific IgE was measured by CAP RAST, and skin prick and patch tests were performed.

Results: Of the total 39 wheat challenges, 22 (56%) were positive. Of the positive reactions, five involved immediate-type skin reactions over a period of 2 h from the commencement of the challenge. In 17 patients, delayed-onset reactions of eczematous or gastrointestinal type appeared. Of the infants with challenge-proven wheat allergy, 20% showed elevated IgE concentrations to wheat, 23% had a positive skin prick test, and 86% had a positive patch test for wheat. The specificities of CAP RAST, skin prick tests, and patch tests were 0.93, 1.00, and 0.35, respectively.

Conclusions: Our study demonstrated that patch testing with cereals will significantly increase the probability of early detection of cereal allergy in infants with atopic eczema and is helpful in the planning of successful elimination diets before challenge. The specificity of the patch test was lower than that of other tests. Therefore, confirmation of the diagnosis with the elimination-challenge test is essential in patients with positive patch test results.

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Food allergy is a common problem in infants and small children, and makes an important contribution to the pathogenesis of atopic eczema in these patients. In food allergy, frequently manifested in infancy as skin or gastrointestinal symptoms, elimination diets result in clinical improvement (1–6). However, demonstrating that certain foods exacerbate eczema is laborious. Despite advances in the understanding of the mechanisms, the diagnostic accuracy of the methods of early detection of clinically significant food allergy is poor (7). In the diagnosis of adverse reactions to foods, the clinical history is often unreliable and, to date, there are no skin tests or other laboratory tests that will confirm or exclude food allergy with certainty (8, 9).

In this study, we evaluated the diagnostic accuracy of skin prick and patch tests and RAST for the clinical reaction to oral wheat challenge in infants with suspected cereal allergy. In particular, we aimed to determine whether patch test could increase diagnostic accuracy in detecting wheat allergy.

Material and methods

Patients

The study material comprised 39 infants (29 boys, 10 girls) under the age of 2 years (mean 1.4 years). They were allocated in 1996–7 to a double-blind, placebo-controlled or open wheat challenge on the basis of suspected wheat allergy at the Department of Dermatology or Department of Pediatrics of Tampere University Hospital. Children who had had immediate-type reactions to wheat were primarily challenged in the open challenge and those with delayed-type reactions in the double-blind challenge. The patients were suffering from atopic eczema ($n=36$) or gastrointestinal symptoms such as vomiting, loose stools, and diarrhea ($n=3$). In 20 patients, both atopic eczema and gastrointestinal symptoms were seen. Prick test and/or RAST for egg and cow's milk were positive in 14 (36%) and nine (23%) patients, respectively. Challenge-proven cow's milk allergy was found in eight patients.

The mean (SD) age at onset of symptoms was 3.7 (2.5) months. There was a positive family history of atopic disorders in 31 (80%) cases. The median (range) durations of exclusive and total breast-feeding were 4 (0–6) months and 7 (0–14) months, respectively. The median (range) time from the onset of symptoms to the clinical challenge was 1.2 (0.4–1.9) years.

Determination of serum IgE and skin prick and patch testing

The serum total IgE concentration and wheat-specific IgE (CAP RAST Pharmacia, Uppsala, Sweden) were measured, and skin prick and patch tests for wheat and various other foods (e.g., cow's milk, soybean, egg, and cereals) were performed. Prick and patch testing were performed as described previously (10). Antihistamine medication was discontinued for periods of 3 days to 6 weeks before skin testing, depending on the drug's duration of action. Prick testing was done on the volar aspect of the forearm with commercially available cow's milk, egg, fish, soybean, and pea allergens of ALK (Allergologisk Laboratorium A/S, Hørsholm, Denmark); 200 mg of cereal flours (wheat, barley, rye, oats, buckwheat); and soy flour diluted in 0.3 ml physiologic saline. Corn was tested with fresh kernels of corn, millet, and rice in flakes dampened with saline. Histamine dihydrochloride 10 mg/ml (ALK) was used as a positive control. Reactions were read after 15 min, and a response was recorded as positive if the mean diameter of the wheal was at least 3 mm and the negative control was 0 at the same time.

For patch testing each day, a "porridge" was made with 0.2 ml isotonic saline solution, milk powder (300 mg), lyophilized egg white (40 mg), and 200 mg of wheat, barley, rye, oats, and soy flour. Approximately 20 mg of each "porridge" was put into aluminum test cups (Finn Chamber, Epitest Ltd, Hyrylä, Finland) and attached to uninvolved skin of the back with Scanpore tape. Microcrystalline cellulose was used as a negative control. The occlusion time of patch testing was 48 h. The results were read for the first time 15 min after removal of the cups (day 2). The second reading was done 72 h after attaching the patches (day 3). In a negative reaction, there was neither a visible nor a palpable change on the skin. Clear redness with palpable infiltration was defined as a positive reaction. This type of reaction tended to grow stronger by the next examination. Irritation reaction included redness with no infiltration. The reaction tended to become weaker by the next examination.

Double-blind, placebo-controlled wheat challenge and open wheat challenge protocol

The patients were subjected to double-blind, placebo-controlled wheat challenge ($n=24$) or open ($n=15$) wheat challenge. Before challenge, the patients spent at least 3–4 weeks on a cereal elimination diet, avoiding wheat, barley, rye, and oats. On the first day of the challenge, rising doses of

the allocated placebo or test formula (1, 5, 10, 20, 50 ml) were given at 30-min intervals. The placebo formula was the amino acid-derived Neocate (SHS Int. Ltd, Liverpool, UK), and the test formula consisted of 5 g Neocate and 10 g wheat flour/100 ml water. The placebo and the test formula preparations looked alike. This preparation is not as good as the preparation in our previous studies for cow's milk challenge (21). Cow's milk powder is easier to mix with Neocate than wheat flour. However, it is difficult to determine whether the preparation is placebo or wheat-containing. A randomization scheme was used to fix the sequence of the challenges so that both the nursing staff, the attending dermatologist, and the parents were unaware of the administered formula's nature. The open challenges were made with the same test formula as in the double-blind, placebo-controlled test protocol. The daily dose at home was 10 g wheat flour mixed with food.

The formulas were prepared and coded in the hospital's milk bank for daily administration. The challenge period was 1 week for both the placebo and the test formula. The challenge was begun in hospital. If no reaction occurred within 3 h in hospital, the challenge was continued at home. For 7 days after commencement of challenge with the placebo or the test formula, the parents recorded any clinical symptoms, specifically skin eruptions and pruritus and gastrointestinal symptoms. When a clinical reaction appeared, the challenge was stopped, and the patients were examined in hospital. All patients were examined on day 7 and those tested with a double-blind challenge also on day 14 of the challenge, and the code was thereafter removed. In two patients, the open challenge period was 2 weeks due to delayed reactions to the challenge. If there were no symptoms during the first challenge week, the next challenge was begun the next week. If there were symptoms during the first week, they were first treated and the next challenge begun thereafter. In this case, the washout period was approximately 1 week.

To judge long-term tolerance and reveal any false-negative result of challenge, all patients negative to wheat challenge continued to consume wheat at home. In patients positive to wheat challenge, wheat was eliminated from the diet. There was a favorable clinical response to the wheat-elimination diet in all patients with challenge-proven wheat allergy.

Statistics

The descriptive values of variables were expressed as means and standard deviations (SD), or as medians and ranges or percentages. Sensitivity, specificity, and positive and nega-

tive predictive values of the tests are presented with 95% confidence intervals (CI).

Ethics

The study protocol was approved by the ethical review committee of Tampere University Hospital.

Results

Of the 39 wheat challenges performed, 22 (56%) were positive. All placebo challenges were negative. Of these 22 positive reactions, 16 occurred within double-blind challenge and six during open wheat challenge. Of the positive reactions, five (23%) involved immediate-type urticaria over a period of 2 h from the commencement of the challenge. The mean (SD) dose and time until reaction were 30.6 (27.5) ml and 0.9 (0.6) h, respectively.

Seventeen (77%) patients exhibited delayed-onset reactions of eczematous or gastrointestinal type. Of these, six patients manifested atopic eczema, one patient diarrhea, and 10 patients both atopic eczema and gastrointestinal symptoms. The mean (SD) dose and time until reaction in 15 patients were 161 (71) ml and 21 (9.4) h, respectively. In two patients, the reaction appeared 1 week after the commencement of the challenge.

Of the infants with challenge-proven wheat allergy, 20% (4/20) showed elevated IgE concentrations to wheat (range, 0.7–6.5 kU/l). Of these four patients, two manifested immediate-type reactions and two delayed-type reactions to the challenge. The wheat-specific IgE was not determined for two patients.

In patients positive to challenge, 23% (5/22) had positive skin prick test for wheat. Two patients showing prick test positivity reacted during the first 2 h to challenge. In three patients, prick test positivity was associated with a delayed-type reaction.

False positive prick and RAST tests were very uncommon. Positive RAST and prick tests were associated with negative oral challenge in 7% (1/14) and 0% of the cases, respectively. False negative prick and RAST test results were much more common.

The skin patch test for wheat was positive in 86% (19/22) of patients with positive wheat challenge. A positive patch test for wheat was associated in five cases with immediate-type reaction and in 14 cases with delayed-type reaction. In 13 patients with patch test positivity, prick test and RAST for wheat were negative.

Table 1. Sensitivity, specificity, and positive and negative predictive values of RAST, skin prick tests, and patch tests for wheat in relation to clinical response to double-blind, placebo-controlled and open wheat challenge in 39 infants with suspected cereal allergy

Test	Sensitivity (95% CI)	Specificity (95% CI)	Predictive value	
			Positive (95% CI)	Negative (95% CI)
RAST	0.20 (0.07–0.44)	0.93 (0.66–1.00)	0.80 (0.28–0.99)	0.45 (0.26–0.64)
Prick	0.23 (0.09–0.46)	1.00 (0.80–0.99)	1.00 (0.48–0.98)	0.50 (0.33–0.68)
Patch	0.86 (0.65–0.97)	0.35 (0.14–0.62)	0.63 (0.44–0.80)	0.67 (0.30–0.93)

The mean serum total IgE was 43 (range, 5–234) kU/l. In nine infants, the concentration of total IgE was below 5 kU/l. In four of these nine infants, all the tests for wheat (challenge, RAST, prick, and patch) were negative. Altogether, 9% (2/22) of the patients with challenge-proven wheat allergy did not react to skin testing or RAST to wheat. Patch testing was a much more sensitive method to diagnose wheat allergy in these patients than skin prick test and RAST. However, specificity was lower. Table 1 presents the sensitivity, specificity, and predictive values of RAST and skin test results in relation to the clinical response to oral wheat challenge.

Table 2 presents prick and patch test and RAST results for egg, cow’s milk, and cereals in this study population. Egg allergy was common in these infants. Wheat, barley, and rye seemed to be often simultaneously positive in patch tests, whereas oats seemed to have less allergenic properties.

In patients positive to wheat challenge, the prick tests for wheat, barley, rye, oats, cow’s milk, and egg were positive in 23%, 14%, 14%, 9%, 18%, and 27%, respectively. Patch test positivity for these foods in patients positive to wheat challenge was seen in 86%, 73%, 77%, 50%, 27%, and 27%, respectively.

Discussion

Polysensitization to various foods appears to be more common than generally believed among infants with atopic eczema (10). However, allergy to ingested cereals has been investigated less extensively than cow’s milk allergy, which is commonly the first manifestation of allergic symptomatology (11). The lack of epidemiologic

Table 2. Number (%) of positive reactions in RAST, skin prick tests, and patch tests for cereals, cow’s milk, and egg in 39 children with suspected wheat allergy

	RAST (%) n=27–36	Prick (%) n=39	Patch (%) n=39
Wheat	5/34 (15)	5 (13)	30 (77)
Barley	4/27 (15)	3 (8)	27 (69)
Rye	6/27 (22)	3 (8)	27 (69)
Oats	2/27 (7)	2 (5)	18 (46)
Cow’s milk	9/36 (25)	5 (13)	10 (26)
Egg	11/29 (38)	10 (26)	11 (28)

studies on cereal allergy makes it difficult to estimate the prevalence of allergic manifestations to them.

Wheat belongs to the group of foods including egg, milk, peanut, and soybean which causes most frequently allergic reactions, and hypersensitivity to wheat accounts for most grain reactivity among patients with food allergies (5, 12). Cereal allergy is common in infants with atopic eczema or cow’s milk and egg allergy, and should be suspected in children not responding properly to cow’s milk and egg elimination diet (10, 13–15).

In the diagnosis of adverse reactions to foods, the clinical history is often unreliable, and, to date, there are no skin tests or other laboratory tests that will confirm or exclude food allergy with certainty (8, 9). Demonstration of food-specific IgE antibodies either with RAST or with skin prick tests refers to IgE-mediated food allergy. In infants under the age of 1 year, the tests suggest relevant food allergy because at this age the secondary development of tolerance has hardly taken place yet (1). In older children, the relevance of RAST and skin test has to be confirmed by elimination challenge because of false positive test results (12, 16). This is partly due to the fact that the tests remain positive after the patient has become tolerant to the food in question. Skin prick test and RAST are of limited use in cases of food allergy not related to an IgE-mediated mechanism. In these cases, a negative test result does not imply that the individual is not sensitized.

Delayed reactions in food allergy are poorly understood. Cell-mediated reactions may be responsible for delayed-type symptoms (17, 18). A specific T-cell-mediated immune response to casein has been reported in the blood of adult patients with milk-related exacerbation of atopic dermatitis (18). We have previously shown that the concentration of TNF-α in feces was elevated particularly in patients manifesting delayed-type reactions to cow’s milk challenge and in cow’s milk-allergic infants before elimination diet (4,

19). These results confirm previous findings that distinct immunologic mechanisms are involved in different clinical manifestations and reaction types of food allergy. The delayed-type allergy to foods may also be an IgE-mediated allergy, even in cases with low total IgE and no detectable specific IgE to foods. The reactions may occur via high-affinity IgE receptors expressed on Langerhans' and dendritic cells, leading to allergen-specific T-cell responses capable of promoting IgE production and delayed-type hypersensitivity reactions (20).

Räsänen et al. (14) found that skin patch tests and lymphocyte proliferation tests were more often positive in children exhibiting delayed-type reactions, whereas the skin prick test and the basophil histamine-release test were more often positive in children manifesting immediate-type reactions to cow's milk. Previous reports have suggested that combining prick and patch tests with food antigens will increase the probability of early diagnosis of food allergy in infants with atopic eczema (10, 13, 14, 21). In the present study, patch testing was a much more sensitive method to diagnose wheat allergy than RAST or prick test in infants with atopic eczema. The patch test was positive for wheat in 86% of patients manifesting positive clinical reactions to wheat challenge. The specificity was lower, a finding which is in agreement with our previous study in infants with cow's milk allergy (22). Therefore, confirmation of the diagnosis with the elimination-challenge test is essential in patients with positive patch test results. One explanation for the low specificity is that some of the patients had become tolerant because there was a delay from the onset of symptoms and clinical diagnosis to the wheat challenge. In two patients, delayed reaction after 1 week from the commencement of the challenge was found. Thus, larger daily amounts of wheat might be useful in the challenge protocol.

Egg allergy was common in these infants. Wheat, barley, and rye seemed to be often simultaneously positive in patch tests, whereas oats seemed to have less allergenic properties, a finding which is in agreement with a previous study (23). Oats is often the first of the cereals to which the previously allergic patients lose their hypersensitivity. The percentage of wheat sensitivity reported here, i.e., 56%, is high. Our patient population was selected to include infants with suspected wheat allergy. We assume that wheat allergy is more common than previously reported, and that it is often underdiagnosed because of low sensitivity of skin prick testing.

Food allergy in infants is considered the main cause of atopic eczema (1–6), while in older persons there are several pathogenetic mechanisms that may influence the clinical course of the disease. When symptoms appear for the first time during the first year of life, it is probable that basic foods such as milk, egg, and cereals are responsible. No single laboratory test is currently capable of providing a definite diagnosis of food allergy.

We have found an extensive panel of skin tests to be beneficial in selecting suitable diets for infants with atopic eczema and/or gastrointestinal symptoms to render them symptomless for oral food challenge tests. In our hospital, all children with atopic eczema under the age of 2 years are routinely tested with RAST, skin prick tests, and patch tests. Our results indicate that patch testing with cereals will significantly increase the probability of early detection of cereal allergy in infants.

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