

Sensitization to cereal allergens in children with atopic dermatitis

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Abstract

Introduction: Allergy to grain proteins affects approximately 14–18% of patients with atopic dermatitis and usually manifests in late reactions and symptoms of the skin and gastrointestinal tract.

Aim: To evaluate the prevalence of allergy to cereals in children with atopic dermatitis, its impact on the course of the disease and the coexistence of sensitization to food and other airborne allergens.

Material and methods: The study included 61 children with atopic dermatitis. Diagnosis of sensitization to cereal allergens was carried out on the basis of skin prick tests, determination of specific IgE, and atopy patch tests.

Results: Twenty-six children (43%) had sensitization to cereal allergens. The other 35 patients were enrolled in the control group. In the study group, immediate-type reactions were confirmed in 46% of patients, late-type in 65%. The most common was allergy to proteins of wheat and rye. There were no significant differences between the SCORAD, peripheral blood eosinophilia and total IgE in the study and control group. There was also more frequent sensitization to other inhalant and food allergens, allergic rhinitis and asthma in the investigated group of children.

Conclusions:

1. Sensitization to cereal allergens is a common phenomenon in children with atopic dermatitis and should be taken into account in the diagnostic process.
2. There was no relationship between the occurrence of sensitization to these allergens and the severity of skin lesions assessed by the SCORAD scale.
3. For children who are allergic to cereal proteins, there is not predisposition to hypersensitivity to pollen allergens and rhinitis or bronchial asthma.
4. In the case of positive results of allergy to cereal proteins and severe exacerbations of atopic dermatitis there should be considered some attempts of elimination and provocation tests.

Key words: cereal allergens, atopic dermatitis.

Introduction

Allergy to grain products, with the prevalence of consumption, is a frequent phenomenon depending on the form of exposure and participation of immune mechanisms. It can cause symptoms of the skin, gastrointestinal and respiratory tract, such as atopic dermatitis, urticaria, rhinitis, baker's asthma or exercise-induced anaphylaxis [1]. In most of these diseases IgE-dependent immunological mechanisms play a major role. Moreover, the consequence of gluten consumption can be coeliac disease, T-cell colitis, or dermatitis herpetiformis. The incidence of allergy to cereal proteins is estimated to be 4% in the population of children aged up to 4 years [2] and increases to 2–9% in children

under 10 years of age [3]. It is believed that IgE-mediated allergy to the protein components of cereal is primary in early childhood and secondary in relation to pollen allergy in older children. The average age at which children reach clinical tolerance to cereal protein is between 5 and 8 years [4].

Observations made by Majamaa *et al.* show that allergy to wheat may also have the nature of a late response, especially in patients with atopic dermatitis. Studies have shown that positive atopy patch tests with cereal allergens were found in more than half of children with a positive oral food challenge [5].

Atopic dermatitis is one of the most common forms of clinical manifestations of food hypersensitivity in young

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children. The spectrum of harmful allergens is variable depending on the age of the patient. In the youngest are milk and its products, and egg white. In older children it is dominated by allergy to foods of plant origin such as citrus fruits, peanuts, and soybeans.

Allergy diagnosis of atopic dermatitis is based mostly on studies that allow detection of immediate (skin tests, specific IgE) or late-type allergy (atopy patch test) [6]. Although these studies consider cereal allergens, there are no reports about the incidence and impact of sensitization to these allergens in patients with atopic dermatitis. This information appears to be important, because quite often there are cases of treatment of atopic dermatitis with a gluten-free diet, by primary care physicians. This is due to the fact that cereal proteins, especially wheat, are among the main food allergens [7]. Allergy to cereal proteins is associated with an allergy to pollen and induction of skin lesions and exacerbation of asthma or allergic rhinitis. It is believed that the nature of the complaints are primarily affected by the way of penetration of allergens into the body (oral, contact, airborne) [5].

Aim

To assess the prevalence of allergy to cereals in children with atopic dermatitis, its impact on the course of the disease and the coexistence of sensitization to other food allergens and airborne allergens.

Material and methods

The prospective study included 61 children (23 girls, 38 boys) aged from 5 months to 16 years, diagnosed with atopic dermatitis according to the criteria of Sampson for infants [8] and Hanifin and Rajka for children over 1 year of age [9] and personal history indicating the relationship of skin lesions and the harmful effects of food and/or airborne allergens. Exclusion criteria were as follows: the extent and severity of skin lesions including their presence on the back and forearms, preventing the procedure of skin prick tests and patch tests, the supply of antihistamine and anti-allergic drugs (including systemic corticosteroids) during the study and in the period immediately preceding it (depending on the half-life of certain drugs) and the use of back and forearm skin ointments containing corticosteroids.

In order to determine the allergic background of the skin lesions and spectrum of allergens and allergic type reactions (immediate, late) diagnostic tests were performed (skin prick tests, patch tests, determination of allergen-specific IgE antibodies).

Skin tests with native food allergens were performed in all children tested by prick to prick, according to the rules developed by the European Academy of Allergology and Clinical Immunology (EAACI) [10]. Sensitization to

aeroallergens was detected using the skin prick tests with standardized, commercial Allergopharma allergens (house dust mites and flour, cat dander, dog, grass pollen, trees, weeds, rye, mould). The result was read after 15 min, treated as a positive reaction when wheal diameter > 3 mm.

Atopy patch tests were performed according to rules developed by Isolauri and Turjanmaa [11]. Tests were performed using standard patch testing with aluminium chambers with an inside diameter of 8 mm (for children under 3 years) and 12 mm (for older children) (Finn Chamber, Epitest Ltd., Finland) with native allergens milk, egg, soy, cereals (wheat, rye, barley, oats, corn, rice, gliadin), and peanuts. The negative control was a microcrystalline cellulose. The results were read after 48 h (assumed to remove allergens from the surface of the back and the initial reading after 15 min) and 72 h (final reading). The test result was interpreted in accordance with the principles of reading by the standards of the EAACI [11].

Serum samples (2 ml) were analysed for concentration of total IgE and specific IgE antibodies to food allergens (Pharmacia Upjohn) with a fluoroimmunoenzymatic assay (UniCAP) according to the manufacturer's instructions. The detection limit of the CAP system is 0.35 kU/l IgE; measurable specific IgE was defined as a positive test result if > 0.7 kU/l.

In order to differentiate allergy to corn from coeliac disease, we performed tests of antibodies to tissue transglutaminase (tTgA).

Further statistical and clinical analysis was conducted in a group of 26 children (42.6%) who had one of the chosen laboratory tests that confirmed sensitization to cereal allergens. The control group comprised the remaining 35 children (15 girls, 20 boys) with atopic dermatitis who had not been confirmed in additional studies to have allergy to wheat.

Analysis of the patients was performed not only to assess the prevalence of allergy to cereals, but also to other food and inhalant allergens, severity of skin lesions, the coexistence of other allergic diseases, and family history of atopy. The activity of the disease process was evaluated based on the SCORAD scale (scoring atopic dermatitis), which takes into account the topography, severity of skin lesions and subjective symptoms (itching, sleep disturbance) [12].

Statistical analysis

The results were statistically analysed. The distribution of values for each parameter in the examined patients and in each group was reported using the mean (\bar{x}), standard deviation (SD), minimum (min) and maximum (max) value, and median (Me). Due to the lack of normal distribution of the parameters in statistical inference, we used nonparametric methods. Assessment of the differences in the distribution of quantitative vari-

ables between the two groups of patients was performed using the Mann-Whitney test.

All the hypotheses were verified at the level of statistical significance $p = 0.05$. Most of the calculations were carried out based on the statistical package Statistica 9.0, StatSoft.

Results

The study included 61 children with atopic dermatitis. Twenty-six (43%) of them, on the basis of additional studies, were allergic to cereal allergens tested (study group). The remaining patients with negative test results were classified in the control group. Both groups were comparable in terms of age (3.88 ± 3.28 years of age vs. 5.33 ± 4.30 years) and gender.

Analysis of the history of the prevalence of atopic dermatitis in the families of the patients showed a statistically more common disease burden in the control group than in the study group (7% vs. 37%, $p = 0.008$). In other allergic diseases (allergic rhinitis, bronchial asthma, food and contact allergy) no statistically significant differences were found.

An analysis of patients in terms of co-occurrence of other allergic diseases was performed. There were no statistically significant differences in prevalence of allergic rhinitis and asthma between the study and control group ($p = 0.703$ and $p = 0.176$). Isolated occurrence of atopic dermatitis without concurrent symptoms from other organs and systems was found in the same proportion (34%) of children in the study and control group. Detailed data are shown in Table 1.

Analysis of the severity of the disease as measured by the SCORAD scale showed no statistically significant differences in children with allergy to corn in comparison to the control group (Fig. 1).

Both in terms of total IgE levels and peripheral blood eosinophilia there were no statistically significant differ-

ences (Figs. 2, 3). Patients who are allergic to corn had immediate-type reactions to allergens of cereals in 46% of respondents, and delayed in 65%. Specific IgE antibodies were mostly positive for wheat glycoprotein (31%); sensitization to rice and maize proteins was also reported.

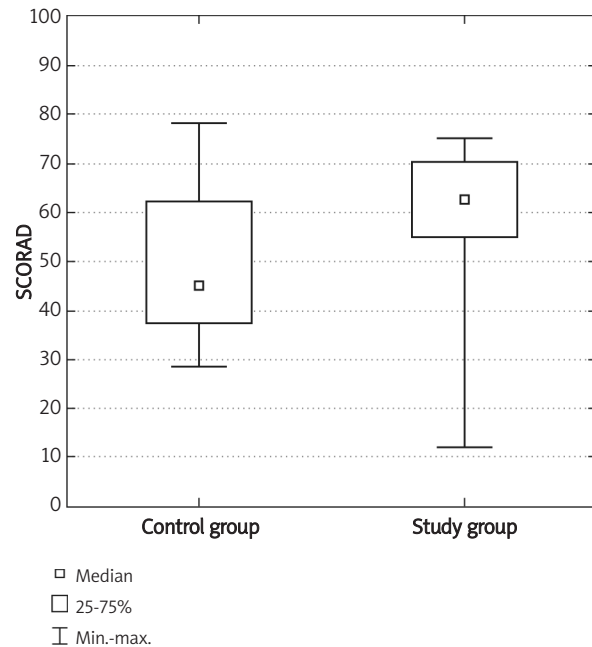


Fig. 1. Comparison of the severity of skin lesions according to the SCORAD scale in the study and control group

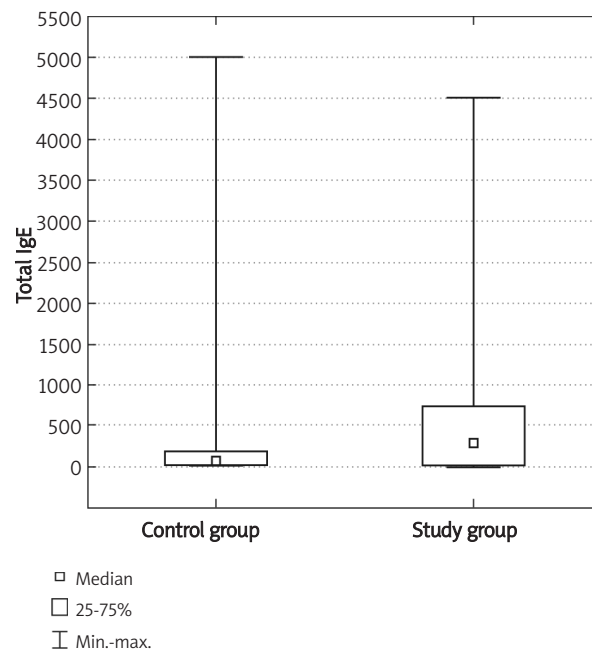


Fig. 2. Comparison of total IgE level in the control and study group

Tab. 1. Characteristics of the study and control group

Examined parameter	Study group (n = 26)	Control group (n = 35)	Value of p
Gender (boys)	18%	20%	0.344
Age [years]	3.88 ± 3.28	5.33 ± 4.30	0.175
Family history:			
atopic dermatitis	7.69%	37.14%	0.008
other allergic diseases	50.0%	57.14%	0.580
Other clinical symptoms:			
allergic rhinitis	26.92%	31.43%	0.703
asthma	3.85%	14.29%	0.176
gastro-oesophageal reflux	23.7%	28.6%	0.411

The patch tests showed the most frequent allergy to rye. The coexistence of sensitization to other cereal proteins was found in 71% of patients with positive patch tests, mostly for wheat and maize. Other food allergens which identified the presence of allergen-specific IgE antibodies or positive patch tests were: milk, eggs, soy, and nuts (Fig. 4).

In terms of sensitization to airborne allergens, positive specific IgE antibodies to allergens of trees and grass

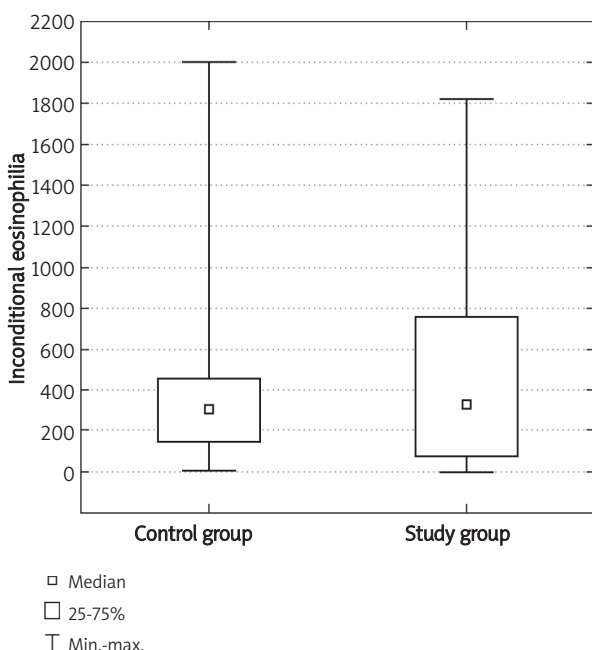


Fig. 3. Comparison of peripheral blood eosinophilia in the control and study group

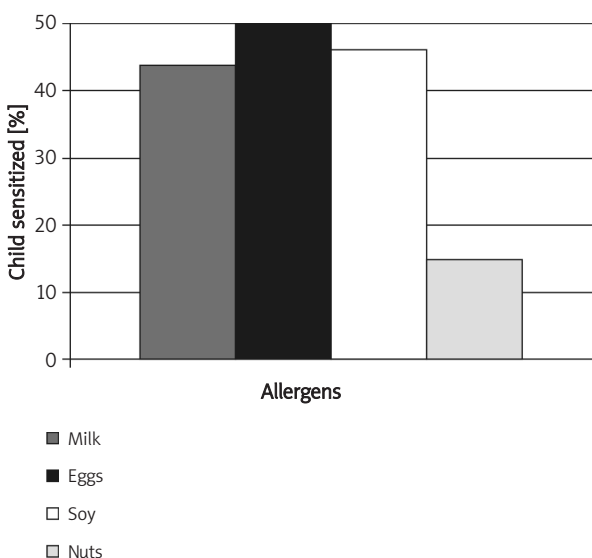


Fig. 4. Sensitization to other food allergens in the examined group of children (n = 26)

pollen were the most frequent and there were no statistically significant differences in the prevalence of sensitization between patients and the control group (Tab. 2). Only one patient in the study group had positive tissue transglutaminase antibodies. IgE antibodies to gluten were found in 4 children. A gluten-free diet was used only in 3 children in the study group (12%). A positive patch test result to gliadin was found in 11 patients.

With regard to pharmacotherapy (topical and systemic steroids, antihistamines), there were no statistically significant differences between the tested and control group.

Discussion

It is believed that in approximately 30% of patients with atopic dermatitis there is a relationship between clinical symptoms and hypersensitivity to food allergens such as milk, eggs, nuts, beans, or cereals [13-15]. Allergy to cereal proteins usually begins in early childhood, concerns patients with atopic dermatitis and is accompanied by mostly diagnosed allergy to milk proteins or eggs [1, 4, 6]. This is confirmed by the results of our research, where the majority of children with allergy to wheat did not exceed 4 years of age, while sensitization to other food allergens (including milk and egg protein) was observed in most subjects (Fig. 4). Allergy to cereals in children with atopic dermatitis is often underestimated. Clinical symptoms usually occur a few days after consumption of cereal products; an immediate response is less common; the effects of delayed reactions are usually gastrointestinal symptoms and exacerbation of atopic dermatitis [1, 4, 16]. IgE-mediated reactions are manifested clinically as: urticaria, wheezing, nausea, abdominal pain and, in severe cases, anaphylactic shock. The study showed that 46% of children allergic to corn had an immediate response, while 65% had a delayed reaction. Attention should be drawn to the increased incidence of delayed reactions, taking into account the fact that the immunological mechanisms of atopic dermatitis appear to be clearly understood [5, 8, 16, 17]. This fact is also emphasized by other clinicians; in a study conducted by Boissieu, it was shown that corn allergy is manifested most commonly as a delayed reaction and negative specific IgE does not exclude this hypersensitivity. It is there-

Tab. 2. Sensitization to aeroallergens in the study vs. control group

Allergen	Study group (n = 26)	Control group (n = 35)	Value of p
House dust mites	50.0%	43.75%	0.743
Tree pollen (mix)	57.14%	40.0%	0.558
Grass pollen (mix)	57.14%	36.36%	0.387
Moulds (<i>Alternaria</i> , <i>Cladosporium</i>)	50.0%	25.0%	0.429

fore important in diagnosis to perform patch tests with a confirmation test result of the elimination and provocation test [7, 16, 17].

Jones *et al.* also demonstrated clinically significant cross allergy between cereals and grass pollen [1, 18]. In a group of children 57% of them had concomitant allergy to grass pollen, while approximately 30% of them manifested symptoms of allergic rhinitis and conjunctivitis. The incidence of both these symptoms and sensitization to pollen was not higher than in the control group. There was also no significant effect of grass pollen allergy on the severity of skin lesions. Some light on such studies was shed by the clinical experience published by Eyerich *et al.* [19]. They found that skin reactions which are an expression of sensitization to aeroallergens are often a late response, as demonstrated by positive patch tests performed with native grass pollen allergens in patients with atopic dermatitis. These observations were confirmed by examining the immune response of the skin and performing additional immunohistochemical examination of skin biopsies from the evaluation of cells or lymphocytes CD4⁺, CD25⁺, and CD45RO⁺ [19].

Thus, it seems that in order to assess the impact of allergens on the severity of skin lesions in children as in adults, it is necessary to perform atopy patch tests with aeroallergens [20, 21].

No differences between the severity of skin lesions in the study group and the control one also confirm the complexity of pathogenic mechanisms in atopic dermatitis and the influence of many other non-allergic factors on the exacerbation of the disease. Lack of a correlation between the severity of skin lesions and an allergy to wheat may also be due to shortcomings in the research methods. Detection of allergen-specific IgE antibodies in serum or positive results of skin and patch tests is not always reflected in the clinical symptoms [13, 22]. The positive predictive value of specific IgE determinations by CAP for allergy to wheat is less than 75% [1, 22]. The low diagnostic value of this test method is explained by the lack of a solution of the insoluble fraction of gliadin. Studies on allergy to proteins in cereals made by immunoblotting showed the main role of gliadin peptides (ω -5 gliadin) [13]. There is postulated, therefore, a need for the determination of gliadin IgE antibodies, whose presence has a much better correlation with a positive provocation test for cereals (wheat) in patients with atopic dermatitis [13]. In all patients we determined IgE antibodies against tissue transglutaminase (tTgA) and standard patch tests were also performed with gliadin. In the group of patients IgE antibodies to gluten were found in 4 children, delayed-type reactions to gliadin in 11 (42%), and tTgA antibodies only in one patient. The results allow us to explain the lack of association between the severity of atopic dermatitis assessed by SCORAD and an allergy to wheat.

Our results indicate the usefulness of a thorough diagnosis before the implementation of a gluten-free diet. This

diagnosis should be expanded to IgE antibodies against gliadin, which can be subject to a screening test in patients with allergy to wheat. However, evidence that food allergy is causing the symptoms comes from the result of the challenge test [7, 23]. As indicated by our research results and no correlation between allergy and the symptoms, it is an essential diagnostic step. Similar observations were made by Pasini *et al.*, who found that the positive results of skin tests and specific IgE to the protein of corn are not clinically significant [24]. Only the research on using immunoblotting showed a correlation between a positive provocation test and sensitization to the major allergen of maize protein with a molecular weight of 50 kDa [24]. This also confirms the known fact that sensitization to food or airborne allergens is only a proof of immune hypersensitivity without clinical relevance for the ongoing disease process. So despite the lack of difference in the severity of skin lesions in the study and control group, one cannot exclude the impact of an exacerbation of allergic skin lesions in the course of deliberate food provocation.

According to the latest recommendations of ESPGHAN (the European Society for Paediatric Gastroenterology, Hepatology and Nutrition) on the prevention of allergy to gluten, one should avoid too early (< 4 months of age) or late (7 months of age) entry of gluten into the diet, and the protective effect of breast feeding during exposure to this allergen [25].

Another clinical problem seems to be allergy to wheat. Of all the cereals, sensitization to wheat is the most common. Clinical manifestation is slightly different than for other cereals. Along with typical gastrointestinal and skin symptoms observed in other food allergies, the effect of allergy to wheat glycoprotein may be effort-induced anaphylactic shock, or so-called baker's asthma. The nature of the symptoms is usually associated with the route of sensitization (oral, inhalant), and hypersensitivity to a certain protein contained in wheat (ω -5 gliadin) [26]. In the group of investigated children sensitization to wheat was found in 42% of them, but there were no signs of a different nature than in non-sensitized children.

Despite the high incidence of allergy to wheat, little can be said about the natural history of this allergy [27]. One of the few trials conducted in a group of 103 children revealed that about 65% of them grew out of the IgE-mediated allergy to corn up to 12 years of age. The average age of acquisition of tolerance was 6.5 years, irrespective of the level of allergen-specific antibodies in serum treated as a prognostic factor. The coexistence of allergy to grass pollen, having the nature of cross-allergy, did not influence the acquisition of tolerance in relation to cereals as a food allergen. This seems to be relevant to the dietary recommendations for patients with allergy to wheat and atopic dermatitis, especially in the reduction of the implementation of a gluten-free diet. In the study group of children there was a higher frequency of sensi-

tization to grass pollen than in the control one. This fact can be explained by the mean age of the children (3.88 ±3.28 years), and the acquisition of sensitization to pollen may be a matter for the future.

Conclusions

1. Sensitization to cereal allergens is a common phenomenon in children with atopic dermatitis and should be taken into account in the diagnostic process.
2. There was no relationship between the occurrence of sensitization to these allergens and the severity of skin lesions assessed by the SCORAD scale.
3. For children who are allergic to cereal proteins, there is not predisposition to hypersensitivity to pollen allergens and rhinitis or bronchial asthma.
4. In the case of positive results of allergy to cereal proteins and severe exacerbations of atopic dermatitis there should be considered some attempts of elimination and provocation tests.

The work was performed at the Department of Paediatrics, Gastroenterology and Allergology, Medical University of Białystok.

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