

Concurrent cereal allergy in children with cow's milk allergy manifested with atopic dermatitis

K.-M. Järvinen*, M. Turpeinen† and H. Suomalainen*

*Department of Dermatology and †Allergology, Helsinki University Central Hospital, Skin and Allergy Hospital, Helsinki, Finland

Summary

Background There is increasing consensus about the significance of food allergens in the pathogenesis of atopic dermatitis (AD) in infancy and childhood, with cow's milk and egg accounting for most of the reactions. Previous studies have indicated that multiple food sensitization, such as cereals, is very common in patients with cow's milk allergy (CMA). Evidence is lacking, however, as to its clinical relevance.

Objective The purpose of this study was to determine the concurrent occurrence of cereal allergy among children with challenge-proven CMA who have residual symptoms, such as AD and/or gastrointestinal symptoms, during cow's milk elimination diet. Further, we sought to evaluate the utility of patch testing in prescreening foods other than cow's milk behind allergic symptoms in children.

Methods The study population comprised 90 children, aged from 2.5 to 36 months (mean 1.1 years), with challenge-proven CMA. As a result of residual symptoms during meticulous cow's milk elimination diet (AD: $n = 80$, and gastrointestinal: $n = 10$), the children were put on a cereal elimination diet (oats, wheat, rye, and barley) and skin prick tests (SPT) and patch testing with cereals were performed. Open cereal challenge was performed to confirm cereal allergy.

Results Cereal challenge was positive in 66 (73%) of the children with CMA. Of them, 17% reacted with immediate reactions and delayed-onset reactions were seen in 83% of the children. SPT was positive in 23%, patch test in 67%, and either SPT or patch test was positive in 73% of the children with cereal allergy. SPT gave the best positive predictive value, whereas SPT together with patch test gave the best negative predictive value.

Conclusions Residual symptoms, such as eczema or gastrointestinal symptoms in CMA children may be a sign of undetected allergy to other food antigens. SPT with cereals aids in diagnosing cereal allergy in small children, especially when used together with patch testing.

Keywords atopic dermatitis, atopic eczema, atopy patch test, cereal allergy, children, cow's milk allergy, skin prick test, wheat allergy

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Introduction

Atopic dermatitis (AD) is a multifactorial, chronically relapsing inflammatory skin disorder, characterized by erythematous and pruritic lesions, excoriations, papules, and lichenification [1, 2], and affecting 10–12% of children [3]. There is increasing consensus about the significance of food allergens in the pathogenesis of AD in infancy and childhood. Clinical hypersensitivity to food has been demonstrated in 30–70% of patients with mild to severe AD in double-blind, placebo-controlled oral food challenges, with cow's milk, egg, peanut, soy, and cereals accounting for most of the reactions [3–6].

The diagnosis of food allergy is clinical, and relies on the disappearance of the symptoms during an elimination diet and their subsequent reappearance after reintroduction of the food. IgE-mediated and delayed-type reactions may each be responsible for approximately one-half of the hypersensitivity reactions [7]. IgE-mediated hypersensitivity is responsible for immediate reactions, and cell-mediated reactions have been suggested to be responsible for delayed reactions, the mechanisms of which are not well understood [8, 9]. Positive skin prick test (SPT) or food-specific IgE in serum traditionally demonstrates an IgE-mediated mechanism. The symptoms in immediate hypersensitivity appear within a short period after ingestion of food, which helps to identify the agents. In the case of delayed-type hypersensitivity, the causal relationship between the ingestion of the food and the appearance of symptoms is more difficult to detect, since the symptoms may appear several hours or even days after the ingestion of the antigen [10]. Furthermore, tests to

Correspondence: Dr Kirsi-Marjut Järvinen, MD, PhD, Department of Pediatrics, Division of Allergy and Immunology, Mount Sinai School of Medicine, Box 1198, One Gustave L. Levy Place, New York, NY 10029, USA. E-mail: kirsi.jarvinen@mssm.edu

demonstrate delayed hypersensitivity have been lacking until recently when the patch test was introduced in a few centres for cow's milk [6, 11–15], wheat [14, 16], and egg [14]. The patch test can induce T cell responses reflecting those that occur in subacute and chronic AD [17], supporting the immunologic specificity of atopy patch test in AD. Early studies of the patch test with cow's milk, wheat, egg, and soy allergy in infants and children have shown improved utility for determining responses to oral food challenges [6, 11–15, 18].

In clinical work, disappearance of the most severe eczema lesions during a food elimination diet is commonly considered satisfactory in the dietary treatment of AD, although mild to moderate lesions might still appear. However, previous studies have indicated that polysensitization, shown by SPT or patch tests to multiple foods including cereals, in patients with cow's milk allergy (CMA) is very common [6]. Evidence is lacking, however, as to the clinical relevance of positive skin test reactions to cereals in CMA children. The purpose of this study was to determine the occurrence of cereal allergy among children with CMA and residual-allergic symptoms. Further, we sought to evaluate whether patch tests would help in prescreening children with possible cereal allergy.

Patients and methods

Subjects

We selected 90 children (59 males, 31 females), aged from 2.5 to 36 months (mean 1.1 years), among patients who were referred to a university hospital because of AD, diagnosed according to the criteria of Hanifin and Rajka [1]. Only children who fulfilled the following two criteria were recruited to the study: (1) they had been subjected to a cow's milk elimination and challenge procedure due to history and symptoms suggestive of CMA (AD, urticaria, and gastrointestinal symptoms) and proven positive, and (2) they had showed a good response to avoidance of cow's milk, and the other common food allergens in childhood such as eggs, peanuts and tree nuts (and soy if suspected) in addition to the common histamine-releasing agents (tomato, citrus fruits, strawberry, chocolate, and fish), but continued to have milder residual symptoms (AD or gastrointestinal symptoms). Children who had responded satisfactorily to such cow's milk elimination diet (showed no residual symptoms) were NOT recruited. The children were born full-term, and had no other chronic diseases or infection at the time of the study. The clinical characteristics of the children recruited are summarized in Table 1. The children received no systemic corticosteroid therapy, and anti-histamine medication was discontinued 3 days to 6 weeks before skin testing depending on the duration of action of the drug.

Informed consent was obtained from the parents. The study protocol was approved by the ethics committee of the Skin and Allergy Hospital, Helsinki University Central Hospital.

Study protocol

A flowchart of distribution of children with atopic eczema and suspected food allergy is shown in Fig. 1. In case of AD in infants and children, certain dietary restrictions are applied

Table 1. Clinical characteristics of the 90 cow's milk (CM)-allergic patients recruited in the study

Mean age (range) at onset of symptoms	3.0 months (1 week to 9.7 months)
Mean age (range) at testing	1.1 years (2.5–36 months)
Mean duration (range) of exclusive breastfeeding	3.1 months (0–7 months)
Positive history of atopy	79%
Mean SCORAD (95% CI) at enrollment	27.9 (21.9–27.6)
Residual symptoms on egg and CM elimination diet (<i>n</i> = 90)	<i>n</i> = 80
Atopic eczema	<i>n</i> = 80
Diarrhoea	<i>n</i> = 10
Reaction in CM challenge (<i>n</i> = 90)	
Immediate	<i>n</i> = 37
Urticaria	<i>n</i> = 29
Morbilliform rash	<i>n</i> = 4
Rash and diarrhoea	<i>n</i> = 2
Rash and diarrhoea and rhinoconjunctivitis	<i>n</i> = 2
Delayed	<i>n</i> = 53
Eczematous rash	<i>n</i> = 26
Diarrhoea	<i>n</i> = 7
Rash and diarrhoea	<i>n</i> = 15
Rash and diarrhoea and rhinoconjunctivitis	<i>n</i> = 5

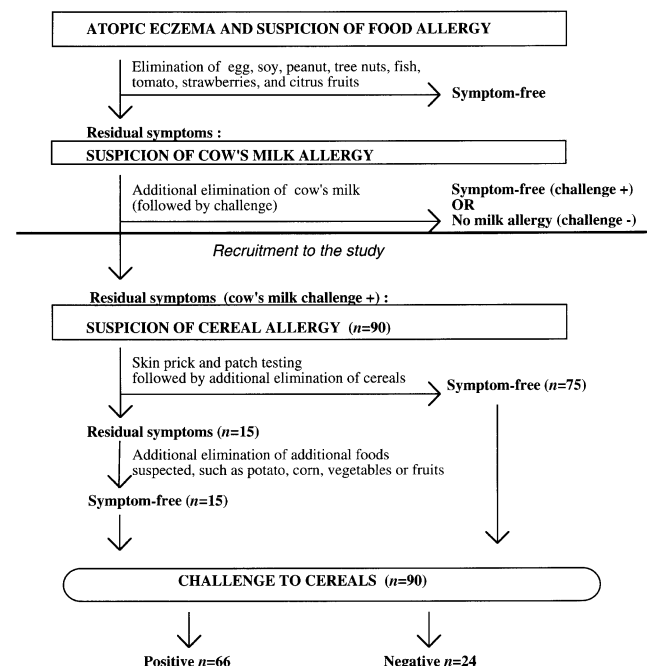


Fig. 1. Flowchart of distribution of children with atopic eczema and suspected food allergy. Residual symptoms on elimination diets lead to further restrictions in the diet as shown. The area below the hatched line represents the patients included in the study.

as diagnostic and treatment procedures: egg, peanuts, and tree nuts, which are the common food allergens in infants and children, and additionally histamine-releasing foods such as tomato, citrus fruits, strawberry, chocolate, and fish are traditionally the first to be eliminated from the diets of the children and breastfeeding mothers. The children commonly

Table 2. Time of onset of reaction and dose eliciting the symptoms of cow's milk or cereal allergy in children with immediate- or delayed-type reaction

	Cow's milk challenge (n = 90)			Cereal challenge (n = 66)		
	Cutaneous (n = 23)	Immediate (n = 37)	Delayed (n = 53)	Cutaneous (n = 6)	Immediate (n = 5)	Delayed (n = 55)
Time of onset of reaction*						
From the last dose	—	0.46 (0.39–0.53)	3.1 (2.7–3.5)	—	0.36 (0.28–0.45)	4.1 (3.4–4.8)
From the beginning	—	1.7 (1.4–1.9)	63 (47–79)	—	0.36 (0.28–0.45)	77 (59–95)
Dose eliciting the symptoms†						
Last dose	—	15 (5–130)	100 (1–200)	—	1 (1–5)	10 (1 to 10)
Cumulated dose	—	23 (5–230)	775 (1–3500)	—	1 (1–5)	35 (2 to 140)

*Mean (95% CI) expressed as h.

†Median (range) expressed as millilitres (cow's milk) or g (cereal).

already had these dietary restrictions when referred to the hospital. All the children included in the study had already been skin prick and patch tested with cow's milk, and had been put on a cow's milk elimination diet because of suspicion of CMA. On a cow's milk elimination diet, the children were given calcium supplementation ($n = 14$), protein hydrolysate or amino acid-based formula ($n = 62$), or soy ($n = 9$). Breastfeeding mothers ($n = 5$) received calcium supplementation. In clinical cow's milk challenge, 37 (41%) children showed immediate reactions such as urticaria and erythema and 53 (59%) children showed delayed-type reactions, such as diarrhoea and eczema (Table 2). Because all the children had residual symptoms, SPTs and patch tests with cereals and other foods according to suspicion were performed. The children (and the breastfeeding mothers) were thereafter put on cereal elimination diet (including rye, wheat, oats, and barley) for a minimum of 2 weeks. As a result of co-sensitization, all these cereals were eliminated from the patients diet [17]. The children and breastfeeding mothers received rice, corn, millet, and/or buckwheat instead. In some cases, some residual symptoms still persisted and these children were individually evaluated for possibility of additional food allergies. Diets restricting foods such as potato, corn, buckwheat, some vegetables, or fruits were started accordingly. All the children were subjected to an open challenge with cow's milk and one cereal separately when they were free of symptoms.

Cow's milk and cereal challenge procedure

The challenge was performed within 3 months of patch testing. It was performed openly, which has been shown to be appropriate in small children [11]. The challenge was started in the hospital with a drop of cow's milk or cereal on the patient's skin and lips, as described earlier for cow's milk challenge [19]. After a negative cutaneous challenge, food was given in increasing doses (1, 10, and 100 mL of cow's milk or 1, 5, and 10 g of cereal) at 0.5-h intervals on day 1. On day 2, normal cow's milk or cereal intake corresponding to the age was commenced. The challenge was performed for the first 3 days in the ward and continued beyond 1 week at home to reveal any late-phase reactions. If any adverse reaction was noticed, the child was examined by an experienced paediatrician or a dermatologist, and the challenge was stopped. The diagnosis was based on typical

symptoms, their amelioration on cow's milk or cereal elimination diet and reappearance on cow's milk or cereal containing diet. Symptoms regarded as positive were anaphylaxis, urticaria, AD, vomiting, and diarrhoea. The time of the reaction was defined as the time since the last dose eliciting the specific symptoms. The reactions that occurred within an hour from the last dose were defined as immediate ones and those that occurred thereafter were delayed ones. Every cereal was challenged one at a time, with 2–4 weeks intervals and a minimum of 1-week symptom-free period between the challenges. Only the first cereal challenge was performed at the hospital; the following cereals were challenged at home and those results are therefore not included in the paper.

Skin prick tests

SPTs were performed on the volar side of the forearm using commercial cow's milk extract (Soluprick, ALK, Hørsholm, Denmark) and cereals (rye, wheat, oats, and barley) as flour suspended 1:10 in 0.9% sodium chloride [17]. Histamine dihydrochloride 10 mg/mL (Soluprick) was used as a positive control, and saline was used as a negative control. The reaction was taken to be positive if the weal was at least 3 mm in diameter and at least half the size of the histamine-induced weal after 15 min.

Patch testing

Patch tests were performed during cow's milk and cereal elimination diet, and were interpreted and scored by an experienced dermatologist before the challenge. Patch testing with cow's milk was performed as described previously [12]. On the morning of the testing, 300 mg of skimmed powder or 200 mg of cereal as flour was mixed with 0.2 mL of isotonic saline solution. In patch testing, approximately 20 mg of milk (containing 450 µg β -lactoglobulin) or cereal preparation was attached on the back by using 12 mm aluminium cups (Finn Chamber, Epitest Ltd., Hyrylä, Finland) and Scanpore tape. Reactions against cow's milk, egg, soy, cereals (rye, wheat, oats, and barley), and gliadin were tested. Microcrystalline cellulose or cream ointment (Humektan®, Orion, Finland) was used as a negative control. Test cups were removed after 48 h and the reactions were read 24 h after the removal. Reactions were scored as negative, irritation (IR), erythema,

erythema with oedema or eczema (+), or erythema with oedema or eczema with vesicles (++). Oedema and eczema were taken as positive reactions.

Statistical analysis

ANOVA and the Mann–Whitney *U*-test were employed to determine the statistical significance of differences in continuous variables between the groups. Because of the skewed distributions, logarithmic transformations were used. The repeated observations were studied by ANOVA for repeated measures and a paired *t*-test. The χ^2 test was applied to determine differences in proportions.

Test sensitivity and specificity were defined as the proportion of individuals with true-positive and true-negative test reactions, respectively. The positive predictive value (PPV) denotes the proportion of individuals with clinical allergy among those with a positive test reaction, and negative predictive value (NPV) describes the proportion of individuals without clinical allergy among those with a negative test reaction.

Results

Responses to cereal elimination diet and challenge

Improvement of eczema was associated with the cereal elimination diet. Severity of AD, assessed according to the SCORAD index, decreased from the mean 27.9 (95% CI, 25.1; 30.7) on cow's milk elimination diet to 6.6 (95% CI, 4.8; 8.4) on cow's milk plus cereal elimination diet. Open cereal challenge was positive in 66 (73%) and negative in the rest of the children. Results of the cereal challenges with details on each cereal are shown in Table 3. Immediate reactions occurred earlier and to lower doses of food, whereas delayed reactions were detected after a longer period of challenge and to larger amounts of food ingested (Table 2). Clinical reactivity to all the four cereals was detected in the majority of children, and usually the cereal first tolerated was oats (clinical observation, data not shown).

Utility of SPT and patch tests

CMA. SPT with cow's milk was positive in 30 (33%) and patch test in 28 (31%) of the 90 children with positive cow's milk challenge. Either SPT or patch test was positive in 47 (52%) of the children with CMA. An example of a child with several positive patch test reactions to foods is shown in Fig. 2. SPT was more often positive (62%) than patch test (35%) in children with immediate reactions to cow's milk, whereas both SPT and as the patch test were infrequently positive (13% and 40%, respectively) in delayed-type reactions to cow's milk (Fig. 3). In seven patients, a positive SPT was associated with delayed reaction in the cow's milk challenge.

Cereal allergy. The sensitivity of SPT and patch tests, when used alone or in combination seemed to be better for cereals than for cow's milk (Fig. 3). SPT with cereal was positive in 15 (23%) and patch test in 44 (67%) of the 66 children with positive cereal challenge. Either SPT or patch test was positive in 48 (73%) of the children with cereal allergy (Fig. 3). SPT was less sensitive than the patch test in detecting cereal allergy, although it was more specific (Table 4). No false-positive SPT results with cereals were found, whereas false-positive patch test results were found in five of the 24 children with a negative cereal provocation. Of the 15 children with a positive SPT to cereals, 12 also had a positive patch test reaction. SPT gave the best PPV, whereas SPT together with patch test gave the best NPV. Use of only the 44 wheat challenges in assessing the utility of these skin tests did not affect these figures markedly. Gliadin, used as an antigen in patch testing, gave a positive reaction in all the patients with a positive patch test reaction to cereals.

The comparison of SPT and patch test in their ability to demonstrate the type of reaction to cereal is presented in Table 5. The patch test was found to be as sensitive as SPT in demonstrating immediate-type hypersensitivity. Moreover, it was far more sensitive in detecting delayed-type reactions to cereals than SPT. Combining these two tests increased the test sensitivity in both immediate and delayed reactions. SPT was more specific than patch test in demonstrating immediate-type reactions, whereas patch test showed better specificity than SPT in late-phase reactions. Seven patients with a

Table 3. Results of the cereal challenges

Challenge	Wheat (<i>n</i> = 44)		Rye (<i>n</i> = 6)		Barley (<i>n</i> = 7)		Oats (<i>n</i> = 33)	
	Pos (30)	Neg (14)	Pos (6)	Neg (0)	Pos (5)	Neg (2)	Pos (25)	Neg (8)
Type of reaction								
Immediate								
Urticaria	8		1		1		1	
Pruritic rash	6		1		1		1	
Delayed	2		0		0		0	
Delayed	22		5		4		24	
Eczematous rash	15		2		4		16	
Diarrhoea	1		2		0		6	
Rash and diarrhoea	6		1		0		1	
Fever	0		0		0		1	
SPT+	5 (17%)	0	2 (33%)	0	2 (40%)	0	6 (24%)	0
Patch test+	21 (70%)	4 (28%)	5 (83%)	0	3 (60%)	0	15 (60%)	1 (13%)
SPT and/or patch test+	23 (77%)	4 (28%)	5 (83%)	0	3 (60%)	0	17 (68%)	1 (13%)

SPT, skin prick test.



Fig. 2. An example of an infant with positive patch test reactions to oats, barley, rye, wheat, gliadin, egg, soy, rice, and buckwheat. Millet and corn show weak positive reactions. Cow's milk and test control are negative.

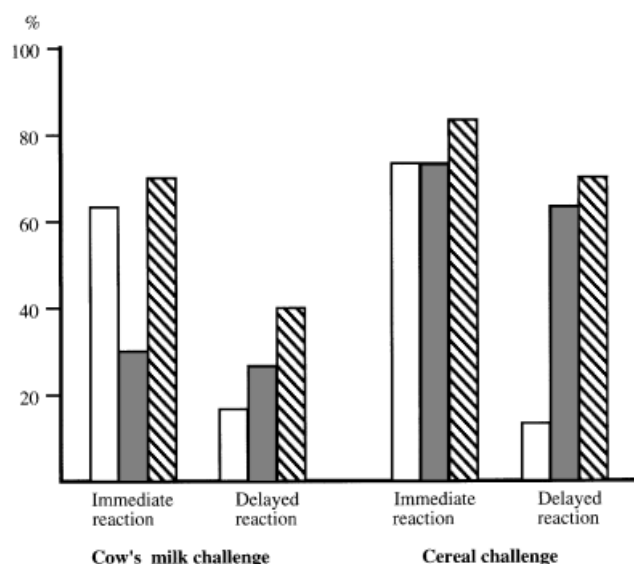


Fig. 3. Comparison of skin prick test (SPT) and patch test (PT) in demonstrating cow's milk or cereal allergy of immediate or delayed type, proven by food challenge, in 90 children less than 3 years of age. Empty bars denote sensitivity of SPT, filled bars of PT, and hatched bars depict the sensitivity of SPT combined with PT (either test positive).

Table 4. Performance of skin prick test, patch tests, and their combination in relation to clinical outcome of cereal (wheat) challenge

Test	Sensitivity	Specificity	Predictive value	
			Positive	Negative
Prick	0.23 (0.17)	1.0 (1.0)	1.0 (1.0)	0.32 (0.36)
Patch	0.67 (0.7)	0.79 (0.71)	0.9 (0.84)	0.46 (0.53)
Prick and patch	0.73 (0.77)	0.83 (0.17)	0.92 (0.85)	0.53 (0.59)

positive SPT with cereals showed a delayed reaction. SPT gave the best PPV for immediate reactions, and patch test for delayed reaction, whereas patch test gave the best NPV for both types of reactions.

Interestingly, both SPT and patch test with cereals were more frequently positive in children having only cutaneous symptoms (27% and 73%, respectively) than those children who manifested with both cutaneous and gastrointestinal symptoms (0% and 50%, respectively), although the difference was not statistically significant ($P = 0.09$). Of the total 66 cereal-allergic patients, positive patch tests were found in seven of the nine patients (78%) who showed urticaria, and in 28 of the 39 (72%) who reacted with eczema, whereas patch test was positive only in four of the nine (44%) of children with diarrhoea and four of the eight (50%) of the children with both skin and gastrointestinal manifestations. Of the 44 cereal-allergic children with positive patch test reactions, seven (16%) reacted with urticaria, 28 (64%) showed eczema, four (9%) manifested with diarrhoea, and four (9%) children showed both rash and diarrhoea. The sensitivity of cereal patch test increased the younger the child (0.76 at <1 year, 0.68 at 1–2 years, and 0.33 at 2–3 years), but at the same time the specificity decreased (0.71 at <1 year, 0.83 at 1–2 years, and 1.0 at 2–3 years).

Discussion

In the present study, we demonstrate that the children with CMA who do not satisfactorily respond to a strict cow's milk elimination diet may have an undetected allergy to cereals. We show that patch testing with cereals aids in diagnosing cereal allergy in small children, especially when used together with SPTs, although a challenge with cereal is still needed to confirm the diagnosis in these children.

Patch tests proved superior to SPTs in detecting a population of cereal-allergic children. This is consistent with findings of Majamaa et al. [18], who reported a sensitivity of 0.86 with patch test with wheat, better than that detected in our population (0.7), but a specificity of 0.35, which is markedly lower than that reported in the present study (0.71). The difference may reflect differences in study populations, since younger children were investigated in their study. We found that the sensitivity of patch test decreased with increasing age, but at the same time the specificity increased. Another recently published report on children up to 11 years of age describes a high sensitivity (0.89) and also a very high specificity (0.94) for the patch test: these figures are even higher than those for SPT (or specific IgE). Such a high specificity for the patch test that is even higher than that for SPT is in contrast with our findings and the results by Majamaa et al. [18], which both report a specificity of 1.0 for the SPT. The differences between these studies may reflect the differences in the age, in the methodology, such as in the preparations, or in the interpretation of the test results. Future studies on this field requires standardization of the most important variables such as age, preparations and, importantly, more objective interpretation of the results.

In the present study, the patch test was as sensitive as SPT in demonstrating immediate-type hypersensitivity to cereals. Moreover, it was far more efficient in detecting delayed-type reactions to cereals than the SPT. Positive SPT was associated with immediate reactions in the open cereal challenge, whereas patch test reactions were related to delayed-type reactions. This is in agreement with several reports on patch tests with cow's milk and wheat [6, 11–13, 18], although one study described no correlation with the type of reactions and test positivity [20], and two others found a relation between the patch test and an immediate reaction to cow's milk [14, 15]. Furthermore, we detected the patch test with cereals to be more predictive of cutaneous manifestations (urticaria and rash) than the gastrointestinal ones.

In mixed populations of children and adolescents (aged 4 months to 25 years), the prevalence of wheat hypersensitivity was 4–10% in the patients with AD, and 8–17% in those with positive food challenges [3–5]. Since then, cereal allergy has been suggested to be more common in children with AD or CMA [6, 21], although epidemiological data on its prevalence are lacking. In the present study, cereal allergy was detected in 73% of the children with CMA and residual symptoms on a milk elimination diet. Such a high prevalence of cereal allergy can only be applied to similarly selected subpopulations of food-allergic children who represent patients referred to a university hospital due to suspicion of severe and/or multiple food allergies, with persistence of at least mild residual symptoms during cow's milk elimination diet. We suggest that in similar tertiary centres, patch testing with cereals in children with residual symptoms during cow's milk elimination diet would significantly increase the accuracy of the diagnostics of cereal allergies. The diagnosis has to be, however, confirmed by elimination and subsequent challenge procedure.

The present study has a few limitations. As mentioned above, due to selection bias, these results can only be applied to similar patient populations of cow's milk-allergic children, who show residual symptoms during milk-, egg- and peanut/tree nut-avoidance diet. It would also have been useful to

recruit a control group with residual symptoms, which would have had no further dietary interventions to evaluate the role of the spontaneous improvement of eczema in this age group. It is also possible that in some of the children, the residual symptoms may have been due to non-adherence to cow's milk elimination diet, which is almost impossible to rule out. However, we were able to demonstrate a favourable response to cereal avoidance diet, followed by a reappearance of the symptoms during cereal challenge in these children. Unfortunately, the challenges were performed openly, instead of a double-blind placebo-controlled food challenge, which is the golden standard for diagnosis. This was due to the high volume of challenges performed on each child (cow's milk and four separate cereals) and the long duration of each challenge (1 week). Because the children stayed in the ward for the first 3 days of the challenge (during which most of the reactions occurred) when only one new food was added to their diet, and due to the fact that only objective symptoms were accounted, we feel confident in claiming that the food challenged was the cause of these delayed-type reactions. Naturally, intercurrent viral infections and staphylococcal skin infections may have increased the number of positive challenges, although special attention was paid to confounding factors, such as an attempt to only challenge children free of infections.

In Finland, cereals are commonly introduced into the infant's diet at the age of 5 months. Cereals (wheat, rye, oats, and barley) belong to the grass family, Graminae [22, 23], and are an essential part of the daily nutrition. Although oats are not as closely related to wheat as rye and barley belonging to the tribe Avenae, and even though not enough is known about the corresponding allergens, the clinical and laboratory observations support the fact that there is significant co-sensitization to all these cereals (18, K-M Järvinen: clinical observation). This is the reason for grouping all the cereals together in the analyses. The prevalence and allergens of cereal allergy have been less extensively investigated compared to other major food allergens in childhood [22, 24]. A recent study on cereal-allergic children and AD indicates that ethanol-soluble gliadin is an important allergen both in immediate and delayed-type wheat allergy [24]. Another recent report showed that ω -5 gliadin, a major allergen in wheat-dependent, exercise-induced anaphylaxis, is a major allergen in children with immediate-allergic reactions to ingested wheat [25]. In the present study, gliadin when used as an antigen in patch testing was usually positive in the patients with a positive patch test reaction to cereals.

Significant sequence homology exists between corresponding prolamines of wheat (gliadins), rye (secalins), and barley (hordeins), but not with oats (avenins), which belongs to a different genus in the Graminae family [26]. A recently published report describes cross-reactivity between γ -70 and γ -35 secalins in rye, and γ -3 hordein in barley with ω -5 gliadin [27]. Consistent with those findings, in the present study wheat, rye, and barley were usually concomitantly positive in patch testing. However, oats was less frequently positive, and demonstrated weaker reactions than the other cereals. This is in agreement with a previous study demonstrating weaker allergenic properties of oats in comparison with the other cereals [17]. Assessment of the frequency of concurrent allergy to several cereals is not possible based on the data of this

paper, since only one cereal per patient was challenged in the hospital and was therefore assessed appropriately for data analyses. Interestingly, in our study some of the children with negative skin tests with oats, but positive ones with other cereals, surprisingly still reacted to oats in a challenge, and thus addresses the need for oral challenge in confirming clinical hypersensitivity.

In conclusion, patch testing with cereals supports the clinical suspicion of cereal allergy in infants, especially when used together with SPTs, and addresses well the population for further elimination diet and challenge strategies. According to our present study, residual symptoms, such as mild eczema in cow's milk-allergic children may be a sign of undetected allergy to other food antigens.

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