

Allergy to ingested cereals in atopic children

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Clinical features, hypersensitivity mechanisms, and differential diagnosis of cereal allergy or intolerance were investigated in children with atopic dermatitis (AD). On oral provocation, 18 children exhibited a positive response to wheat, three to rye, one to barley, and one to oats. Cereal-induced symptoms were dermatologic, gastrointestinal, or oropharyngeal, and their onset after provocation was immediate (eight cases), delayed (14 cases), or both immediate and delayed (one case). A combination of type I allergy tests (prick test, RAST, and histamine-release test) detected all immediate reactors and 9/14 delayed reactors. Of the five subjects remaining negative in these tests, three were positive in the patch or lymphocyte-proliferation tests. Subjects with cereal allergy or intolerance frequently possessed IgE, IgA, and IgG antibodies against gliadin, but only one of these children was HLA-DR3-positive, and none had reticulins antibodies typical of celiac disease. Combining tests of immediate and delayed hypersensitivity can confirm allergy to cereals in a more reliable way. The coexistence of cereal allergy and celiac disease seems to be rare.

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Cereal products can cause various adverse reactions and diseases. Allergy to inhaled flour or grain dust may manifest itself as rhinitis or asthma. When ingested, cereals can cause celiac disease, dermatitis herpetiformis, and food allergy. The manifestations of food allergy, including allergy to cereals, are diverse and include dermatologic, gastrointestinal, and respiratory symptoms of immediate or delayed onset. Allergy to ingested cereals has been investigated less extensively than celiac disease or baker's asthma.

Cereals contain various antigenic or possibly toxic protein components with different physicochemical properties. Cereal proteins can be extracted and classified according to their solubility in different solvents (2). The main antigenic fractions are albumins, globulins, gliadins, and glutenins (2). It is well known that celiac disease is associated with gliadins. In asthmatic bakers, albumins have been regarded as the major antigenic components, but reactivity to other protein fractions has also been found (5, 26). It has not been determined whether cereal proteins differ in their capacity to induce or elicit food allergy.

The present investigation described the clinical features of allergy or intolerance to ingested cereals and studied the usability of various skin and laboratory tests in the diagnosis of this condition. In addition, reactivity to gliadin was measured in children with cereal allergy or intolerance.

Material and methods

Subjects and provocations

The study was conducted at the Department of Dermatology, Tampere University Hospital, Tampere, Finland, to which children suffering from atopic dermatitis (AD) with or without suspected food allergy are referred. The subjects selected for the present study had AD and symptoms suggestive of food allergy and were therefore challenged with cereals. Many of them were older children who had been followed at the Department of Dermatology because of cereal and other food allergies diagnosed earlier, and they were rechallenged with cereals for the present study.

Twenty-three children with cereal allergy or intolerance and 16 non-cereal-allergic children participated in the study. Their AD was inactive at the time of the study. Cereal allergy or intolerance was proved or rejected by challenge combined with follow-up. Cereal products were totally eliminated from the child's diet at least 2 weeks before the challenge. When necessary, other foodstuffs were also withdrawn from the diet. The challenge was open or single-blind. Older children were challenged in a single-blind fashion. In the latter case, cereals were concealed in buckwheat porridge, to which none of the subjects was sensitized. The challenge began with

a drop of gruel (10% cereal, cooked in water) on intact skin. The oral doses were 1, 2, 5, 10, 20, 50, and 100 ml gruel given at intervals of 1 h. If the child developed a positive contact urticarial response to the gruel drop, oral provocation was started from 1 ml; otherwise, the first oral dose was 10 ml. If symptoms appeared, the challenge was stopped and the child was observed at the clinic for at least 2 h. If subjects did not develop symptoms after the last dose, they were likewise observed for at least 2 h before discharge. If they remained symptom-free on the following day, the parents were advised to continue with gruel, porridge, or bread *ad libitum*. The children returned to hospital when symptoms appeared or at the latest after 1 week. After provocation, they attended the clinic for 1–3 months and also later if necessary.

Skin tests

Prick tests were done with noncommercial cereal flour preparations. To make these, grains of wheat, rye, barley, and oats were ground, and the flours were suspended in saline, about 200 mg/0.3 ml. Prick tests were read at 15 min. The reactions were graded as follows: + a reaction of one-quarter of, ++ a reaction half the size of, +++ a reaction equal to, and ++++ a reaction twice as large as the wheal to the histamine standard (10 mg/ml). Reactions $\geq$ ++ were regarded as positive.

The five children who were challenge-positive but negative in type I allergy tests were also patch-tested. Patch tests were done with wheat, rye, barley, and oats flours and saline as negative control with Finn chamber[®] aluminum cups on Scanpor[®] tape (Epitest Ltd, Hyrylä, Finland). About 10 mg flour was placed per chamber on filter paper disks and moistened with a drop of saline. The occlusion time was 48 h, and the results were read 30–60 min after removal of the aluminum cups and again at 72 h. The reactions were graded as follows: ?+ erythema, + erythema plus edema.

Laboratory tests

Specific and total IgE antibodies were measured with commercial radioimmunoassays (CAP, RAST, RIA for specific IgE; IgE RIA for total IgE, Kabi Pharmacia, Uppsala, Sweden). RAST values $\geq$ 0.7 were regarded as positive.

Cereal flour antigens for histamine-release test and lymphocyte-proliferation test (LPT) were obtained by extraction from wheat, rye, barley, and oats flours with sodium acetate buffer, pH 3.8, followed by extraction with sodium phosphate buffer, pH 7.0, as previously described (4). The extracts were concentrated by ultrafiltration with a cutoff of 1 kDa, and

freeze-dried. In the final cereal flour antigen preparations, the acetate- and phosphate-soluble fractions were combined.

The basophil histamine-release test (BHRT) was done with cereal extracts prepared as described above and gliadin (British Drug Houses, Poole, UK), as previously described (20). In brief, washed whole blood cell suspensions containing basophils were incubated with serial dilutions of antigens or medium only (tubes for spontaneous histamine release) at 37°C for 30 min. For measurement of total blood histamine, the samples were heated at 100°C for 10 min. The histamine content of the supernatants was measured by radioenzymatic assay with histamine-*N*-methyl-transferase isolated from rat kidney (12). The detection limit of this assay was 0.1 ng/ml. The final results were expressed as the percentage of released histamine out of total blood histamine. Values were regarded as positive when the difference between spontaneous and antigen-induced histamine release was at least 8%.

The LPT was done with cells from the five children with a positive challenge but negative type I allergy tests. The LPT was done as previously described by incubating venous blood mononuclear cells in the presence of serial dilutions of cereal antigens for 6–7 days and measuring lymphocyte activation on the basis of the uptake of ¹²⁵I-labeled iododeoxyuridine (20). Only medium was added to the control cultures. The results were expressed as stimulation indices (SI = uptake of isotope in stimulated culture/uptake of isotope in control culture). SI values of at least 3.0 were regarded as positive.

IgA and IgG antibodies against gliadin were measured by a solid-phase enzyme-linked immunoassay previously described in detail by Vainio et al. (22). The limits for positivity were $\geq$ 0.25 EU/ml (ELISA units/ml) for IgA antibodies and $\geq$ 15.0 EU/ml for IgG antibodies.

Serum IgA reticulin antibodies were measured by indirect immunofluorescence with cryostat sections of rat kidney, liver, heart, and stomach as antigens (10). Titers $\geq$ 5 were regarded as positive.

Because celiac disease is strongly associated with HLA-DR3 (8, 25), patients who developed gastrointestinal symptoms after cereal challenge were HLA-DR-typed for differential diagnosis. The typing was done with a two-stage microlymphocytotoxicity test. Immunomagnetic beads (Dynal AS, Oslo, Norway) coated with monoclonal antibodies against HLA-DR antigens were used for the isolation of lymphocytes (24). The cells were incubated in the test plates in the presence of antisera for 20 min at room temperature, and then rabbit complement was added. After 20 min, acridine orange and ethidium bromide were added, and the reactions were read with a fluorescence microscope.

Statistics

Correlations between various test results were calculated by the Spearman rank correlation test. Sensitivity and specificity were calculated as follows: sensitivity = percentage of children with cereal allergy correctly identified by immunologic tests out of all children with cereal allergy or intolerance; specificity = percentage of children without cereal allergy correctly identified by immunologic tests out of all children without cereal allergy or intolerance.

Results

Characteristics of subjects with cereal allergy or intolerance

Upon challenge, 23 children developed symptoms from cereals, whereas 16 children remained negative. Eight children developed immediate symptoms (nos. 2–9), 14 reacted with delay (nos. 10–23), and one subject (no. 1) exhibited both immediate and delayed reactions (Table 1). A period of 2 h was chosen as the limit between immediate and delayed responses, but most immediate reactors developed symptoms within 30 min. Delayed reactors exhibited symptoms several hours after intake of the last measured-out dose (100 ml) or days after commencement of the provocation. The symptoms of the patients upon challenge were dermatologic, oropharyngeal, gastrointestinal, or all three; no respiratory symptoms were seen in this study. Immediate reactors developed generalized or localized urticaria or erythema (eight cases), or itching or swelling of mouth and throat (three cases). In delayed reactors, the symptoms were eczema (13 cases), loose stools or diarrhea (five cases), or abdominal pain (four cases).

Several older children with cereal allergy were included in our study, and it was therefore of interest to see whether these children had something in common. Of the nine children who had not become tolerant to cereals by 5 years of age, most exhibited other atopic diseases in addition to AD and multiple food allergies. Five had asthma, three asthma and rhinitis, and one rhinitis. Allergies to egg, milk, fish, or nuts were seen in six cases.

Responses in skin and laboratory tests

Results of tests for type I allergy to cereals are shown in Table 1. RAST detected 16/23 cases with cereal allergy or intolerance and gave 3/16 false-positive results. In the prick test, true-positive reactions were seen in 18/23 cases and false-positive ones in 3/16. BHRT yielded 16/22 true-positive and 2/16 false-positive reactions. Calculated on the basis of these data, the sensitivity and specificity of the RAST,

Table 1. Reactivity to cereals in type I allergy tests

Subject no.	Age (years)/sex	Antigen	Total IgE kU/l	RAST kU/l	Prick test	BHRT* %
<i>Children with cereal allergy or intolerance</i>						
1	7.9/M	Wheat	468	41.5	+++	<u>56.8</u>
2	10.9/M	Oats	631	13.5	++++	<u>61.5</u>
3	10.1/M	Rye	27400	>50	++	<u>52.0</u>
4	12.7/F	Wheat	3910	36.0	++	<u>53.1</u>
5	2.8/F	Barley	79	<0.4	++	<u>38.5</u>
6	2.2/M	Wheat	1950	47.3	+++	<u>65.6</u>
7	2.3/M	Rye	65	1.2	++++	<u>28.4</u>
8	1.4/M	Wheat	190	22.9	+++	<u>64.1</u>
9	7.6/M	Wheat	374	0.6	++	n.d.
10	1.9/F	Wheat	1630	1.8	++	<u>50.3</u>
11	1.8/M	Wheat	2190	17.7	+++	<u>63.3</u>
12	2.8/M	Wheat	53	1.5	++	<u>33.6</u>
13	15.3/F	Wheat	25330	>50	+++	<u>51.8</u>
14	4.2/M	Wheat	36	3.5	+++	<u>58.4</u>
15	5.1/M	Wheat	1630	2.7	++	<u>45.6</u>
16	8.6/M	Wheat	2060	2.0	++	<u>21.3</u>
17	2.5/M	Wheat	6580	22.1	+++	<u>44.7</u>
18	3.0/F	Wheat	143	2.5	++	<u>9.4</u>
19	4.8/M	Wheat	123	<0.4	–	2.3
20	3.3/M	Rye	11	<0.4	–	4.2
21	4.0/M	Wheat	9	<0.4	–	6.6
22	5.4/F	Wheat	241	<0.4	–	7.9
23	1.8/F	Wheat	7	<0.4	–	6.5
<i>Atopic controls</i>						
24	1.4/F	Wheat	344	<0.4	–	7.9
25	2.9/F	Wheat	26	<0.4	–	2.9
26	1.9/F	Oats	28	<0.4	–	4.1
27	4.0/M	Wheat	819	<0.4	–	2.7
28	3.2/M	Wheat	16	<0.4	–	4.0
29	2.8/F	Wheat	2520	<0.4	–	7.8
30	1.8/M	Wheat	181	0.4	+	8.2
31	14.8/M	Wheat	51	<0.4	–	6.8
32	9.4/F	Wheat	613	<0.4	++	7.1
33	9.2/M	Wheat	407	<0.4	++	9.5
34	12.8/M	Wheat	231	<0.4	–	6.3
35	1.2/F	Barley	261	1.0	–	3.8
36	11.5/M	Barley	84	0.4	+	7.9
37	6.8/F	Wheat	74	0.7	–	<u>14.6</u>
38	11.5/F	Wheat	1940	1.2	++	<u>19.9</u>
39	1.9/M	Wheat	745	0.6	–	3.6

* Results obtained at optimal antigen concentrations (1–100 µg/ml) are shown, and positive values are underlined. In subjects 2–9, challenge reactions were immediate, in nos. 10–23 delayed, and in no. 1 both immediate and delayed. n.d. = not done.

prick test, and BHRT were 69.6 and 81.3%, 78.3 and 81.3%, and 72.7 and 87.5%, respectively. In addition, there were significant correlations between results of different immunologic tests (prick test and RAST, $P < 0.001$; prick test and BHRT, $P < 0.001$; and RAST and BHRT, $P < 0.001$).

It is noteworthy that 9/9 subjects with immediate-onset symptoms exhibited one or more positive reactions in type I allergy tests, whereas these tests failed to detect 5/14 subjects with late-onset symptoms. The five children with cereal-induced symptoms but negative type I allergy tests were subsequently studied with tests of delayed allergy. In three subjects (nos. 20, 21, and 23), a positive response

was seen in the patch test, LPT, or both (Table 2). In two subjects (nos. 19 and 22), no mechanism of allergy to cereals could be verified by the tests available (Tables 1 and 2). These children had been repeatedly challenged once or twice a year and had hitherto been positive.

Reactivity to one cereal protein, gliadin, was investigated in greater detail in children with cereal allergy or intolerance. Half the patients' group evinced type I allergy to gliadin and were positive in BHRT or in both BHRT and RAST (Table 3). IgG antibodies against gliadin were detected in 6/18 children with cereal allergy or intolerance, and IgA antibodies were detected in 3/18 (Table 3).

Cereal allergy and celiac disease

Because some subjects exhibited gastrointestinal symptoms upon cereal provocation or had IgA or IgG antibodies against gliadin, they were further investigated to confirm or exclude coexistent celiac disease. None of our patients had a family history of celiac disease or detectable levels of IgA reticulin antibodies (data not shown). Eight children developed gastrointestinal symptoms in response to provocation, subject no. 17 exhibited only gastrointestinal symptoms, and nos. 1, 15, 18, 19, 20, 21, and 23 exhibited both gastrointestinal and dermatologic symptoms. These eight children were typed for HLA-DR antigens to establish whether they belonged to a risk group for development of celiac disease. Only one subject (no. 15) was HLA-DR3-positive (Table 3). This patient was sensitized only to wheat and could eat other cereals with impunity. In a subsequent 2-year follow-up, he became tolerant to wheat and has at present mild atopic eczema and allergic rhinitis. The serologic screening tests for celiac disease (gliadin and reticulin antibodies) have likewise been negative.

Discussion

The term "food allergy" refers to an immunologically mediated adverse reaction and should preferably be used when involvement of specific hypersensitivity mechanisms can be confirmed. Immunologic reac-

Table 3. Reactivity to gliadin and HLA-DR locus antigens in children with cereal allergy or intolerance

Subject no.	Gliadin antibodies			BHRT* %	HLA-DR
	IgE kU/l	IgA EU/ml	IgG EU/ml		
1	53.6	1.23	32.26	<u>62.2</u>	DR1
2	15.9	0.10	15.50	<u>46.8</u>	n.d.
5	<0.4	0.10	5.15	<u>4.3</u>	n.d.
6	5.8	0.12	7.05	<u>67.7</u>	n.d.
7	<0.4	<0.10	5.19	<u>7.4</u>	n.d.
8	7.1	<0.10	3.17	<u>60.5</u>	n.d.
10	<0.4	0.12	22.50	<u>5.5</u>	n.d.
11	2.5	0.32	43.20	<u>58.5</u>	n.d.
13	2.6	1.23	13.66	<u>58.9</u>	n.d.
14	<0.4	<0.10	4.06	<u>82.4</u>	n.d.
15	0.7	<0.10	10.00	<u>15.3</u>	DR3,4
16	0.5	<0.10	5.88	<u>8.5</u>	n.d.
17	4.4	0.14	21.07	<u>85.4</u>	DR1,2
18	<0.4	0.13	6.40	<u>9.9</u>	DR4,5
19	<0.4	0.16	32.15	<u>2.1</u>	DR2,6
20	<0.4	<0.10	0.80	<u>1.7</u>	DR1,8
21	<0.4	<0.10	1.02	<u>2.6</u>	DR2,4
23	0.4	<0.10	5.93	<u>6.1</u>	DR6,8

* Positive values underlined. n.d.=not done. EU=ELISA units.

tivity to cereals could be verified in 21/23 challenge-proven cases in the present investigation by combining type I and type IV allergy tests. Our challenge-positive cases were therefore designated as cereal allergy or intolerance.

Cow's milk allergy has been a common topic in studies on food allergy; hence, epidemiologic data on the prevalence of this food allergy are available. Cereal allergy has been investigated less extensively, and its prevalence, clinical features, and diagnosis are less clear. We cannot present any epidemiologic data on the frequency of cereal allergy, but, from our clinical experience, allergy to ingested cereals is more common than generally believed. Especially among older children and adults, one more frequently encounters atopic patients with allergy to cereals than to milk. Several older children with cereal allergy or intolerance were included in the present study. We found that retention of allergy to cereals in subjects over 5 years of age was associated with allergies to other foodstuffs and with respiratory atopic diseases. In a follow-up study by Guillet & Guillet, food allergy was a prognostic factor for the development of respiratory symptoms (9). There is evidently a clustering of allergic and atopic diseases reflecting more severe disturbances of basic immunologic mechanisms.

The discrepancy between different centers performing food challenges in the onset of provocation-induced symptoms is surprising. Some investigators rarely see delayed reactions to foodstuffs (6), whereas, according to the experience of others (1, 13,

Table 2. Patch test and lymphocyte proliferation test (LPT) with cereals

Subject no.	Patch test	LPT* (SI)
19	—	1.56
20	+	2.59
21	?+	4.41
22	—	0.85
23	+	12.44

* Results obtained at optimal antigen concentrations (25–100 µg/ml) are shown.

14) and ourselves (20), delayed reactions are common, at least in milk and cereal allergies. Investigators supporting the view that most food-allergic reactions are immediate-onset generally apply a fast provocation schedule. It is conceivable that administration of a relatively large amount of food in a short time favors the development of early symptoms. Some immediate food reactions are so obvious that there is no need to refer the patient to hospital for further investigation. Therefore, the real proportion of immediate food reactions is probably higher than that seen in hospitals or allergy research centers; nevertheless, delayed reactions are common, at least in the case of some foodstuffs.

How food challenges should be done is also in dispute. A protocol of placebo-controlled, double-blind challenges is firmly favored by US centers (6), but this has also been criticized (15). In fact, there is no ideal challenge protocol. In open challenges, patients' and doctors' attitudes and expectations may affect the outcome. The main difficulty with the double-blind food challenge is how to apply this protocol to delayed reactors. Some patients require several days' provocation and large antigen doses before symptoms develop. For increased reliability of open or blind food challenges, it would be worthwhile to ignore vague symptoms, lengthen the challenge schedule when necessary, and follow up the patient after challenge.

Tests such as the prick test, RAST, and BHRT are generally applied to confirm the involvement of type I allergy mechanisms in adverse reactions to foodstuffs. According to previous investigations, the value of these tests has been doubtful in the case of cereal allergy (4, 11, 19). However, the numbers of challenged patients in these studies were small, and there was no clear distinction between immediate and delayed reactions. In the present investigation, all subjects with cereal-induced immediate symptoms were positive in one or more type I allergy tests, but 5/14 subjects with a delayed reaction pattern remained negative in these tests. These five children were further studied with tests of type IV allergy, with a positive outcome in three cases. Patch testing is generally used to study allergy to low-mol.-mass, haptenic contact sensitizers, but this method can also be used in food allergy (7, 18, 20). Food patch tests tend to be weaker than reactions induced by ordinary contact sensitizers; thus, it may be more difficult to distinguish allergic from irritant reactions. The LPT is another test that could be applied if type I allergy tests remain negative. This test has previously been used to confirm allergy to milk, soy, and egg (1, 17, 20, 23).

Cereals, like many foodstuffs, contain various antigenic proteins. Special interest has been focused on the gliadin fraction because of its connection with

celiac disease. Here we investigated whether atopic subjects with cereal allergy or intolerance reacted to gliadin. Half of the patients exhibited a positive response to gliadin in type I allergy tests. In earlier investigations, IgE antibodies against gliadin were found in some patients with baker's asthma (5, 6). When ingested or inhaled, gliadin is evidently capable of inducing type I allergy, at least in some subjects. IgA or IgG antibodies against gliadin were elevated in about 40% of our patients with cereal allergy or intolerance. Determination of these antibodies is used as a serologic test for celiac disease. The test is not specific for celiac disease, about 10% false-positive results having been reported in healthy controls (3, 21). Among atopics and subjects with cereal or other food allergies, the proportion of false-positive values in IgA/IgG gliadin antibodies appears to be even higher.

Upon challenge with cereals, eight of our atopic children developed gastrointestinal symptoms. Diagnosis of cereal allergy does not rule out celiac disease, and the possibility of coexistent celiac disease was therefore further investigated. The diagnosis of celiac disease is based on the histologic analysis of a small intestinal biopsy and favorable response to an elimination diet. However, an intestinal biopsy is useless if the patient avoids gluten-containing cereals because of allergic symptoms. Measurement of IgA reticulin antibodies is a reliable serologic test in childhood celiac disease (10), but, like the biopsy, it is dependent on gluten challenge. Reticulin antibodies were measured in our patients with cereal allergy or intolerance, but the negative results obtained were inconclusive in many cases because of inadequate intake of gluten-containing cereals. Some 85–95% of Scandinavian children with celiac disease express the HLA-DR3 antigen (8, 25). Our patients with cereal-induced gastrointestinal symptoms were therefore HLA-DR-typed, and one subject was found to be DR3-positive. This patient became tolerant to wheat with time and probably does not have celiac disease. Evidently, our patients with gastrointestinal symptoms suffered from cereal allergy without coexistent celiac disease. With the aid of newer methods such as determination of HLA-DQ gene markers and γ/δ -T-cell-receptor-positive cells in intestinal biopsies, the diagnosis and differential diagnosis of celiac disease will be improved, and selection of susceptible patients for follow-up will be better accomplished (16).

Our patient material was restricted to children with AD. In this group, type I or IV hypersensitivity to cereals could be verified in 21/23 challenge-proven cases. It is an advantage if a panel of different laboratory tests can be used to confirm clinical hypersensitivity. Subjects sensitized to cereals frequently react to gliadin in immunologic tests; never-

theless, the coexistence of cereal allergy and celiac disease seems to be rare.

References

1. ALBANI S, AVANZINI MA, PLEBANI A, et al. Diagnostic value of a lymphocyte stimulation test in cow milk protein intolerance. *Ann Allergy* 1989; 63: 489–92.
2. BALDO BA, SUTTON R, WRIGLEY CW. Grass allergens, with particular reference to cereals. *Progr Allergy* 1982; 30: 1–66.
3. BARNES RMR, BARTON PG, DOIG JE, FINN R, HARVEY MM, JOHNSON PM. Distribution of serum antibodies to wheat gliadin and bovine milk in atopic and non-atopic healthy adults. *J Clin Lab Immunol* 1983; 12: 175–8.
4. BJÖRKSTÉN F, BACKMAN A, JÄRVINEN KAJ, et al. Immunoglobulin E specific to wheat and rye flour proteins. *Clin Allergy* 1977; 7: 473–83.
5. BLANDS J, DIAMANT B, KALLÓS P, KALLÓS-DEFFNER L, LØWENSTEIN H. Flour allergy in bakers. I. Identification of allergenic fractions in flour and comparison of diagnostic methods. *Int Arch Allergy Appl Immunol* 1976; 52: 392–406.
6. BOCK SA, SAMPSON HA, ATKINS FM, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. *J Allergy Clin Immunol* 1988; 82: 986–97.
7. BRENNEMAN JC, SWEENEY M, ROBERT A. Patch tests demonstrating immune (antibody and cell-mediated) reactions to foods. *Ann Allergy* 1989; 62: 461–9.
8. EK J, ALBRECHTSEN D, SOLHEIM BG, THORSBY E. Strong association between the HLA-Dw3-related B cell alloantigen-DRw3 and coeliac disease. *Scand J Gastroenterol* 1978; 13: 229–33.
9. GUILLET G, GUILLET M-H. Natural history of sensitizations in atopic dermatitis. A 3-year follow-up in 250 children: food allergy and high risk of respiratory symptoms. *Arch Dermatol* 1992; 128: 187–92.
10. HÄLLSTRÖM O. Comparison of IgA-class reticulin and endomysium antibodies in coeliac disease and dermatitis herpetiformis. *Gut* 1989; 30: 1225–32.
11. HANNUKSELA M. Diagnosis of dermatologic food allergy. *Ann Allergy* 1987; 59: 153–6.
12. HARVIMA RJ, HARVIMA IT, FRÄKI JE. Optimization of histamine radio-enzyme assay with purified histamine-N-methyltransferase. *Clin Chim Acta* 1988; 171: 247–56.
13. HILL DJ. Clinical recognition of the child with food allergy. In: HARMS HK, WAHN U, eds. Food allergy in infancy and childhood. Berlin: Springer-Verlag, 1989: 61–70.
14. HILL DJ, HOSKING CS. Diet-related eczema. *Clin Exp Allergy* 1989; 19: 81–2.
15. HILL DJ, HOSKING CS. Some limitations of double-blind, placebo-controlled food challenges in young children. *J Allergy Clin Immunol* 1991; 87: 136–7.
16. HOLM K, MÄKI M, SAVILAHTI E, LIPSANEN V, LAIPPALA P, KOSKIMIES S. Intraepithelial $\gamma\delta$ T-cell-receptor lymphocytes and genetic susceptibility to coeliac disease. *Lancet* 1992; 339: 1500–3.
17. KONDO N, AGATA H, FUKUTOMI O, MOTOYOSHI F, ORII T. Lymphocyte responses to food antigens in patients with atopic dermatitis who are sensitive to foods. *J Allergy Clin Immunol* 1990; 86: 253–60.
18. LANGELAND T, BRAATHEN LB, BORCH M. Studies of atopic patch tests. *Acta Derm Venereol (Stockh)* 1989; Suppl. 144: 105–9.
19. NOLTE H, SCHIÖTZ PO, KRUSE A, SKOV PS. Comparison of intestinal mast cell and basophil histamine release in children with food allergic reactions. *Allergy* 1989; 44: 554–65.
20. RÄSÄNEN L, LEHTO M, REUNALA T. Diagnostic value of skin and laboratory tests in cow's milk allergy/intolerance. *Clin Exp Allergy* 1992; 22: 385–90.
21. UNSWORTH DJ, WALKER-SMITH JA, HOLBOROW EJ. Gliadin and reticulin antibodies in childhood coeliac disease. *Lancet* 1983; i: 874–5.
22. VAINIO E, KALIMO K, REUNALA T, VIANDER M, PALOSUO T. Circulating IgA- and IgG-class antigliadin antibodies in dermatitis herpetiformis detected by enzyme-linked immunosorbent assay. *Arch Dermatol Res* 1983; 275: 15–18.
23. VAN SICKLE GJ, POWELL GK, McDONALD PJ, GOLDBLUM RM. Milk- and soy protein-induced enterocolitis: evidence for lymphocyte sensitization to specific food proteins. *Gastroenterology* 1985; 88: 1915–21.
24. VARTDAL F, GAUDERNACK G, FUNDERUD S, et al. HLA class I and II typing using cells positively selected from blood by immunomagnetic isolation: a fast and reliable technique. *Tissue Antigens* 1986; 28: 301–12.
25. VERKASALO M, TIILIKAINEN A, KUITUNEN P, SAVILAHTI E, BACKMAN A. HLA antigens and atopy in children with coeliac disease. *Gut* 1983; 24: 306–10.
26. WALSH BJ, WRIGLEY CW, MUSK AW, BALDO BA. A comparison of the binding of IgE in the sera of patients with baker's asthma to soluble and insoluble wheat-grain proteins. *J Allergy Clin Immunol* 1985; 76: 23–8.

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