

Allergy to cow's milk proteins: what contribution does hypersensitivity in skin tests have to this diagnosis?

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Food allergy is an immunologically mediated adverse reaction to food protein. Cow's milk protein allergy (CMPA) is the most frequent type and is the one that is most difficult to diagnose. This study had the objective of analyzing the accuracy of hypersensitivity and specific IgE skin tests among children with CMPA and predominantly gastrointestinal clinical manifestations. The participants in this study were 192 children aged one and five (median of 2 yr). Among these, 122 underwent open oral challenge to the suspected food. After evaluating the sensitivity, specificity and positive and negative predictive values (respectively, PPV and NPV) of skin and specific IgE tests in relation to the gold standard (open oral challenge); all the children underwent the skin prick test (SPT), specific IgE test and atopy patch test (APT) for cow's milk, eggs, wheat and peanuts and the open oral challenge for the food to which the child was sensitive or had suspected sensitivity. Presence of food allergy was confirmed for 50 children (40.9%). Among these cases, 44/50 (88%) were of allergy to cow's milk protein. Children who presented a positive response to an oral challenge to cow's milk protein were considered to be cases, while the controls were children with negative response. Twenty-two of the 44 cases (50.0%) presented symptoms within the first 4 h after the challenge. The SPT presented 31.8% sensitivity, 90.3% specificity, 66.7% PPV and 68.4% NPV. The APT presented 25.0% sensitivity, 81.9% specificity, 45.8% PPV and 64.1% NPV. The specific IgE test presented, respectively, 20.5%, 88.9%, 52.9% and 64.6%. Despite the operational difficulty and the possible exposure risk, oral challenge is the best method for diagnosing CMPA, because of the low sensitivity and PPV of skin and specific IgE tests.

Food allergy is an immunologically mediated adverse reaction to food protein that affects about 6% of all children under the age of five (1). Children with symptoms of food intolerance frequently receive this diagnosis even when the triggering mechanism is not immunologic (2). This contributes toward introducing a restrictive and inadequate diet that has negative repercussions on growth and development (3).

The reactions to food allergies are classified as IgE mediated, lymphocyte mediated or mixed. In the IgE-mediated cases, the clinical response to ingestion of the food is quick, thus making it easy to establish a cause–effect association. The skin prick test (SPT), specific IgE assaying and, more recently, microarray tests are complementary methods used to investigate these conditions (4). These methods have technical limitations that must be considered when interpreting the results. It is important to differentiate sensitivity to

the food from clinical intolerance, given that a positive test does not necessarily mean that a food allergy exists (5).

When food allergy is triggered by cow's milk proteins, gastrointestinal symptoms predominate but may only appear days or weeks after exposure to the antigen, thus making it difficult to establish a causal association (4, 6). The atopy patch test (APT) has been mentioned as an alternative for refining the diagnosis of food allergies that are not mediated by IgE. The results have been promising among children whose clinical manifestation was atopic dermatitis (4, 7–9) but of little help in cases in which the clinical manifestations were predominantly gastrointestinal (4, 10).

The complementary methods used in diagnostic investigations into food allergies, particularly skin tests, should not be indicated indiscriminately or separately (10). The form of clinical presentation and the likely physiopathological mechanism should guide the investigation. The gold standard

for diagnosing food allergy is double-blind, placebo-controlled oral challenge (11). However, because of difficulties in putting this into practice (12), single-blind or open oral challenge has been used more often, especially among children below the age of three, i.e., age group that has the greatest frequency of cow's milk protein allergy (CMPA) (11, 13).

Excessive use of skin tests and specific IgE assays, without proper criteria, causes inadequate case management. The present study had the objective of analyzing the accuracy of these tests for complementary investigation into food allergies among children with predominantly gastrointestinal clinical manifestations.

Materials and methods

The participants in this study were 192 children aged between one and five, who had been referred to the Allergy and Immunology Outpatient Clinic of the Pediatric Service of Hospital das Clínicas, Federal University of Pernambuco (UFPE), which is a public hospital, between May 2006 and December 2007, with a diagnostic hypothesis of food allergy. Among these children, 122 underwent an open oral challenge to the suspected food and the other 70 were excluded from the study.

The children who presented a positive response to the oral challenge were considered to be cases, while the children with a negative response formed the comparison group. A diagnostic accuracy study was performed, in which the sensitivity, specificity and positive and negative predictive values (respectively, PPV and NPV) of skin and specific IgE tests were evaluated in relation to the gold standard (positive response to the open oral challenge).

To characterize the study participants, the following variables were analyzed: gender, age, reports of rhinitis and asthma diagnoses in the parents, clinical manifestations that led to investigation into food allergies (gastrointestinal, respiratory and skin complaints) and frequency of food proteins. Associations between these variables and positive oral challenge results were investigated. At the time of recruitment, the adult responsible for each child answered questions on a structured form, and the objective of the study was explained. After the adult signed the free and informed consent statement, the children were scheduled to undergo the complementary examinations. All of the children underwent the SPT, specific IgE assay and APT for cow's milk, eggs, wheat and peanuts and they underwent the open oral challenge to the food to which they were sensitive or presented suspected sensitivity.

Skin prick test (SPT)

Standardized extracts (IPI-ASAC[®], São Paulo, Brazil) of alpha-lactalbumin, beta-lactoglobulin, casein, egg yolk, egg white, wheat and peanuts were used to carry out the SPT. Duplicate independent readings were carried out by the physician who was the principal investigator and by another physician with experience from the pediatric allergy and immunology outpatient clinic. In the event of disagreement

regarding the size of the papules, the arithmetic mean from this would be applied. The tests were considered positive when the papules were ≥ 3 mm in diameter after 20-min observation, in relation to the negative control.

Atopy patch test (APT)

The APT was carried out using non-standardized extracts. Powdered cow's milk with 3.5% fat, egg white *in natura*, egg yolk *in natura*, wheat flour and ground and sieved peanuts *in natura* were used. All the extracts contained 4 g of protein. Pure Vaseline was tested as the negative control and was used as a vehicle for the foods. The extracts were put in contact with the dorsal region of the thorax, using filter paper of 1 cm² in area, attached using hypoallergenic tape (Micro-pore[®] Sumaré-SP-Brazil). The first reading was carried out 72 h after attachment, 20 min after removing the hypoallergenic tape with the filter paper. The second reading was made 48 h after the first reading. All the readings were performed in duplicate and independently by the physician who was the principal investigator and by another physician from the pediatric allergy and immunology outpatient clinic. Tests were considered positive if they presented at least a hypere-mic reaction associated with palpable edema at the site where the extract had been applied.

Specific IgE assay

The specific IgE was evaluated according to the Immuno-CAP[™] 100[®] technique (Phadia, Uppsala, Sweden). The patients $\geq$ class 1 (0.35–0.7 kU/l) were considered to be positive. Specific IgE assays were measured for alpha-lactalbumin, beta-lactoglobulin and casein.

Oral challenge – open provoking

The technique was performed in accordance with Isolauri (16). Return visits for control occurred after 7, 15 and 30 days. The following signs and symptoms reported by the adults accompanying these children were investigated on these occasions: vomiting, diarrhea, constipation, abdominal pain, skin alterations and respiratory manifestations.

The following foods were tested: cow's milk – powdered cow's milk with 3.5% fat; egg yolk – *in natura*, cooked yolk; egg whites – pure powdered egg albumin; peanuts – Brazilian peanut candy; and wheat – flour. These foods were prepared such that they provided 4 g of protein in 100 ml of volume while the test was performed (17).

Ethical matters and statistical analysis

The project was approved by the Research Ethics Committee of the Health Sciences Center of the Federal University of Pernambuco, Brazil, and appropriate follow-up was provided for all the children with confirmed diagnoses.

The statistical analysis was performed using the Epi-Info software, version 6.04. Associations between the clinical symptoms presented and the existence of any food allergy

Table 1 Characterization of the sample, with regard to age, gender, family antecedents of atopy and symptoms presented

Children	Food allergy n (%)	No food allergy n (%)	p-value
Age	Median 2 yr	Median 2 yr	
Gender	♂ 29 (58.0)	♂ 39 (54.2)	
Family antecedents of atopy*	24/50 (48.0) (+) 26/50 (52.0) (-)	31/72 (43.0) (+) 41/72 (57.0) (-)	0.72
Gastrointestinal symptoms†	40/50 (80.0)	58/72 (80.5)	0.87
Skin symptoms‡	29/50 (58.0)	34/72 (47.2)	0.32
Respiratory symptoms§	34/50 (68.0)	42/72 (58.3)	0.37

*Positive family antecedents of atopy: child's father or mother had a reported diagnosis of rhinitis or asthma.

†Gastrointestinal symptoms: diarrhea, vomiting, constipation, abdominal pain and abdominal distension.

‡Skin symptoms: compatible with eczema and urticaria.

§Respiratory symptoms: compatible with wheezing and rhinitis.

was investigated, while taking open oral challenge to the food in question as the gold standard. The chi-squared test was used to calculate p-values for a 95% confidence interval, along with the sensitivity, specificity, PPV and NPV of each complementary method, and comparisons with the established gold standard were also made.

Results

Out of the 122 children who underwent the open oral challenge, the presence of food allergy was confirmed for 50 (40.9%). The foods involved were as follows: cow's milk protein for 44/50 cases (88%), egg white for 3/50 (6.0%), wheat for 2/50 (4.0%) and peanuts for 1/50 (2.0%).

The children who participated were between the ages of one and five and the median age was two. A smaller percentage of children with food allergy had family antecedents of positive results for atopy compared with the group without food allergy. The most frequent symptoms found among the children were related to the gastrointestinal tract (Table 1).

Because of the high frequency, the diagnostic accuracy of the tests was only determined for CMPA; 22/44 (50%) presented symptoms within the first 4 h after the challenge. The earliest and most frequent symptom was urticaria. Severe reactions were only triggered in two children, with the appearance of nasal catarrh, coughing and dyspnea.

While 8/15 (53.3%) children with positive SPT had immediate reaction, the same happened to 4/15 (26.7%) with specific IgE. Only 3/10 (30% of the children) with positive APT displayed late reactions to open oral challenge. The data shows that 7/22 (31.81%) children with immediate reactions had concordance with SPT positive and 4/22 (18.19%) with sIgE.

Among children with late reactions, 7/22 (31.8%) had APT positive. The late reaction most often observed was diarrhea. The sensitivity of the skin tests and specific IgE assays was low, as were the PPV and NPV (Table 2).

Discussion

Among the children with a diagnosis hypothesis of food allergy who underwent the oral challenge to the food, the diagnosis was confirmed in 50 cases (40.9%). This shows that, even with a suggestive clinical history, it is necessary to deepen the investigation, given that food allergy was confirmed in less than 50% of the suspected cases. Most of these children were male and the median age was two. This is the age group with the greatest occurrence of the disease and it occurs because of immaturity of the gastrointestinal tract and early exposure to proteins that are not from the mother's milk (18).

The main allergen associated with a positive oral challenge was cow's milk, which was responsible for 88.0% of the cases. In a population-based study in England on children up to 6 yr of age, Venter et al. (18) also found that the main proteins causing food allergy were proteins from cow's milk, followed by those from peanuts and eggs. The cow's milk protein has been reported to be the main cause of food allergy within this age group by several authors, regardless of the geographic area in which the study was carried out (1, 7, 18).

Obtaining a detailed clinical history with emphasis on establishing a temporal relation between the introduction of the suspected food and the appearance of symptoms is fundamental for making a diagnostic hypothesis of food allergy. Bush (19) reported that, to define a condition of food allergy, it is important to compile a food diary to make it easier to identify a cause-effect relationship. However, this is usually not enough and it is necessary to use complementary methods to assist in defining the condition.

The presence of family antecedents of atopy has been reported to be a risk factor for the occurrence of allergic conditions among children (20). In the present study, this was not observed and one possible explanation for this is that,

Table 2 Evaluation of sensitivity, specificity, PPV and NPV of the atopy patch test (APT), skin prick test (SPT) and IgE assay, compared with open oral challenge (gold standard)

	Sensitivity	Specificity	PPV	NPV
SPT	31.8 (19.1–47.7)	90.3 (80.4–95.7)	66.7 (43.1–84.5)	68.4 (58.0–77.4)
APT	25.0 (13.7–40.6)	81.9 (70.7–89.7)	45.8 (26.2–66.8)	64.1 (53.4–73.7)
Specific IgE assay	20.5 (10.3–35.8)	88.9 (78.7–94.7)	52.9 (28.5–76.1)	64.6 (54.3–73.9)

PPV, positive predictive value; NPV, negative predictive value.

among family members, only the presence of allergic diseases in which the IgE-mediated mechanism predominated were investigated. This may not be adequate as an atopy marker for this group, in which the predominant symptoms were not mediated by IgE.

In this study, the frequency of gastrointestinal symptoms was similar among the children with confirmed diagnoses of CMPA and those with negative oral challenge results. This emphasizes the importance for this age group of differential diagnosis in relation to other clinical entities such as infectious diarrhea of persistent course, non-specific chronic childhood diarrhea, regurgitation during childhood and gastroesophageal reflux disease (6, 7).

With regard to the oral challenge, we observed that most of the children presented symptoms a few hours after exposure to the suspected food. This suggested that the physiopathologic mechanism involved in these cases was not predominantly mediated by IgE. In a review focusing on food allergy and gastrointestinal symptoms, Dupont emphasized that mechanisms not mediated by IgE are the ones most frequently found (6). Thus, there is a need for clinical monitoring of these children for days or even weeks after reintroducing the food, so that late reactions can be diagnosed.

Most of the complementary methods used in investigations into food allergies (skin tests and specific IgE assays) identify IgE-mediated reactions. These are less frequent among children with predominantly gastrointestinal symptoms, but easier to diagnose, as they occur not more than 4 h after exposure to the triggering protein (12). This explains the low sensitivity of the skin tests and specific IgE assays that were observed in this study, as most of the children presented gastrointestinal symptoms for which the physiopathologic mechanism involved was predominantly not mediated by IgE (7). The PPV was also low and reflected the fact that screening based on clinical history, even if it was performed in detail, was not capable of excluding children with other diseases that shared the same symptoms, as was highlighted earlier.

Skin tests with immediate reading are frequently used in investigations into food allergies (20). They are practical and easy to put into practice, and give quick answers, but their usefulness is debatable in most situations. Even when they are well indicated, the technical issues involved must be considered, as these can make interpretation difficult (5). Another point that must be emphasized is that positive results from the test only identifies the presence of sensitivity, which is not enough to confirm the diagnosis of food allergy. On the other hand, if the test is negative, it is likely that there is no allergy in cases with an IgE-mediated triggering mechanism (5).

The clinical history must guide the choice of method to apply in the investigation. Through the history, the reaction can be classified as immediate or late, i.e., whether the physiopathologic mechanism is most likely to be mediated by IgE or not. In a study on 385 children with a median age of 22 months, in which all the subjects underwent the SPT and oral challenge, Verstege et al. (21) found PPV of 60–70% and NPV of 80–90%. This finding suggests that a negative

response to the test makes it unlikely that there is an IgE-mediated reaction. However, depending on the papule diameter, a positive response requires complementary diagnostic confirmation as such findings may only indicate sensitivity. In this study, the sensitivity to this test was low (31.8%) but the specificity was good (90.3%), while the PPV of 66.7% was similar to that found by Verstege et al. (21). The NPV of 68.4% was below the values reported by other authors (7, 21). Positive answer either to SPT or sIgE and the occurrence of immediate reactions in open oral challenge were low, (53.3%) and (26.7%), respectively. The data support the idea that, for CMPA, skin tests are of little diagnostic use and sometimes may not even be able to detect sensitivity to the protein.

It is necessary to avoid situations in which these tests continue to be requested for children with these clinical characteristics and that, based on an incorrect diagnosis, restrictive diets with deleterious effects on these children's nutritional status and growth are indicated.

Mehl et al. (4) evaluated 501 children with a median age of 13 months and determined the total IgE/specific IgE ratio, with the aim of defining the presence of food allergy conditions, using oral challenge as the gold standard. They found that establishing this relation was complex and that it was no better than the result from the specific IgE assay by itself. They also reported that oral challenge usually continued to be the best option for diagnosing food allergy. In this study, it was observed that the specific IgE assay presented low sensitivity and moderate specificity (20.5% and 88.9%, respectively). The low PPV (52.9%) demonstrated that it was impossible to diagnose food allergy using only this method. The NPV was also low (64.6%) and thus left doubt regarding the non-existence of an allergic reaction to the food.

There are still no methods available, with backing from the literature, which can help to elucidate the diagnoses of cases of food allergy with late manifestation (4, 8). The APT has been mentioned as useful by some authors and it may become an alternative in specific cases (22, 23). Through introducing the APT into the food allergy diagnosis, it was sought to make a practical and accessible complementary method available for clarifying conditions that might have an immunological mechanism without IgE mediation (22, 23). Some authors have taken the view that the APT, together with methods investigating IgE-mediated responses among children with atopic dermatitis and clinically suspected food allergy, would make it possible to do without the oral challenge (24, 25). Osterballe et al. (10) observed children with suspected food allergy, with and without atopic dermatitis, and validated their oral challenge results. Thus, they did not find any justification for using oral challenge. Mehl et al. (4) evaluated 437 children with suspected food allergy, by means of the SPT, specific IgE assay, oral challenge and APT, and found that 90% had atopic dermatitis. They found that performing the oral challenge test to confirm the diagnosis was only unnecessary in 14% of the cases. They also emphasized the technical difficulties in performing the APT, including the lack of adequate standardization, and did not recommend its use as a diagnostic aid (4).

The results found in this study regarding the APT showed low sensitivity (25.0%) but good specificity (81.9%). Only 3/10 (30%) presented late reactions as expected for non-IgE response. The low PPV (45.8%) and NPV (64.1%) showed that the APT was of little use and that the diagnostic investigation needed to be supplemented.

Double-blind, placebo-controlled oral challenge is considered to be the gold standard for diagnosing conditions of food allergy among children. However, it is not used routinely (11). It is not a harm-free examination and may present risks (26). The reactions range from local hyperemia, itching and urticaria, to severe reactions such as anaphylaxis. It may not be conclusive, as it does not demonstrate the adverse reaction mechanism, especially in relation to late reactions. The IgE-mediated response is quick and easily perceptible, occurring no more than 4 h after exposure to the antigen. The child would still be under medical observation over this period. The reactions mediated by cells appear later on, when the children are under direct observation by their families, which may influence the result from the examination. It was found in this study that most of the responses to the open oral challenge were late (27/50 cases; 54%). Therefore, it is important for the child to be followed up for at least 30 days after returning home. There is a need to standardize the procedures, so as to enable comparisons with studies conducted by other investigators (11).

Open oral challenge is, in practice, the technique most used for diagnosing food allergy. It is comparable with double-blind, placebo-controlled oral challenge for children younger than 1 yr of age (11). According to the European Academy of Allergy and Clinical Immunology, open oral challenge can be performed on children up to 3 yr of age (13). After this age, the positive response must be confirmed using a double-blind, placebo-controlled oral challenge (11).

In this study, most of the children were younger than 3 yr of age (mean and median of 2 yr of age). Thus, the results obtained have a high chance of being as accurate as if the study had been conducted using double-blind, placebo-controlled oral challenge.

Prescription of a restrictive diet is only justified in cases in which the likelihood of a positive diagnosis of food allergy is high. In the light of current knowledge, a restrictive diet should only be indicated for children who are very young and have predominantly gastrointestinal symptoms, if their oral challenge findings are positive. These diets sometimes exclude several essential nutrients, which may cause great damage to the child's development and growth. When such a diet is indicated, dietary guidance from a well-trained professional is needed, with the aim of guaranteeing the supply of macro and micronutrients that are important at this age.

In conclusion, despite the operational difficulties and the risk to which the child is exposed, and because of the absence of specific tests that are very accurate, oral challenge using the suspected food is still considered to be the best method for diagnosing CMPA among very young children with predominantly gastrointestinal symptoms. Such children should continue to be followed up for a period of 30 days after carrying out the test, with return visits scheduled for medical evaluations and observation of possible late reactions.

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