



Association of food allergy and atopic dermatitis exacerbations



Emmy M. Roerdink, BS^{*}; Bertine M.J. Flokstra-de Blok, PhD[†]; Janine L. Blok, MD, PhD[‡]; Marie-Louise A. Schuttelaar, MD, PhD[‡]; Bodo Niggemann, MD, PhD[§]; Thomas Werfel, MD, PhD[¶]; Sicco Van der Heide, PhD^{||}; Jeanet Kukler, BS^{*}; Boudewijn J. Kollen, PhD[†]; Anthony E. Dubois, MD, PhD^{*}

^{*} Department of Pediatric Pulmonology and Allergy, University of Groningen, University Medical Center Groningen, GRIAC Research Institute, Groningen, the Netherlands

[†] Department of General Practice, University of Groningen, University Medical Center Groningen, GRIAC Research Institute, Groningen, the Netherlands

[‡] Department of Dermatology, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands

[§] Department of Pediatric Pneumology and Immunology, University Hospital Charité, Berlin, Germany

[¶] Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany

^{||} Department of Laboratory Medicine, University of Groningen, University Medical Center Groningen, GRIAC Research Institute, Groningen, the Netherlands

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ABSTRACT

Background: Atopic dermatitis (AD) and food allergy frequently coexist in children.

Objective: To examine the association between food allergy and AD.

Methods: Between 2001 and 2011, children referred to our tertiary care center underwent double-blind, placebo-controlled food challenges (DBPCFCs) for one or more suspected food allergies as part of regular care. Immediate reactions were observed and recorded by allergy nursing staff, whereas late reactions were ascertained by semistructured telephone interview 48 hours after challenge. To test to which degree specific IgE results were predictive in the outcome of DBPCFCs in children with and without (previous and current) AD, logistic regression analysis was performed.

Results: A total of 1186 DBPCFCs were studied. Sensitization to foods occurred significantly more often in children with previous AD. The association between specific IgE results and the outcome of DBPCFCs was significant for children with and without (previous and current) AD but stronger for children without current AD. The positivity rate of DBPCFCs in children with mild, moderate, and severe AD was 53.3%, 51.7%, and 100%, respectively. Children with AD and a history of worsening AD as their only symptom reacted as often to placebo as to challenge food.

Conclusion: Children with current AD are more frequently asymptotically sensitized to the foods in question than those without AD. In addition, children suspected of food allergy should be considered for testing, regardless of the severity of their AD. Our results suggest that children with exacerbation of AD in the absence of other allergic symptoms are unlikely to be food allergic.

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory multifactorial disease with a relapsing course. Worldwide, approximately 5% to 20% of children are affected by AD, causing a considerable reduction in quality of life of affected patients and their families.^{1,2} Several factors suggest a role for IgE-mediated allergy in the pathogenesis of AD. AD is frequently the first manifestation of the atopic march, and children are at greater risk for developing rhinoconjunctivitis or asthma later in life.³ In addition, approximately two-thirds of patients have a positive history of other atopic symptoms.⁴ Finally,

AD is associated with an increase in specific IgE (sIgE) to foods, which is often already detectable early in childhood.⁵ In general, more severe AD has been reported to be associated with higher prevalence of food allergy.⁶ Consequently, children with mild AD are often not considered to be at significant risk for food allergy; therefore, it is usually not recommended to perform IgE testing and oral challenge testing in these patients.

Because reliable laboratory parameters to establish a diagnosis of food allergy are still lacking, in most cases, double-blind, placebo-controlled oral food challenges (DBPCFCs) remain the gold standard in the diagnosis of food allergy.⁷ Three different clinical reactions have been recognized in patients with AD after food challenge⁸: (1) immediate-type reactions, which commonly occur within 2 hours after ingestion of food, such as urticaria, angioedema, and respiratory symptoms; (2) pruritus, occurring within

Correspondence: Emmy M. Roerdink, BS, University Medical Center Groningen, PO Box 30.001, Hanzeplein 1, 9700 RB Groningen, the Netherlands; E-mail: emroerdink@gmail.com.

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2 hours after the ingestion of food with subsequent scratching, leading to a deterioration of AD; and (3) late reactions (ie, a flare of AD occurring after 6 to 48 hours). Late reactions have also been described to evolve after an immediate-type reaction. Immediate-type responses to certain types of food have been well defined by several studies of patients with AD. However, only a few studies have examined the occurrence of isolated late AD responses, and the observed prevalence in these studies varied.^{9,10}

To study the role of food allergies in AD more extensively, we performed an analysis of children with AD undergoing DBPCFCs at our tertiary care referral center. Our aim was to compare rates of sensitization and clinical reactivity to foods in patients with and without AD. We also examined the association between the severity of AD and prevalence of clinical food allergy. Finally, we looked at the role of food allergy in the occurrence of isolated immediate and late eczematous reactions with and without other symptoms.

Methods

Study Population

Between 2001 and 2011, children referred to our tertiary referral center underwent DBPCFCs as part of regular care because of symptoms of AD or other symptoms, such as gastrointestinal or respiratory symptoms, that were suggestive of food allergy. Children were excluded from DBPCFCs in case of unstable comorbidity that could compromise safety or if they or their parents were unwilling to undergo the test, which was the case in less than 2% of the patients. Descriptive characteristics of the children and details of their DBPCFCs were collected in an electronic database. Only the first challenge performed per child for any given food was used in the analyses. This study was exempted from medical ethical approval after assessment of the Medical Ethical Committee of the University Medical Center Groningen because the DBPCFCs were performed as a routine diagnostic test.

Double-Blind, Placebo-Controlled Food Challenges

A history of previous reactions was obtained, including their nature and frequency. DBPCFCs were performed on 2 separate days, randomly administering either verum or placebo, as previously described.¹¹ During the DBPCFCs, the occurrence of symptoms was registered. Food sIgE was determined using serum samples collected within 6 months of the DBPCFC verum-test day. The serum samples were analyzed using the CAP-FEIA System (Thermo Fisher Scientific, Uppsala, Sweden).

Immediate symptoms were defined as symptoms that occurred during the challenge or within 2 hours after the last dose. Symptoms were considered intermediate when they occurred between 2 and 6 hours and late when they occurred between 6 and 48 hours after the last challenge dose. Immediate and intermediate symptoms were registered while the patient was still under medical supervision.

Two days after each day of the DBPCFCs, late symptoms were registered by a telephone follow-up. During this telephone follow-up, parents were asked about the occurrence of symptoms (including nature and moment of occurrence) after leaving the hospital.

Two days after the second challenge day, the result was determined (positive or negative DBPCFC result). Patients with a positive DBPCFC result were advised to continue the avoidance of the tested food. Conversely, patients with a negative DBPCFC result underwent an open challenge and/or were advised to reintroduce the tested food. Tolerance was confirmed by telephone interview 1 month later.¹¹

AD Measurement During the DBPCFCs

Children and/or parents were questioned about previous and/or current AD. Children with current AD were defined as children having symptoms of AD at the time of presentation and challenge. Children without current AD were divided into those who had had AD previously and those who had never had AD at any time.

Before the DBPCFCs, the children were examined and the presence of AD was quantified using the SCORAD (SCORing Atopic Dermatitis) index by the allergy nurse performing the test.^{12,13} The SCORAD index contains both objective criteria (such as the extent of AD, intensity items such as erythema and oozing and crusting) as subjective items (pruritus and sleep loss).

SCORAD was also performed before each dose of the challenge. The children were carefully examined for the presence and extent of AD. The severity of AD was categorized based on SCORAD before the first challenge day as mild (SCORAD <15), moderate (SCORAD of 15–40), or severe (SCORAD >40). The different clinical reactions in patients with AD after food challenge were categorized as follows.

Clinical reactions in patients with AD after food challenge were as follows: immediate reactions (<2 hours after last dose), including exacerbation of AD only (flush of increased erythema at sites of eczema), only symptoms other than AD, and both exacerbation of AD and other symptoms; intermediate reactions (2–6 hours after last dose) (symptoms occurring 2–6 hours after ingestion of food are not included in the classification of clinical symptoms described in the introduction⁶; however, AD reactions may occur in this period and are therefore included in this study), including exacerbation of AD after immediate reaction and exacerbation of AD without previous immediate reaction; and late reactions (>6–48 hours after last dose), including exacerbation of AD after immediate reaction and exacerbation of AD without previous immediate reaction. These reactions were studied using the SCORAD as a quantitative measurement for AD. An increase of 2 points or more in the SCORAD was considered an increase of AD (exacerbation of AD). The outcome of the DBPCFCs was studied in children in whom suspected food allergy was reported by history to result in an isolated exacerbation of AD and compared with those reporting only other symptoms and those reporting other symptoms in addition to exacerbations of AD.

Statistical Analysis

Descriptive statistics were used for the outcome of DBPCFCs in children with and without AD (previous history and current history of AD). Verum and placebo reactions were determined in children with and without AD. Because spontaneous fluctuations in AD are common, the prevalence of clinical reactions to foods was corrected for the prevalence of events after placebo challenges, as follows. The true clinical reactivity (TCR) was defined as the percentage of reactions to verum challenge minus the percentage of reactions after placebo challenge. The TCR thus reflects the true prevalence of reactivity in the tested group as a whole. Only events occurring within 48 hours after the last dose were considered. In addition, the prevalence of positive DBPCFC results for children with mild, moderate, and severe AD was reported and the corresponding TCR was calculated.

To test the association between sensitization and a previous history of AD, a χ^2 test was performed. The sIgE test result was considered positive if the IgE level was 0.35 kU/L or higher and negative if the IgE level was less than 0.35 kU/L. To test to which degree sIgE results were predictive in the outcome of DBPCFCs in children with and without AD, a univariate logistic regression analysis was performed, using a continuous variable for sIgE.

The clinical reactions in children with AD were recorded and categorized during and after DBPCFCs. The McNemar test was

performed to test whether verum reactions occurred more frequently than placebo reactions within the same group of individuals for different types of clinical reactions.

The verum and placebo reactions in children with a history of only AD were determined, and the TCR was calculated.

$P < .05$ was considered significant. SPSS statistical software, version 20 (SPSS Inc, Chicago, Illinois), was used to analyze the data. The events per variable rule was used to ensure adequate power in the logistic regression analyses.¹⁴

Results

In total, 1186 DBPCFCs were performed in 682 children. Of these 682 children, 577 (84.6%) had ingested the suspected food. Of these 577 children, a previous history of AD (at some point in their lives) was present in 485 children (84.1%). A current history of AD was present in 317 children (54.9%), whereas 247 children (42.8%) did not have a current history of AD, and for 13 children (2.3%) data were missing. Table 1 gives the descriptive data on these children with and without current AD.

Sensitization to Foods and AD

Sensitization to foods occurred in 75.8% of children with a previous history of AD, in contrast to 55.6% of children without a previous history of AD. This difference was significant (Pearson $\chi^2 = 12.64$, $P < .01$). For children with a previous history of AD, sIgE results were associated with the outcome of DBPCFCs (odds ratio [OR], 1.045; 95% confidence interval [CI], 1.028–1.062; $P < .01$). For children without a previous history of AD, sIgE results were also associated with the outcome of DBPCFCs (OR, 1.153; 95% CI, 1.031–1.289; $P = .01$). The ORs of children with and without a previous history of AD were not significantly different ($P = .06$). In addition, for children with a current history of AD, sIgE results were associated with the outcome of DBPCFCs (OR, 1.035; 95% CI, 1.018–1.052; $P < .01$) and for children without a current history of AD (OR, 1.113; 95% CI, 1.054–1.175; $P < .01$). However, the ORs of children with and without a current history of AD were significantly different ($P = .01$). Thus, the association between sensitization and clinical reactivity was significantly stronger in children without than in those with current AD.

Severity of AD and Rate of Positive DBPCFC Results

Of the 317 children with AD at the start of the challenge, 214 children (67.5%) were categorized as having mild AD, 60 (18.9%) as having moderate AD, and 2 (0.6%) as having severe AD. Positive DBPCFC results were seen in 114 (53.3%) of the children with mild

AD, 31 children (51.7%) with moderate AD, and 2 (100%) with severe AD. In the group of patients with mild AD, 121 developed verum reactions after DBPCFCs and 41 placebo reactions (immediate and/or late reactions). Of the children who reacted on both verum and placebo, 7 reacted with more severe reactions on placebo, and therefore the result of the DBPCFC was negative. In the group with moderate AD, 32 verum reactions and 17 placebo reactions occurred. In the group with severe AD, 2 verum and no placebo reactions occurred. This results in a TCR of 80 (37.4%) (mild AD), 15 (25.0%) (moderate AD), and 2 (100%) (severe AD). Thus, the rate of positive test outcomes in patients with mild and moderate AD was comparable. When corrected for placebo reactions, the TCR for mild AD was even nominally higher than for moderate AD.

Clinical Reactions in Patients With AD

Clinical reactions with different time courses after DBPCFCs are given in Table 2. Exacerbations of AD occurring within 2 hours after ingestion of the last dose were rarely seen in isolation but occurred more frequently together with other symptoms, where they were seen more frequently on verum than placebo days ($P < .01$). Intermediate reactions, occurring within 2 to 6 hours after ingestion of the last dose, were rarely seen and were not seen more often on verum days than on placebo days. Late eczematous reactions, occurring after 6 to 48 hours after ingestion of the last dose, were only rarely reported via telephone follow-up.

History of Exacerbation of AD With and Without Other Symptoms

Of all 317 children with AD and a history relating to the suspected food, 6 children had a history of only an exacerbation of AD after having eaten certain foods. The other children had a history of noneczematous symptoms in addition to an exacerbation of AD or a history of only noneczematous symptoms. In the children reporting isolated AD exacerbations after foods in their history, no reactions occurred on verum days, and 3 reactions occurred on placebo days during oral challenges.

Discussion

In this study, all children seen at our tertiary care center for suspected food allergy underwent DBPCFCs. DBPCFCs are considered the gold standard for diagnosing food allergy. We were able to find that children with a previous history of AD were more often sensitized to foods than children without previous AD. One proposed mechanism of the association between AD and food

Table 1
Descriptive Details of Children With and Without Current AD

Characteristic	AD (n = 317)	No AD (n = 247)
Male sex, No. (%)	197 (62.1)	152 (61.5)
Age, mean (SD), y	5.8 (4.5)	6.7 (4.7)
sIgE results, ^a median, kU/L	3.7 ^b	1.1 ^c
Suspected food, %		
Cow's milk	42.9	37.7
Peanut	24.6	26.3
Hen's egg	16.7	11.3
Cashew nut	6.0	9.7
Hazel nut	3.2	6.1
Other	6.6 ^d	8.9 ^e
Outcome challenge positive, No. (%)	165 (52.1)	118 (47.8)

Abbreviations: AD, atopic dermatitis; sIgE, specific IgE.

^aSpecific IgE results for the relevant food(s).

^bn = 299.

^cn = 247.

^dAlmond, soy, wheat, and walnut.

^eAlmond lupine seed, soy, wheat, walnut, pistachio, and macadamia nut.

Table 2
Clinical Reactions in 272 Patients With AD^a

Reaction	Verum, No. (%)	Placebo, No. (%)	P value (McNemar test)
Immediate reactions (<2 hours after last dose)			
Exacerbation of AD only	2 (0.7)	1 (0.4)	
Only symptoms other than AD	110 (40.4)	25 (9.2)	<.01
Both exacerbation of AD and other symptoms	12 (4.4)	0	<.01
Intermediate reactions (2–6 hours after last dose)			
Exacerbation AD after immediate reaction	6 (2.2)	6 (2.2)	
Exacerbation AD without previous immediate reaction	2 (0.7)	3 (1.1)	
Late reactions (>6–48 hours after last dose)			
After immediate reaction	0 (0)	0	
No previous reaction	4 (1.5)	3 (1.1)	

Abbreviation: AD, atopic dermatitis.

^aMissing data occurred in 272 (14.2%) of 317 children.

allergy has been theorized to be increased skin permeability, resulting in increased exposure of the immune system to food allergens, which in turn results in sensitization. Such sensitization would be additional to sensitization that can occur via the gut. This is sometimes referred to as the outside-in theory and could explain why children with AD have a higher prevalence of food allergies,¹⁵ as seen in the present study.

Of even greater interest is our finding that sIgE results were less predictive of the outcome of DBPCFCs in children with current AD than children without current AD. In contrast to previous AD where severity may vary, current AD is known to be associated with more severe AD in early life,¹⁶ which may thus explain why current AD is not only associated with a higher prevalence of sensitization to foods but also with a lesser relevance of the sensitizations that occur: severe AD may predispose to sensitization to foods, but this sensitization is relatively frequently asymptomatic. In contrast, mild infantile AD (not persistent beyond infancy) is more weakly associated with sensitization to foods, but this sensitization is relatively more often associated with clinical reactivity to foods.

Previous studies concluded that children with more severe forms of AD seem to be at higher risk for food allergy than children with milder AD. For example, Hill et al⁶ found that children with severe forms of AD had a relative risk of 5.9 for having a IgE-mediated food allergy compared with children without AD (but with a strong family history of allergy). Guillet and Guillet¹⁷ found that milder forms of AD were not influenced by allergic factors, as opposed to severe AD. We found that 53.5% of children with mild AD and a history suspected of food allergy had positive DBPCFC results, which is comparable to the percentage found in moderate AD. This finding suggests that in children with AD and a history suggestive of food allergy, mild AD does not rule out food allergy; therefore, children with a suggestive history should undergo testing regardless of the severity of their AD.

We found that exacerbations of AD without other symptoms occurring at any time were rare. Reactions on verum days did not occur significantly more often than on placebo days. If an eczematous reaction occurred, other symptoms almost always occurred as well.

Several authors found prevalences of isolated skin symptoms in 30% to 83% of patients with AD undergoing food challenges,^{18–21} which is considerably higher than the prevalence found in our study. However, these studies reported all types of skin symptoms occurring during the challenge. In addition, prevalences might have been overestimated because these percentages were not corrected for spontaneous fluctuations of AD.

Two more detailed studies on challenge reactions in children with AD suspected of food allergy have been performed.^{9,10} In the study by Breuer et al,⁹ 106 challenges resulted in 49 positive results, of which 21 (43%) were immediate (within 6 hours) isolated eczematous reactions. There were 22 late eczematous reactions after immediate reactions, 6 isolated late eczematous reactions, and 2 placebo reactions. Niggemann et al¹⁰ found that on verum days immediate isolated eczematous reactions occurred in 47 (40.5%) of 81 immediate reactions. Only one positive placebo reaction occurred. Late eczematous reactions (after 2 hours) occurred in 22 (18.9%) of 29 late reactions. In 6 cases, immediate and late reactions occurred, of which 5 were isolated eczematous reactions and 1 was AD and urticaria.

The studies of Breuer et al⁹ and Niggemann et al¹⁰ found higher percentages of immediate and late isolated eczematous reactions after DBPCFCs than our study. False-positive challenge results seem an unlikely explanation for this discrepancy because both studies found very few placebo reactions. Unforeseen forms of selection bias may have occurred and caused these differences, but there is no indication that the study population in these reports is

different from those described here. A difference in the way late reactions were ascertained may also have contributed to the difference in the prevalence observed in this study when compared with those cited above. In those studies, patients were observed by trained hospital staff. In contrast, we obtained information from parents using semistructured telephone interviews. It is thus possible that relatively subtle worsening of AD may have escaped the notice of parents. However, time-related factors may be involved. The main authors of these reports^{9,10} have reviewed the present study and conclude that the prevalences of isolated eczematous reactions are currently probably lower than previously reported. Both authors described such reactions as rare. The notion that AD exacerbations unaccompanied by other symptoms are rarely caused by foods is further supported by the finding that the TCR of patients presenting with a history of isolated eczematous reactions was nil.

There are limitations to this study. First, the study population was from a tertiary care referral center. The conclusions here may therefore not be generalizable to the general population. Second, the prevalence of AD in our study population was high, which may have limited our ability to compare children with *previous* AD to those who had never had AD with regard to the association of sIgE to clinical reactivity in the DBPCFCs. Third, we had few children with severe AD. However, the lack of difference in food allergy rates in patients with mild and moderate AD is robust, and although food allergy rates in severe AD may be even higher, the prevalence in the mild AD group is high enough to warrant investigation in clinical practice. Another limitation of this study is that we chose a low SCORAD increment as indicative of worsening AD. Although the main purpose of this approach was to maximize sensitivity of the measurement, it could also have introduced spurious results. However, the number of placebo reactions in this study was low, so undue noise because of an overly sensitive way of using SCORAD does not seem to have occurred. In addition, this study was performed retrospectively. However, to limit possible recall bias, all historical information on the patients was collected before DBPCFCs were performed. Thus, patients and parents were not aware of the test outcome until after the histories had been documented.

In conclusion, in children referred to a tertiary care center suspected of food allergy, we found that those with a current history of AD are more often sensitized to the suspected food. However, the association between sIgE results and the outcome of DBPCFCs was significantly stronger for children without current AD than for those with current AD. This finding implies that children with AD are more frequently asymptotically sensitized to the foods in question. We also found that children with mild AD and a history suspected of food allergy had a substantial rate of positive DBPCFC results. Children suspected of food allergy should therefore be considered for food allergy testing, regardless of the severity of their AD. In contrast to earlier studies, our population of children with AD and a history suggestive of food allergy rarely developed isolated eczematous reactions at any time point during food challenges. When AD exacerbations occurred, they almost always did so in combination with other symptoms. Furthermore, the TCR of challenge-proven food allergy in children with histories of isolated eczematous reactions to foods in this study was nil. Our results thus suggest that children with an exacerbation of AD in the absence of other symptoms in their history are unlikely to be food allergic. The generalizability of this conclusion deserves further study.

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