

Original articles

THE PREVALENCE AND DIAGNOSTIC VALUE OF SPECIFIC IgE ANTIBODIES TO INHALANT, ANIMAL AND PLANT FOOD, AND FICUS ALLERGENS IN PATIENTS WITH NATURAL RUBBER LATEX ALLERGY.

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Key words : Fruit, Immuno-CAP, Latex, prevalence, sensitivity, specificity.

ABSTRACT

Background: It is well recognised that natural rubber latex allergy can be associated with serological cross-reactivity to plant allergens, especially tropical fruits and Ficus. In contrast, data on the frequency and clinical value of specific IgE antibodies against these allergens remain rare. In addition, little is known about the prevalence and diagnostic value of specific IgE antibodies to classical inhalant and animal allergens in NRL allergic patients.

Objective: The purpose of this study was to investigate the prevalence, the sensitivity, and the specificity of these different specific IgE antibodies in patients suffering from NRL allergy.

Methods: Serum samples of 42 NRL allergic adults were investigated. All had a history of NRL allergy con-

firmed by a positive skin test for latex and a positive latex-specific IgE. Samples were analysed for IgE antibodies against 9 plant food allergens (avocado, banana, chestnut, fig, kiwi, papaya, peanut, pineapple and tomato) and *Ficus benjamina*. A specific IgE quantification for 3 animal food allergens (codfish, cow's milk, egg's white) and 8 common inhalant allergens (*Dermatophagoïdes pteronyssinus*, birch pollen, timothy grass pollen, mugwort pollen, cat and dog epithelium, *Aspergillus fumigatus* and *Cladosporium herbarum*) was also performed. Because double blind placebo-controlled challenges could not be considered, for ethical reasons, patient's food allergy or immediate hypersensitivity for Ficus and inhalant allergens was documented by a standardised questionnaire. Diagnosis of atopy was based on a relevant history and the presence of a specific IgE antibody to at least one classical inhalant allergen. For some IgE determinations presence or absence of cross-reactivity was investigated by CAP-inhibition tests.

Results: A specific IgE antibody to at least one of the investigated inhalant and animal food allergens was found in respectively 76% and 12% of the serum samples. A plant food-specific IgE antibody was observed in 88% of the serum samples, most frequently to papaya (71%) and least frequently to kiwi (17%). Twenty-nine percent of the serum samples contained Ficus-IgE. According to the questionnaire and the threshold of 0.35 kUa/L, sensitivity of the plant food IgE antibodies varied between 0% for papaya and 73% for avocado. Specificity varied between 28% for papaya and 91% for kiwi. For Ficus-IgE sensitivity was 20% and specificity 70%.

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Conclusions: For inhalant and animal food allergens sensitivity and specificity of the IgE quantification correlated generally well with the values obtained in non-NRL allergic adults. Determination of specific IgE to the investigated plant foods and Ficus was not always a sensitive neither a specific test to establish the clinical diagnosis of this allergy.

INTRODUCTION

During the last 15 years, IgE-mediated NRL allergy has been recognised to be an increasing international health problem (1,2). An association between NRL allergy and hypersensitivity to banana was first reported in 1989 (3). Today it is well recognised that NRL allergy is associated with serologic and/or clinical cross-reactivity for different plant allergens and in 1994 a "latex-fruit syndrome" has been postulated (4). The immunochemical basis of this cross-reactivity seems to be, at least in part, attributable to the ubiquitous well-conserved pathogenesis-, or rather, defence-related proteins of higher plants (5-7). About 50% (30-80% depending on patient selection, clinical data and test assay) of NRL allergic patients have a concomitant plant-food allergy (4,8). Well-known cross-reacting plants include avocado, banana, chestnut, kiwi, tomato, and Ficus species (4,8-10). In contrast, significant data on the frequency and the diagnostic significance of IgE antibodies to these plant allergens remain rare. Fruit-specific IgE antibodies were observed in 69% of the serum samples of 136 NRL allergic patients (8). However, only 42.6% of these patients were reporting a fruit allergy, and on the contrary, fruit-specific IgE antibodies were detected in only one-third of the patients with a compelling history of fruit allergy. In addition, little is known about the prevalence and diagnostic value of specific IgE antibodies to classical inhalant and animal food allergens in patients suffering from NRL allergy. Recently, an IgE-mediated hypersensitivity for crustacean and fish was estimated to occur in respectively 12% and 8% of 49 patients suffering from a NRL allergy with concomitant food allergy according to a convincing history (11). Therefore, the purpose of the present study was to further evaluate the prevalence of these different specific IgE antibodies in serum samples of NRL allergic adults, and subsequently, to investigate the diagnostic accuracy of these specific IgE antibodies in this population.

METHODS

Subjects

A total of 42 patients (2 men, 40 women - mean age 33 years) were enrolled. Patients were selected if they presented with a compelling history of NRL allergy with symptoms such as urticaria, rhinitis, conjunctivitis, angio-oedema, bronchospasm, generalised anaphylaxis with hypotension, or shock. Job status, glove wearing, number of surgical and obstetrical procedures, and frequency of urogenital and/or rectal contacts with NRL devices (e.g., catheterisations and condoms) were also noted. All had a positive skin test with latex and positive latex-IgE (12). Diagnosis of inhalant allergy was based on a history of childhood eczema, rhinoconjunctivitis or asthma, confirmed by a specific IgE antibody to at least one common inhalant allergen. All participants responded a standardised questionnaire about immediate food hypersensitivity, particularly to avocado, banana, chestnut, fig, kiwi, papaya, peanut, pineapple, tomato, cow's milk, egg's white and fish. Food allergy was diagnosed by a convincing history of allergic symptoms occurring within 60 minutes. Immediate hypersensitivity for Ficus and other ornamental plants was also evaluated. For ethical reasons, double blind placebo-controlled food challenges were not considered because of the high number of possible allergens involved.

Specific IgE

Quantification of total IgE and specific IgE to house dust mite (*Dermatophagoïdes pteronyssinus*), birch, timothy grass, mugwort, cat, dog, *Cladosporium herbarum*, *Aspergillus fumigatus*, cow's milk, egg's white, codfish, avocado, banana, chestnut, fig, kiwi, papaya, peanut, pineapple, tomato, Ficus and *Hevea* latex was performed according to the manufacturer's instructions (Immuno-CAP, Upjohn-Pharmacia CAP System, Brussels, Belgium). Values of allergen-specific IgE equal or below 0.35 kUa/L were considered negative. Sera were not diluted to quantify allergen-specific IgE that exceeded 100 kUa/L. In the absence of a gold standard, sensitivity and specificity of allergen-specific IgE was determined according to the questionnaire data.

Inhibition tests

Inhibition tests were carried out by incubating 100 µL serum of the patient with 3 different concentrations of latex: 10, 100 and 1000 µg/mL (final concentration) or buffer during 1 h at room temperature, followed by determination of allergen-specific IgE using the CAP-system.

RESULTS

Questionnaire data

General characteristics

Evaluation of the questionnaire revealed that 98% of our patients had reactions to NRL gloves, 69% being employed in a medical profession. Other important NRL-containing sources that elicited clinical symptoms were balloons (33%) and condoms (12%). Eighty-eight percent presented with contact urticaria, 76% with angio-oedema, 67% with conjunctivitis, 57% with rhinitis, and 62% suffered from asthma after exposition to NRL containing materials. Hypotension and shock were reported only once and had occurred during general anaesthesia. Gastrointestinal symptoms were not reported. According to the questionnaire, atopy was suspected in 71% of the patients with atopic dermatitis, rhinitis, conjunctivitis, and asthma reported in 48, 67, 55 and 48 percent of the patients respectively.

Plant-derived food and Ficus hypersensitivity

Immediate hypersensitivity reactions due to the ingestion of the investigated plant foods were reported, in a decreasing order, to banana (50%), kiwi (48%), chestnut (48%), tomato (40%), pineapple (33%), avocado (26%), peanut (19%), fig (10%) and finally papaya (7%). Twelve percent reported no reaction at all. Five of our patients suffered from an isolated plant food hypersensitivity, and none against all investigated vegetable foods. Fifty-eight percent of our patients reported their plant food allergy symptoms to be present before or starting simultaneously with their NRL allergy. An oropharyngeal allergy syndrome and urticaria were most often reported (in 71% and 62% of the patients respectively), and 50% suffered from asthma. Rhinoconjunctivitis was reported by approximately 40% of our patients. Twenty-five percent had suffered from gastrointestinal symptoms with abdominal pain and cramps. Severe life-threatening anaphylaxis with hypotension and shock was not

reported. Immediate hypersensitivity reactions to Ficus were reported by 12% of the patients and included itching, contact urticaria, rhinoconjunctivitis and asthma, especially when the plant was dusted off.

Hypersensitivity to cow's milk, egg's white and fish

Respectively 4, 7, and 4 patients reported hypersensitivity to egg's white, cow's milk, and fish. All of them, except one suffering from a fish allergy, were atopic. Except for one patient, these animal food allergies were isolated.

Total serum IgE and latex-specific IgE

In our patients the median (range) of total serum IgE was 220 kU/L (7 - 2000).

According to the inclusion criteria, all patients had circulating IgE antibodies against natural rubber latex between 0.95 and 100 kUa/L (median 13 kUa/L). In 76% of the serum samples, a specific IgE to at least one of the investigated inhalant allergens was detected, in decreasing order, house-dust mite (64%), timothy grass (55%), birch (48%), cat epithelium (43%), dog epithelium (38%), *Cladosporium herbarum* (33%), mugwort (24%) and *Aspergillus fumigatus* (17%). Specific IgE was observed to be positive for cow's milk, codfish and egg's white in 12%, 7% and 5% respectively. Plant food-specific IgE antibodies were found in 88% of the patients suffering from NRL allergy. In 71% of these serum samples IgE antibodies against more than one of the investigated plant food allergen were detected, and 7% of these serum samples contained IgE antibodies against the 9 plant allergens tested. Serum-specific IgE antibodies were found against papaya in 71%, avocado 52%, banana and tomato 45%, fig and pineapple 43%, chestnut 36%, peanut 34%, and finally kiwi 17%. Twenty-nine percent of the serum samples showed a Ficus-specific IgE. Figure 1 summarises the prevalence of specific IgE-antibodies to inhalation, animal food, plant-related food, and Ficus allergens. Figure 2A summarises the sensitivity and specificity of the different IgE determinations to the investigated plant allergens. According to the questionnaire about exposure and reactivity to the distinctive allergens and the classical threshold of 0.35 kUa/L, sensitivity varied between 0% for papaya and 73% for avocado. The lowest specificity was observed for papaya (28%) whilst the specificity for kiwi fruit reached 91%. For inhalant allergens the sensitivity, generally exceeding 80%, varied between

Figure 1: Prevalence of the specific IgE antibodies to the individual inhalation, animal food, Ficus, and plant food allergens.

HDM: House dust mite; GP: timothy grass pollen; TP: birch pollen; WP: mugwort pollen; Clad: Cladosporium herba; Asp: *Aspergillus fumigatus*.

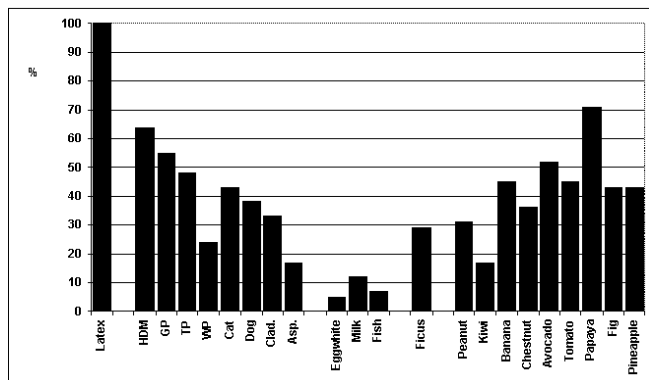


Figure 2A: Sensitivity and specificity of the different specific IgE antibodies to plant allergens.

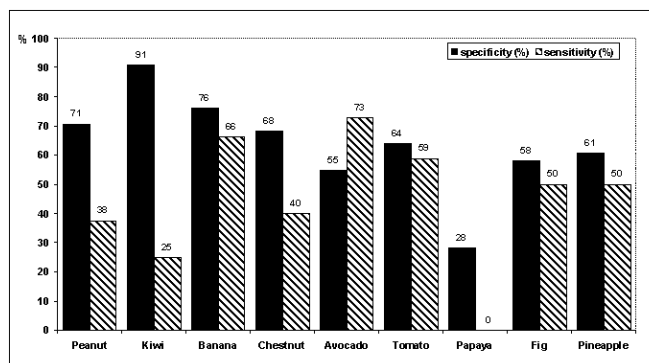
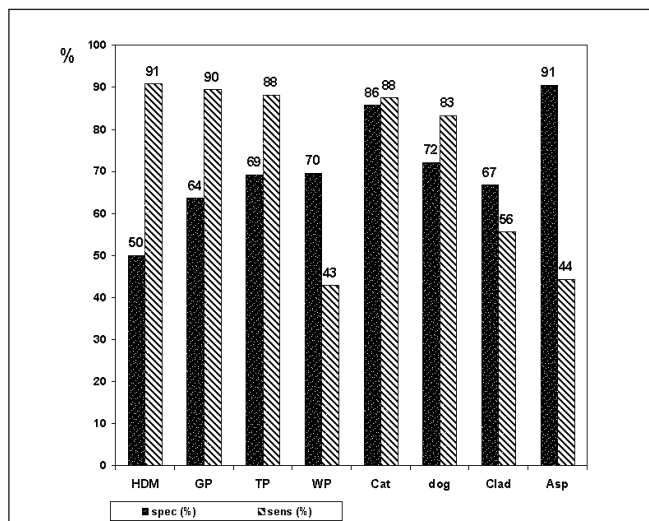


Figure 2B: Sensitivity and specificity of the different specific IgE antibodies to common inhalant allergens.

HDM: house dust mite, GP: grass pollen, TP: tree pollen, WP: weed pollen, Clad: Cladosporium herbarum, Asp: *Aspergillus fumigatus*.

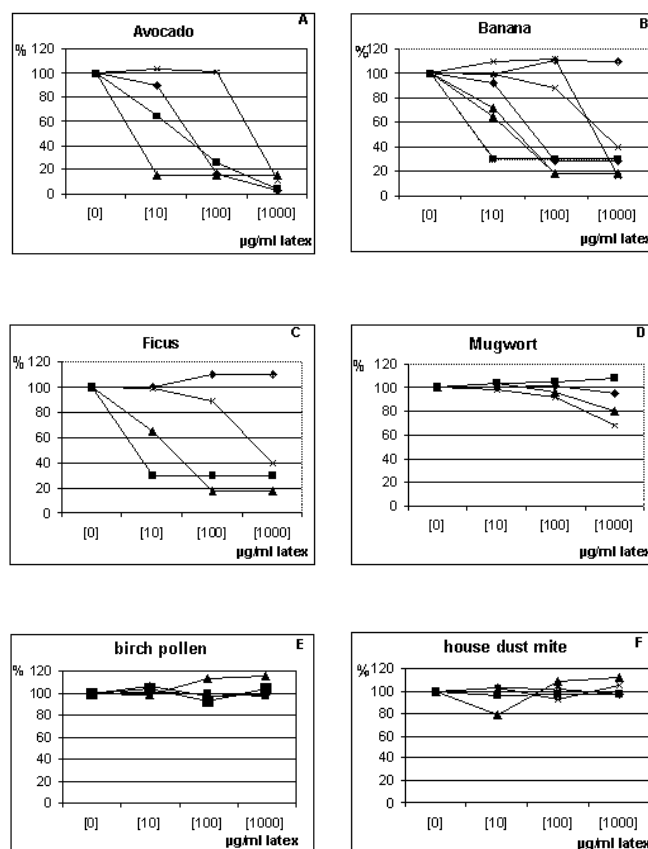


43% for mugwort and 91% for house dust mite. The specificity, was generally lower, varying from 50% for house dust mite and 91% for *Aspergillus fumigatus* (Figure 2B). Finally, for egg's white, cow's milk and codfish, sensitivity was 25%, 14%, and 25%, and specificity was 97%, 89%, and 95% respectively.

CAP inhibition assay

In CAP-inhibition assays, pre-incubation of sera with latex extracts generally almost completely inhibited specific IgE to avocado, banana and Ficus (Fig 3). The inhibition of mugwort-specific IgE was not frequent and clearly weaker with a maximum inhibition of 32% (Fig 3). No significant inhibition of specific IgE against birch pollen and house dust mite was observed (Fig 3).

Figure 3: In CAP-inhibition assays, pre-incubation of sera with latex extracts generally almost completely inhibited specific IgE for avocado (A), banana (B) and Ficus (C). The inhibition of mugwort-specific IgE was not complete with a maximum inhibition of 32% (D). No significant inhibition of specific IgE against birch pollen (E) and house dust mite (F)



DISCUSSION

Seventy-one percent of our NRL-sensitive patients reported classical atopic manifestations. A positive specific IgE to at least one common inhalant allergen could almost always confirm the diagnosis of atopy. IgE antibodies against house dust mite, timothy grass, birch and cat epithelium were the most prevalent with a distribution quite similar to those reported in adult atopics without a NRL allergy (13). Sensitivity and specificity of these IgE determinations correlated generally well with the values in other adult atopic populations (14). Some of our patients suspected egg's white, cow's milk, or fish as causative for their food allergy, and almost all of them were atopic, thereby confirming the few reports incriminating non-plant food, such as milk or fish in NRL allergy to be coincidental in atopic individuals (10). Patients with allergy to NRL are reported to have cross-reactive IgE antibodies and/or clinical cross-allergy to one or more foods, although the particular food or foods are not always specified. In our study, history revealed and confirmed that hypersensitivity reactions were due to, in decreasing order, banana, kiwi, chestnut, tomato, pineapple, avocado, peanut, fig and papaya. In contrast, IgE-reactivity was observed for, in decreasing order, papaya, avocado, banana, tomato, fig, pineapple, chestnut, peanut and finally kiwi, with frequencies significantly higher than the frequencies generally observed in an adult atopic population. In order to evaluate the clinical significance of these serological observations, the results were compared with the responses obtained by a standardised questionnaire. For ethical reasons, double blind, placebo-controlled food challenges could not be performed with all the different fruits and vegetables. According to the proposed 0.35 kUa/L threshold, most of the specific IgE determinations to the investigated plant foods in our study were confirmed to have a rather low sensitivity, seldom exceeding 50%. The low sensitivity of the investigated plant food IgE determinations probably mirrors the discrepancy between perception of food allergy and the results of double blind, placebo-controlled food challenges that constitute the "gold standard" for diagnosing food allergy. In a large cross-sectional survey where 20.4% of the respondents reported suffering from food intolerance, less than 2% actually experienced symptoms when subjected to a double blind, placebo-controlled food challenge (15). Non-IgE-mediated food hypersensitivity and non-immunological food intolerance reactions such as

susceptibility to pharmacological substances (e.g., tyramine or other amines), erroneously described and/or interpreted as an IgE-mediated food allergy might also have influenced the sensitivity calculation. In agreement with previous studies (4,8) the best specific IgE-sensitivity was obtained for avocado. Specificity of the plant-food specific IgE antibodies was observed to be somewhat higher but varied considerably, probably partially reflecting the nutritional habits of our patients, many of them seldom or never consuming tropical fruits. For example, 30 out of our 42 patients reported never having eaten papaya, nevertheless, 23 of them (77%) had a positive papaya-specific IgE. These data seem thereby to re-emphasise that immunochemical cross-reactivity of allergens is an important drawback when using IgE determination for diagnosis of food allergy, mainly affecting specificity of the assay. There might be a clear discrepancy between sensitisation, as revealed by serological tests, and the clinical manifestation(s) of that sensitisation. For example, a majority of grass-allergic patients express serological but clinically irrelevant positivity to cereals (16). In the case of natural rubber latex allergy, the interpretation of a positive specific IgE to plant-derived foods should therefore be done very critically. Sensitivity and specificity did not improve significantly when the results of the different specific IgE determinations were re-evaluated according to thresholds obtained by ROC-analysis (data not presented). In only a limited number of reports there is information on the sequence of sensitisation to NRL and other allergens. Lavaud et al. (17) described a patient with recurrent anaphylactic reactions during cystoscopy, all related to NRL, in a patient with pre-existing hypersensitivity to banana and avocado. Blanco et al. (4) described NRL allergy prior to avocado in four patients, the reverse in two patients and concomitant development of both allergies in four other patients. In our series, up to 58% of the patients with an immediate hypersensitivity for the investigated plant foods, reported this allergy to be present before or to have occurred simultaneously to their NRL allergy. These data seem to confirm that there is a potential for NRL allergy in certain plant food allergic patients and vice versa (18). In agreement with others (3,4,7,8,10,17,19), we were able to demonstrate, in CAP-inhibition assays, serologic cross-reactivity between natural rubber latex and avocado, banana and Ficus. Generally, complete inhibition was observed when serum samples were pre-incubated with natural rubber latex and subsequently evaluated for specific IgE against the investigated fruits. In contrast, and

as expected, no inhibition was found with house dust mite (8). For pollen, no inhibition with birch pollen and some weak inhibition with mugwort pollen were observed. This probably reflects the fact that the prevalence of sensitisation to distinctive pollen allergens varies widely in different regions. In our region hypersensitivity for birch pollen is primarily due to the sensitisation for the major birch pollen allergen Bet v 1 (20), an allergen without homologue in natural rubber latex (21,22). On the other hand, for mugwort allergy, sensitisation is frequently due to profilin (22-24). In contrast to Bet v 1, profilin has been isolated from natural rubber latex (25,26). In addition, the putative role of profilin in fruit-pollen-latex cross-reactivity has clearly been demonstrated (21,24,25).

Taken together, our data re-emphasise that knowledge of immunochemical cross-reactions is very important when using serologic assays for diagnosis of food allergy in NRL allergy. There might be a clear discrepancy between sensitisation, as revealed by serological tests, and the clinical manifestation(s) of that sensitisation. Nevertheless, correct identification of patients with a clinically relevant cross-reactivity is of paramount importance because these patients might be at risk for major NRL induced anaphylaxis.

SAMENVATTING

Achtergrond: Natuurlijke rubber latex allergie is niet zelden vergezeld van een kruisreactiviteit, zij het *in vitro* of *in vivo*, voor plantaardige allergenen, veelal tropisch fruit en ficus. Gegevens betreffende de diagnostische waarde van een specifieke IgE bepaling ten opzichte van deze vruchten en ficus in een populatie natuurlijke rubber allergische patiënten, daarentegen, blijven uit. Een vaststelling die evenzeer geldt voor de specifieke IgE bepalingen voor klassieke inhalatie- en voedingsallergenen.

Doelstelling en methode: Een studie te verrichten naar de prevalentie en diagnostische waarde van een positief IgE bepaald volgens de Immuno-CAP techniek voor de klassieke inhalatieallergenen (*Dermatophagoides pteronyssinus*, berkenpollen, timothy graspollen, bijvoetpollen, katten- en hondenepitheel, *Aspergillus fumigatus* en *Cladosporium herbarum*), 9 plantaardige (avocado, banaan, kastanje, vijg, kiwi, papaja, pinda, ananas, tomaat) en 3 dierlijke (kabeljauw, koemelk, kippeneiwit) voedingsallergenen binnen een populatie van natuurlijke rubber latex allergische

patiënten. De grenswaarde voor positiviteit werd gesteld op 0.35 kUa/L, zoals aangegeven door de producent.

Resultaten: In deze studie, uitgevoerd op 42 individuele sera, blijkt 76% seropositiviteit te bestaan voor minstens 1 inhalatieallergeen terwijl 12% van de stalen IgE-reactiviteit vertoont voor minstens 1 dierlijk voedingsallergeen. De sensitiviteit van deze IgE bepalingen varieert hierbij tussen 43% voor bijvoetpollen en 91% voor de huisstofmijt. De specificiteit schommelt tussen 50% voor de huisstofmijt en 91% voor *Aspergillus fumigatus*. De meest opvallende vaststelling is, ongetwijfeld, het feit dat ruimschoots 88% van de serumstalen IgE reactiviteit vertoont voor minstens 1 van de geteste plantaardige voedingsallergenen. Een papaja-specifiek IgE werd aangetroffen in 71% van de stalen. Ficus-specifiek IgE werd aangetroffen in 29% van de sera. Gezien de inherente praktische en vooral ethische beperkingen van de dubbelblinde placebo gecontroleerde voedselprovocatie werd de sensitiviteit en de specificiteit van deze specifieke IgEs voor voedsel berekend aan de hand van een gestandaardiseerde anamnese. De sensitiviteit schommelde tussen 0% voor papaja en 73% voor avocado. Specificiteit varieerde tussen 28% voor papaja en 91% voor kiwi. Voor Ficus-IgE bedroeg de sensitiviteit 20% en specificiteit 70%.

Conclusie: In deze populatie van natuurlijke rubber latex allergische patiënten blijkt de prevalentie, sensitiviteit en specificiteit van IgE voor inhalatie en dierlijke voedsel in overeenstemming met deze in een groep van volwassen atopici zonder natuurlijke latex rubber allergie. Tevens blijkt dat de dosering van specifiek IgE voor plantaardig voedsel en Ficus vaak noch sensitief noch specifiek is voor een correcte diagnose van deze allergieën.

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