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Sensitivity and specificity of specific IgE, skin prick test and atopy patch test in examination of food allergy

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ABSTRACT

The aim of this study is the evaluation of the specificity and sensitivity of the skin prick tests (SPTs), specific IgE and atopy patch tests (APT) in atopic dermatitis patients suffering from food allergy. A total of 301 patients were examined, complete dermatological and allergological examination was performed in all patients. The food allergy was confirmed to peanuts in 62 patients (20%), to egg in 16 patients (5%), to soy in 9 patients (3%), to wheat in 12 patients (4%) and to cow milk in 6 patients (2%). The specificity of SPT, specific IgE and APT is considered as good; the sensitivity of APT is low. The positive results in isolation cannot confirm the food allergy; however, together with other diagnostic methods, such as clinical history and open exposure test, these tests are valuable tool in examination of food allergy.

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Atopic dermatitis; food allergy; specific IgE; skin prick test; atopy patch tests; challenge tests; sensitivity; specificity

Introduction

Atopic dermatitis (AD) is a chronic, intermittent, inflammatory, genetically predisposed skin disease characterized by severe pruritus and xerosis (Leung & Bieber, 2003). Food is closely associated with the pathogenesis of atopic dermatitis (Sampson, 2003). Some extensive studies were performed in children and it was confirmed that foods, such as cow's milk or hen's egg, can directly cause flares of AD in small children (Leung & Bieber, 2003). But 80% of them outgrow their food allergy. The role of food allergy remains controversial in older children and adult patients suffering from AD, few studies concerning the food allergy in this group of patients are available. AD starts with chronic skin inflammation after a postnatal preclinical phase, but without any evidence for IgE sensitization; it is followed by the emergence of sensitization usually toward food allergen and other environmental factors leading to the classical IgE-associated AD phenotype (Valenta, Mittermann, Werfel, Garn, & Renz, 2009). Non-IgE-mediated mechanisms are sometimes implicated in the AD flare-ups associated with ingestion of the foods in question (Rancé, Boguniewicz, & Lau, 2008). One of the latest systematic review confirms a strong and dose-dependent association between AD, food

sensitization and food allergy; AD of increased severity and chronicity is particularly associated with food allergy (Tsakok et al., 2016).

Diagnosis of food allergy is based on personal history, measurement of specific IgE (serum-specific IgE level – sIgE, skin prick tests – SPTs), atopy patch tests (APTs), challenge tests (open exposure test – OET, double-blind, placebo-controlled food challenge test – DBPCFC). The DBPCFC is considered as the gold standard for diagnosis of food allergies, but it is rarely employed by physicians outside of an academic context. The open food challenge is a more viable option for most clinicians, though it is not without its own pitfalls (Niggemann et al., 2001). Food-specific IgE tests, including serum assays and SPTs, are sensitive for detecting the presence of food-specific IgE (sensitization), but specificity for predicting clinical allergy is limited. Therefore, positive tests are generally not, in isolation, diagnostic of clinical disease. However, rationale test selection and interpretation, based on clinical history and understanding of food allergy, epidemiology and pathophysiology, makes these tests invaluable (Chokshi & Sicherer, 2016). The APT is defined as a patch test procedure to assess the delayed type of hypersensitivity reactions against those protein allergens known to elicit IgE-mediated type I reactions in atopic patients. This patch test procedure uses intact protein allergens instead of haptens in an optimized test setting and with a special reading key (Edwards & Martinez, 2014). A general problem is that an APT with food has mostly been studied in infants and children since the food allergy plays a role in this age group. There are several aspects of APT that deserve further investigation to achieve a better standardization (Wollenberg & Vogel, 2013).

Our study evaluates our experiences with these tests (sIgE, SPT and APT) in examination of food allergy in patients suffering from AD. The aim of our study was to evaluate the specificity and the sensitivity of sIgE, SPT and APT to egg's white and yolk, peanuts, soy, cow's milk and wheat in patients suffering from AD in the age 14 years and older.

Methods

Patients over 14 years of age with AD (as defined by the criteria of Hanifin and Rajka (1980) were examined at the Department of Dermatology at the Faculty Hospital in Hradec Králové (Czech Republic) from January 2006 to April 2014.

Inclusion criteria for the study: age 14 years and over, AD evaluated with scoring of atopic dermatitis (SCORAD) index (Celakovska & Bukač, 2013; Kunz et al., 1997). Exclusion criteria: long-term therapy with cyklosporin or systemic corticoids, pregnancy and breastfeeding. This study was approved by Ethics committee and there is no conflict of interest.

Examinations

After discontinuation of antihistamines and topical steroids for at least 5 days and systemic steroids and ultraviolet therapy for at least 2 months, the SPT, specific IgE and the APT to egg's white and yolk, peanuts, soy, cow's milk and wheat were examined.

The OET with soy, egg, wheat and cow milk was recommended to perform in all examined patients. The diagnostic hypoallergenic diet was recommended to introduce before these OETs in all patients. The OET was not done in patients with early allergic reaction (as oral allergy syndrome, breathlessness and anaphylaxis). Because of anaphylactic

reaction, danger peanuts were not examined in the challenge test. The detailed description of examinations is recorded in our previous publications (Celakovska, 2015; Celakovska & Bukač, 2015; Čelakovská, Ettlerová, Ettler, & Bukač, 2015; Čelakovská, Ettlerová, Ettler, Vaněčková, & Bukač, 2015a, 2015b; Čelakovská, Ettlerová, Vaněčková, & Ettler, 2011).

The diagnosis of food allergy to wheat flour, cow milk, egg, peanuts and soy. (1) Patients with the positive result in OET (early and/or late reactions) with examined food and with the positive result at least at one of the diagnostic method (sIgE, APT and SPT) were considered as the patients with food allergy. The early and the late reactions in OET were evaluated. Early reactions were defined as clinical symptoms within 2 h after the ingestion of this dose in OET and late symptoms if occurring after more than 2 h. (2) Patients with the early reaction after the ingestion of examined food in their history from their childhood and with the positive result at least in one of the diagnostic method (sIgE, APT and SPT) were considered as the patients with food allergy also. The open exposure test was not performed in these patients because of anaphylactic reaction danger (Celakovska, 2015; Čelakovská et al., 2011, 2015, 2015a, 2015b; Celakovska & Bukač, 2015).

Sensitization to food was confirmed in patients with positive results in sIgE and/or SPT and/or APT and negative results in OET and in history (Celakovska, 2015; Čelakovská et al., 2011, 2015, 2015a, 2015b; Celakovska & Bukač, 2015).

Statistical analysis

The comparison of the results in the specific IgE, SPT and APT and really confirmed food allergy in the OET was performed; according to these results, we have calculated the specificity and sensitivity of the specific IgE, SPTs and APTs. Sensitivity (the true positive rate) measures the proportion of positives that are correctly identified as such, and specificity (the true negative rate) measures the proportion of negatives that are correctly identified as such.

Results

Patients

Altogether 301 persons suffering from AD were included in the study: 110 men and 191 women entered the study with 27.1 (SD 9.1 years), min. 14 max. 63 years; with the median SCORAD 30.5 points, SD 12.4 (max. 79.5 points, min. 12.5 points) at the beginning of the study.

Clinical outcomes of challenges. All 301 patients were subjected to SPTs, APTs, and sIgE to wheat, peanuts, cow's milk, soy and egg's white and yolk. The OET with these foods was recommended to perform in all included patients, but OET was not done in patients with early allergic reaction (as oral allergy syndrome, breathlessness, and anaphylaxis). Because of anaphylactic reaction, danger peanuts were not examined in the challenge test.

The food allergy was confirmed to peanuts in 62 patients (20%), to egg in 16 patients (5%), to soy in 9 patients (3%), to wheat in 12 patients (4%) and to cow's milk in 6 patients (2%), Table 1 shows the characteristics of patients.

Specific IgE

The survey of the results of sIgE is shown in Table 2.

Table 1. Characteristics of patients.

301 Patients suffering from AD were included in the study

- 110 Men and 191 women, 27.1 years (SD 9.1 years), min.14 max. 63 years
- The median SCORAD 30.5 points, SD 12.4 (max. 79.5 points, min. 12.5 points)
- The food allergy to peanuts in 62 patients (20%)
- The food allergy to egg in 16 patients (5%)
- The food allergy to soy in 9 patients (3%)
- The food allergy to wheat in 12 patients (4%)
- The food allergy to cow milk in 6 patients (2%)

The comparison between the results of the specific IgE and really confirmed food allergy in the OET was performed and the specificity and sensitivity were calculated. The specificity of sIgE is for soy 93.8%, for egg 86.6%, for wheat 98.6%, for peanuts 92.8% and for milk 93.8%. The sensitivity of sIgE for testing food allergens is for soy 33.8%, for egg 75%, for wheat 66.6%, for peanuts 33.8% and for milk 50%.

Patients with positive results in sIgE and with negative OET are considered as patients with food sensitization – they are designated as the patients with false-positive results at the table. According to these results, the sensitization in sIgE is confirmed to milk in 18 patients (6%), to wheat in 4 patients (1.3%), to peanuts in 17 patients (5.6%), to egg in 38 patients (12.6%) and to soy in 18 patients (6%).

Skin prick test

The survey of the results of SPT is shown in Table 3.

The comparison between the results of SPT and really confirmed food allergy in the OET was performed and the specificity and sensitivity were calculated.

The specificity of SPT is for soy 87.3%, for egg 93.3%, for wheat 94.1%, for peanuts 87.8% and for milk 97.9%. The sensitivity of sIgE for testing food allergens is for soy 44.4%, for egg 68.7%, for wheat 16.1%, for peanuts 38.7% and for milk 33.3%. Patients with positive results in SPT and with negative OET are considered as patients with food sensitization – they are designated as the patients with false-positive results at the table. According to these results, the sensitization in SPT is confirmed to milk in 6 patients (2%), to wheat in 17 patients (5.6%), to peanuts in 29 patients (9.6%), to egg in 19 patients (6.3%), and to soy in 37 patients (12.2%).

Atopy patch tests

The survey of the results of APT is shown in Table 4.

Table 2. The results of specific IgE (sIgE) in 301 patients included in the study.

Examined food	No. of patients with confirmed food allergy in the challenge tests	No. of patients with IgE-positive results	True positive sIgE results	False-positive sIgE results	False negative sIgE results	Specificity of sIgE	Sensitivity of sIgE
Milk	6 (2%)	21 (7%)	3 (1%)	18 (6%)	3 (1%)	93.8%	50%
Wheat	12 (4%)	12 (4%)	8 (2.6%)	4 (1.3%)	4 (1.3%)	98.6%	66.6%
Peanut	62 (20%)	38 (12.6%)	21 (7%)	17 (5.6%)	41 (13.6%)	92.8%	33.8%
Soy	9 (3%)	21 (7%)	3 (1%)	18 (6%)	6 (2%)	93.8%	33.3%
Egg	16 (5%)	50 (16.6%)	12 (4%)	38 (12.6%)	4 (1.3%)	86.6%	75%

Table 3. The results of SPTs in 301 patients included in the study.

Examined food	No. of patients with confirmed food allergy in the challenge tests	No. of patients SP-positive results	True positive SPT results	False-positive SPT results	False negative SPT results	Specificity of SPT	Sensitivity of SPT
Milk	6 (2%)	8 (2.6%)	2 (0.6%)	6 (2%)	4 (1.3%)	97.9%	33.3%
Wheat	12 (4%)	19 (6.3%)	2 (0.6%)	17 (5.6%)	10 (3.3%)	94.1%	16.1%
Peanut	62 (20%)	53 (17.6%)	24 (8%)	29 (9.6%)	38 (12.6%)	87.8%	38.7%
Soy	9 (3%)	41 (13.6%)	4 (1.3%)	37 (12.5%)	5 (1.6%)	87.3%	44.4%
Egg	16 (5%)	30 (10%)	11 (3.6%)	19 (6.3%)	5 (1.6%)	93.3%	68.7%

The comparison between the results of the APT and really confirmed food allergy in the OET was performed and the specificity and sensitivity were calculated.

The specificity of APT is for soy 94.8%, for egg 94.7%, for wheat 97.5%, for peanuts 96.6% and for milk 98.9%. The sensitivity of sIgE for testing food allergens is for soy 44.4%, for egg 31.3%, for wheat 42%, for peanuts 10.7% and for milk 25%.

Patients with positive results in APT and with negative OET are considered as patients with food sensitisation – they are designated as the patients with false-positive results at the table. According to these results, the sensitization in APT is confirmed to milk in 3 patients (0.9%), to wheat in 7 patients (2.3%), to peanuts in 7 patients (2.3%), to egg in 15 patients (5%), and to soy in 15 patients (5%).

The comparison of the results in specificity and sensitivity of the SPTs, specific IgE and APTs is shown in Table 5.

Discussion

IgE-mediated food allergies are an important public health problem, affecting 5% of adults and 8% of children, with numerous studies indicating that the prevalence is increasing. The question of food allergy in patients suffering from AD was evaluated in the several studies (Celakovska, 2015; Čelakovská et al., 2011, 2015, 2015a, 2015b; Celakovska & Bukač, 2013, 2015). Food allergic reactions can range in severity from mild to severe and life threatening. Accurate diagnosis of food allergy is necessary not only to provide appropriate and potentially life-saving preventive measures but also to prevent unwarranted dietary restrictions (Bergmann, Caubet, Boguniewicz, & Eigenmann, 2013; Peters et al., 2013). Once an underlying food allergy is confirmed, the avoidance of the incriminated food is generally recommended and usually leads to an improvement of the AD

Table 4. The results of APT in 301 patients included in the study.

Examined food	No. of patients with confirmed food allergy in the challenge tests	No. of patients APT-positive results	True positive APT results	False-positive APT results (sensitization)	False negative APT results	Specificity of APT	Sensitivity of APT
Milk	6 (2%)	4 (1.3%)	1 (0.3%)	3 (0.9%)	5 (1.6%)	98.9%	25%
Wheat	12 (4%)	12 (3.9%)	5 (1.6%)	7 (2.3%)	7 (2.3%)	97.5%	42%
Peanut	62 (20%)	13 (4.3%)	6 (1.9%)	7 (2.3%)	56 (18.6%)	96.6%	10.7%
Soy	9 (3%)	19 (6.3%)	4 (1.3%)	15 (4.9%)	5 (1.6%)	94.8%	44.4%
Egg	16 (5%)	20 (6.6%)	5 (1.6%)	15 (4.9%)	11 (3.6%)	94.7%	31.3%

Table 5. The specificity and sensitivity of specific IgE, APTs and SPT to examined foods.

Food allergen	OET – confirmed food allergy	Examination					
		APT		sIgE		SPT	
		Specificity %	Sensitivity %	Specificity %	Sensitivity %	Specificity %	Sensitivity %
Peanuts	62 (20%)	96.6	10.7	92.8	33.8	87.8	38.7
Egg	16 (5%)	94.7	31.3	86.6	75	93.3	68.7
Soy	9 (3%)	94.8	44.4	93.8	33.3	87.3	44.4
Wheat	12 (4%)	97.5	42	98.6	66.6	94.1	16.1
Cow's milk	6 (2%)	98.9	25	93.8	50	97.9	33.3

Note: OET, open exposure test; APT, atopy patch test; SPT, skin prick test; sIgE, specific IgE.

(Asero, Fernandez-Rivas, Knulst, & Bruijnzeel-Koomen, 2009; Bergmann et al., 2013; Celakovská, Ettlerová, Ettler, Bukač, & Bělobrádek, 2012; Peters et al., 2013).

At this study, we evaluated the occurrence of food allergy in 301 patients suffering from AD. The occurrence of food allergy is confirmed to peanuts in 62 patients (20%), to egg in 16 patients (5%), to soy in 9 patients (3%), to wheat in 12 patients (4%) and to cow milk in 6 patients (2%). In comparison with our previous study, where 240 patients was examined, the food allergy was confirmed in 20% of patients to peanuts, in 6% to egg, in 3.3% to soy, in 2.5% to wheat and in 0.8% to milk (Čelakovská et al., 2015b). The rising occurrence of food allergy to wheat and to milk is observed.

The specificity and the sensitivity of sIgE, SPT and APT were evaluated according to the results in OET. In evaluation of the specificity and sensitivity of these single tests, we can observe different results. Regarding the specificity of APT, it may be considered good, because it is over 94% for each type of food allergy. Regarding the sensitivity of APT, we have a small number of observations, but in the case of peanuts or eggs, the sensitivity is 10.7% and 31.3%, respectively, and that means, 90% (69%, respectively) of test results are false negative. APT was a useful tool in diagnosing of food allergy to egg in two patients at this study; these patients had no positive results in SPT and sIgE, but the delayed reactions appeared during the OET and APT test was positive with egg also.

Regarding the sIgE, the specificity is lower for egg – 86.6%, but for other foods, it is about 93% and for wheat 98.6%. Sensitivity of sIgE is considered as good for egg and for wheat (75% and 66%, respectively), lower sensitivity was calculated for peanuts (33.8%), for soy (33.3%) and for milk 50%.

Regarding the SPT, the specificity is in general good; the sensitivity of SPT is considered good for egg 68.7%, but for other foods is lower – 38.7% for peanuts, 44.4% for soy, 16.1% for wheat and 33.3% for cow milk.

Patients with positive results in sIgE and with negative OET are considered as patients with food sensitization – they are designated as the patients with false-positive results given in Tables 2–4.

We evaluated, if our results of SPT had agreed with those of sIgE in patients with confirmed food allergy. Regarding the milk, soy and wheat allergy – there is no agreement in results of SPT and sIgE; regarding the peanut allergy – true positive results were recorded in sIgE in 21 patients and in SPT in 24 patients, the agreement between SPT and sIgE was in 10 patients. Regarding the egg allergy, true positive results were recorded in sIgE in 12 patients and in SPT in 11 patients, the agreement between SPT and sIgE was in 6 patients. There are some studies evaluating the diagnosis and management of food allergy, mainly

in children population. Keefe conducted a systematic review of literature published within the last 5 years. According to his conclusion, the mainstays of diagnosis and management in food allergy remain relatively unchanged; though we rely heavily on SPT, component testing will likely contribute to improved diagnostic accuracy (Keefe et al., 2014). Fleischer et al. found that most children diagnosed with food allergy on the basis of immunoassays were able to reintroduce the suspected food into their diet following challenge (Fleischer et al., 2011). Food challenges are also useful in establishing the diagnosis of non-IgE-mediated processes that cannot be detected by SPT or sIgE testing (Järvinen & Sicherer, 2012; Lieberman, Cox, Vitale, & Sampson, 2011). A recent study confirmed 100% correlation between a positive DBPCFC and a positive single-blind OET among patients with peanut allergy (Glaumann, Nopp, Johansson, Borres, & Nilsson, 2013). Several methods exist by which OET may be conducted, with many clinicians using individualized protocols. These protocols can vary in terms of timing, dosing, the agent used and the definition of a positive or negative challenge (Keefe et al., 2014). Spergel et al. evaluated the incidence of food allergy development in infants with AD and the predictive value of food-antigen-specific immunoglobulin E measurements for cow's milk, egg white, peanut, wheat, seafood mix and soybean. In a large cohort of infants at risk for development of food allergy, sIgE levels were not clinically useful for predicting food allergy development (Spergel et al., 2015). Soares-Weiser et al. investigated the accuracy of tests used to diagnose food allergy; SPTs, specific-IgE component-resolved diagnosis and the APT were compared with the reference standard of DBPCFC. Seven databases were searched and international experts were contacted; according to their conclusion, the evidence base is limited and weak and is therefore difficult to interpret, but overall, SPT and sIgE appear sensitive although not specific for diagnosing IgE-mediated food allergy (Soares-Weiser et al., 2014). Mehl et al. investigated the concordance of SPT and sIgE serum assays with regard to suspected food allergy, the concordance between SPT and sIgE was surprisingly low for cow's milk and hen's egg on an individual basis. Therefore, the tests should not be used interchangeably. Especially in children who receive a negative test result the alternative test should also be used. Their data indicate again that oral food challenges are still the method of choice to diagnose food allergies (Mehl, Niggemann, Keil, Wahn, & Beyer, 2012). On the other hand, according to Yang, the SPT for detecting atopic sensitization is not preferred in young infants with AD because of concerns about poor skin reactivity. This study aimed to evaluate whether the results of SPT agreed well with those of specific serum immunoglobulin E antibody test in young infants with AD; 199 infants tested for egg white and 192 infants tested for cow's milk by both SPT and sIgE on the same day were identified and reviewed retrospectively. The conclusion is that the results of SPT agreed well with those of sIgE. This finding provides a rationale for using SPT and suggests that SPT can be used along with sIgE to detect food sensitization in young infants with AD (Yang et al., 2014). Perry et al. sought to determine the value of food-specific IgE levels in predicting challenge outcome. A retrospective chart review of 604 food challenges in 391 children was performed; the conclusion is that allergen-specific IgE concentrations to milk, egg, peanut, wheat and soy serve as useful predictors of challenge outcome and should be considered when selecting patients for oral challenge to these foods (Perry, Matsui, Kay Conover-Walker, & Wood, 2004). Gusta examined the accuracy of the ratio of sIgE to total IgE ("Ratio") in predicting the outcome of challenges performed to confirm the development of tolerance. Medical

records of children diagnosed with food allergy who participated in oral food challenge at an allergy outpatient clinic (2009–2013) were reviewed for IgE antifoed serology and concomitant oral food challenge outcomes, which were analyzed for associations by using logistic regression models and receiver operator characteristics curves. Their findings suggest that the Ratio is more accurate than sIgE alone in predicting outcomes of challenges performed to confirm the development of tolerance to select food allergens, especially to peanut and tree nuts (Gupta, Lau, Hamilton, Donnell, & Newhall, 2014). According to Bellini, SPT and specific IgE tests are very useful but limited in their predictive accuracy. A validation of such results in a prospective study could be useful to confirm the outcome of the data in the predictivity of OET (Bellini, Ricci, Remondini, & Pession, 2014). According to Schoos, little is known about the agreement between the two methods (sIgE and SPT) in young children. SPT and sIgE levels were assessed simultaneously for 16 common inhalant and food allergens in 389 children. The conclusion is that there is a substantial disagreement between SPT and sIgE for diagnosing allergic sensitization in young children, which increases with age for food sensitization. Choice of assessment method therefore has major impact on results with wide implications for both clinical practice and research (Schoos et al., 2015).

Conclusion

The specificity of SPT, specific IgE and APT is considered as good; the sensitivity of APT is low. The positive tests in isolation cannot confirm the food allergy. However, together with other diagnostic methods, such as clinical history and OET, these tests are valuable tool in confirmation of food allergy.

Disclosure statement

No potential conflict of interest was reported by the authors.

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