EVALUATION OF COW'S MILK ALLERGY IN A LARGE GROUP OF ADOLESCENT AND ADULT PATIENTS WITH ATOPIC DERMATITIS

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Summary: Few studies concerning the occurrence of cow's milk allergy with the use of double-blind, placebo controlled food challenge test in adolescents and adult patients suffering from atopic dermatitis exist. Aim: To evaluate the occurrence of cow's milk allergy in adolescents and adults suffering from atopic dermatitis. Method: Altogether 179 persons suffering from atopic dermatitis were included in the study: 51 men and 128 women entered the study with the average age of 26.2 (s.d. 9.5 years). Complete dermatological and allergological examinations were performed. Results: The positive results in specificIgE and in skin prick tests were recorded in 12% of patients. According to the open exposure tests and double-blind, placebo controlled food challenge tests these patients are only sensitized to cow's milk without clinical symptoms of allergy. Double-blind, placebo controlled food challenge test confirmed food allergy to cow milk only in one patient (worsening of atopic dermatitis), the oral allergy syndrome was observed in another one patient, occurrence of this allergy was altogether 1.1%. Conclusion: Cow's milk allergy rarely plays a role in the worsening of atopic dermatitis in adolescent and adult patients.

Key words: *Atopic dermatitis; Cow's milk allergy; Specific IgE; Atopy patch tests; Skin prick tests; Challenge tests; Double-blind; Placebo controlled food challenge test*

Introduction

Food allergy predominantly affects children with atopic dermatitis (AD) and commonly represents a transitory phenomenon due to the development of tolerance. In adult patients with AD, studies investigating the co-prevalence of AD and food allergy are still scarce and exact data are not available (1).

Cow's milk is usually the first food given to an infant, and reaction to cow's milk is often the first symptom of an atopic condition (2). Cow milk allergy (CMA) is classified as IgE and non-IgE mediated and it represents a form of food hypersensitivity (3, 4). In patients with cow's milk allergy and atopic dermatitis, resolution occurs in 90% by the age of 4 years. Non-IgE-mediated cow's milk allergy often disappears before the age of 1 year (2). The role of food allergy to cow's milk remains controversial in adolescents and adult patients suffering from atopic dermatitis, no studies concerning the food allergy to cow's milk in this group of patients are available.

Diagnosis of food allergy is based on a personal history, measurement of specific IgE (serum specific IgE level – sIgE, skin prick tests – SPT, atopy patch tests – APTs), challenge tests: open exposure test – OET, double-blind, placebo controlled food challenge test – DBPCFC). DBPCFC always remains the golden standard in diagnosis of food allergy (5).

Aim of the study is to evaluate, if cow's milk can deteriorate the course of atopic dermatitis in this group of patients and to follow-up the patients with confirmed food allergy to cow's milk with the assessment of the severity of atopic dermatitis during 12 months after the elimination of this food allergen

Methods

Patients over 14 years of age with atopic dermatitis (as defined by the criteria of Sampson and Seymour and modified by the method of Hanifin and Rajka (6)) were examined at the Department of Dermatology at the Faculty Hospital in Hradec Králové (Czech Republic) from January 2005 to April 2010.

Inclusion criteria for the study:

– age 14 years and over,
– moderate and severe form of atopic dermatitis – evaluated with SCORAD index (7),
– mild form of atopic dermatitis only with a suspicion to food allergy to various food allergens or with a suspicion to adverse food reactions.

Scoring of atopic dermatitis

The diagnosis of atopic dermatitis was made with the Hanifin-Rajka (6) criteria at the outpatient department of

Department of Dermatology and Venereology, Faculty Hospital and Medical Faculty of Charles University, Hradec Králové, Czech Republic.

Severity of eczema was scored in agreement with SCORAD index (7).

Examinations

After discontinuation of antihistamines and topical steroids for at least 5 days and systemic steroids and UV therapy for at least 2 months, the skin prick tests, the atopy patch tests, and the challenge test with cow milk (CM) were performed.

Skin prick test and specific IgE

Commercial food extract Soluprick (ALK Abelló, Denmark) was used for skin prick tests.

SPT were placed on the volar side of the forearm according to the extent of atopic dermatitis. SPT were carried out by a standardized method using the lancet with a 1 mm tip. The results was read after 15 minutes and was assessed by comparison with the wheal induced by histamine (10 mg/ml) and a negative control. A wheal with a diameter greater than 3 mm in comparison with a negative control was scored as positive one.

The serum level of the specific IgE related to the cow milk has been measured with the method of FEIA (Pharmacia CAP system, Uppsala, Sweden). The level of specific IgE higher than 0.35 U/ml was assessed as positive.

Atopy patch tests

Atopy patch tests were performed on non-lesional, non-abraded, untreated skin of the back during a remission.

A technique similar to conventional patch tests has been used by performing atopy patch testing – CURATEST F strip (Lohmann & Rauscher International GmbH & Co.KG D-56579, Rengsdorf, Germany) with a 12 mm cup size. After discontinuation of antihistamines and systemic and topical steroids for at least 5 days the atopy patch tests with native cow milk has been applied. The occlusion time of atopy patch tests was 48 hours, the first results were evaluated 30 min after removal of the tests and the second results were analysed 72 hours after the application of the tests.

Grading of positive APTs reactions was similar to the criteria used in conventional contact allergy patch testing with the modifications of the European task Force on Atopic dermatitis (EFTAD) Consensus Meetings (8). Only reactions from + (erythema, infiltration) onwards were designated positive.

The diagnostic hypoallergenic diet

The elimination diet without milk and cow's milk products was introduced following the patient's informed consent. The severity of atopic dermatitis was evaluated with SCORAD system at the beginning of the study and then at the end of this diet before open exposure test and during open exposure test till 48 hours after the challenge.

Open exposure test (OET)

Consecutively open exposure tests were performed after the elimination diet. This test was performed in intervals without symptoms or during a stable period with regard to atopic dermatitis. It was recommended to make the oral provocation under the same conditions which the patient had during the diet. The OET with cow's milk was performed with 200 ml of fresh milk (one dose = 200 ml of cow milk during 60 minutes in the incremental dosages in intervals of 10 minutes) 3times – at 8.00 a.m., 6.00 p.m., next day at 8.00 a.m.

The food challenge results were scored as positive if one or more of the following objective and subjective clinical reactions were noted: itching, rush, urticaria, angioedema, vomiting, wheezing, abdominal pain, diarrhea, pruritus, or worsening of atopic dermatitis (evaluated with SCORAD). Early reactions were defined as clinical symptoms within 2 hours after the ingestion of the dose in OET and late symptoms if occurring after more than 2 hours.

If the test with cow milk was negative, the patient introduced cow's milk in the diet regimen. The severity of atopic dermatitis was evaluated during the average daily intake of cow's milk over a period of 3 months.

Double-blind, placebo-controlled food challenge (DBPCFC)

In case the physician or the patient recorded worsening of the atopic dermatitis or some other reactions during the open exposure test, the patient continued in the elimination of cow's milk and the diagnosis of the food allergy to cow's milk has been defined with more precision by a double-blind, placebo controlled food challenge (DBPCFC). This test was performed with the use of the lyofilised food and placebo (glucose) in the gelatine capsules. The lyophilized cow milk was blinded in opaque capsules. One capsule contained 250 mg of dried food. 31 capsules are in one dose (it is 7750 mg corresponding to 100 ml of cow milk) were administered at the same time as in the open challenge test (the doses of capsules were administered at 8:00 a.m., 6:00 p.m., 8:00 a.m.). The first dose of DBPCFC was administered under supervision of medical doctor on an empty stomach gradually 1, 2, 4, 8, 16 capsules with 15minutes intervals. The second and the third dose were served in a home setting. The early (two hours after the first dose) and the late reactions were observed.

The diagnosis of food allergy was confirmed if challenge with food was positive and negative with the placebo. The patient continued in the elimination diet if DBPCFC was positive. If the test was negative the tolerance to cow

milk in diet was proved. The severity of atopic dermatitis was evaluated in patients with positive result in DBPCFC in 3, 6, 9, and 12 months after elimination of cow milk.

Results

Patients

Altogether 179 persons suffering from atopic dermatitis were included in the study: 51 men and 128 women entered the study with the average age of 26.2 (s.d. 9.5 years min. 14 max. 63; with the median SCORAD 32. 9 points, s.d. 14.11 (max. 79.5 points, min. 12.5 points) at the beginning of the study.

Clinical outcomes of challenges

Personal history – 16 patients from 179 had a clinical suspicion of CMA and eliminated cow's milk for some time, but neither the early nor the late reaction was observed in 15 of them after open exposure tests. Only in one patient with suspicion of cow's milk allergy the oral allergy syndrome was recorded, the DBPCFC was not done in this patient.This patients with oral allergy syndrome feels burning of the mouth after ingestion of milk.

Specific IgE – 17 patients from 179 expressed positive specific IgE to cow's milk, however CMA was confirmed by DBPCFC only in one patient of them. Negative specific IgE was found in 162 patients. Allergy to cow's milk by OET was not confirmed in any of these individuals .

Skin prick tests – Skin prick tests to cow's milk was positive in five of 179 patients howeverCMA was confirmed by DBPCFC in only one of them. Negative results of skin prick tests were recorded in 174 patients and allergy to cow's milk in OET was not confirmed in any of them.

Atopy patch test – atopy patch tests were performed and found to be positive in four patients of 179. Allergy was not confirmed in these four patients. Negative results in APT were recorded in 175 patients and allergy to cow's milk in OET was confirmed in one of these patients.

Open exposure tests – the positive result in OET to cow's milk was recorded in eight patients from 179.

Double-blind, placebo-controlled food challenge – was performed in patients with positive results in OET.

From eight patients with positive result in OET, the cow's milk allergy in DBPCFC was confirmed in one case (worsening of atopic dermatitis). DBPCFC did not confirm cow's milk allergy in four cases. DBPCFC was not done because of oral allergy syndrome in one patient, another patient refused to perform DBPCFC and one patient suffered from intolerance of the gelatine capsules during DBPCFC.

The results of these examination and comparison with the results in DBPCFC are demonstrated in table 1. Altogether the occurence of cow's milk allergy is 1.1% (two patients out of 179 – one patient with positive result in sIgE, SPT to cow's milk and with worsening of atopic dermatitis in DBPCFC, one patient with oral allergy syndrome).

In patients with positive reactions in open exposure test and negative reaction in DBPCFC the severity of atopic dermatitis was evaluated during the average daily intake of milk over a period of 3 months. No other reactions to cow milk were recorded in these patients.

The decrease of SCORAD was recorded in the patient with confirmed CMA in DBPCFC and the difference in SCORAD was statistically significant (table 2).

Tab. 1: The results of examinations to cow milk in the diagnostic work-up of food allergy in the comparison with the confirmed food allergy in DBPCFC

Examination in 179 patients to cow's milk									
APT		sIgE		SPT		Personal history		OET	
+4	−175	**+17**	−162	**+5**	−174	**+16**	−163	**+8**	−171
DBPCFC +1 (worsening of atopic dermatitis)									

\+ number of patients with positive result,
− number of patients with negative result

Tab. 2: SCORAD index (points) in one patient with confirmed cow's milk allergy in DBPCFC before elimination diet and the 3, 6, 9, and 12 months follow-up after the elimination of food allergen

Patient Man, 48 years, food allergy to cow's milk confirmed in DBPCFC	SCORAD I before elimination diet	SCORAD 3. month	SCORAD 6. month	SCORAD 9. month	SCORAD 12. month
	53,5	28,2	25	24	20

Statistics

Our study was evaluated statistically – Fisher's exact test was used for the evaluation of the importance of the diagnostic methods in diagnostic work-up of food allergy with regard to the results of DBPCFC with cow's milk.

The correlation of these examinations with the result of DBPCFC was found only for skin prick tests; p-value = 0.034, but this result is considered as exploratory, because of small numbers of patients with positive result to cow's milk in DBPCFC

Discussion

There are no studies dealing with the same question in adolescent and adult patients with atopic dermatitis to compare our results with.

For comparison of our results there are no studies dealing with the same question in adolescent and adult patients with atopic dermatitis. Many studies have addressed the frequency of sensitizations to food allergens rather than investigating the prevalence of clinically relevant food allergy (1, 9, 10). The diagnostic procedures indicated to confirm the diagnosis of food allergy, in particular late-type reactions, remain time-consuming because double-blind, placebo-controlled food challenges need to be performed.

According to some studies, both atopic dermatitis and food allergy are, in the majority of individuals, transitory conditions that improve with increasing age (11, 12, 13). CMA affects about 2–3% of children in the first year of life (14, 15, 16, 21).

In our study the CMA affecting the course of atopic dermatitis was confirmed only in one patient of 179 and oral allergy syndrome was recorded in another one patient. DBPCFC confirmed the CMA in a 48 years old man, who suffered from atopic dermatitis in last seven years. He suffered almost permanently from eczematous lesions in the last two years (redness, papules, sometimes madidation) at the predilection sides – face, flexures, and back. The examination for food allergy was performed in intervals with milder symptoms of atopic dermatitis. During OET and DBPCFC, not only the early reaction was seen, but the late reaction could be observed several hours after food challenge as worsening of atopic dermatitis during this test. This patient was systematically scored and the severity of atopic dermatitis was evaluated in 3, 6, 9, and 12 months after elimination of cow's milk. The decrease in SCORAD was statistically significant.

The oral allergy syndrom was described after the milk ingestion in another one patient, the DBPCFC was not done in this case, but it was concluded as early allergic reaction without worsening of atopic dermatitis.

The positive outcomes in the OET with cow's milk were not confirmed by DBPCFC in another four patients. This course reflects the daily variation of atopic dermatitis and emphasizes the importance of the DBPCFC. The severity of atopic dermatitis and possible other reactions were evaluated in all these patients three months after the average daily intake of this food, but we did not record any reactions during this period and later. According to Niggemann, sometimes foods induce some clinical symptoms, while they are tolerated on other occasions (22). Physical exercise is the best – known augmentation factor; drugs, alcohol, warm bath, hormonal factors or stress are other augmentation factors (22).

Retrospective analyses by Niggeman and Breuer have shown that the patient's history of food related eczema does not have a high diagnostic importance (23, 24). In our study, one patient suffered from oral allergy syndrome after milk ingestion and another 15 patients had a suspicion of CMA by history however this could not be confirmed after the re-introduction of cow's milk into their diet. On the other hand, the patient with confirmed CMA suffered in last two years almost permanently from eczematic lesions and had not any suspicion to CMA.

For IgE-mediated disorders, skin prick tests provide a rapid means to detect sensitization. (25, 26, 27). Serum tests to determine food-specific IgE antibodies (CAP System) provide another modality to evaluate IgE-mediated food allergy. Undetectable serum food-specific IgE levels might be associated with clinical reactions for 10 to 25% (24). Our results have shown, that 5 patients (2.7%) with the positive results in SPT and 17 patients (9.5%) with positive result in sIgE to cow's milk are only sensitized to this food without clinical symptoms.The SPT reactions were evaluated as mild and sIgE were recorded from 0.5 to 1.2 U/ml at these patients without clinical symptoms of CMA. A number of investigators have examined the use of the atopy patch test in addition to skin prick tests for the diagnosis of non-IgE-mediated food allergy, primarily in patients with atopic dermatitis and allergic eosinophilic esophagitis (8, 28, 29).The authors recommend that the clinical relevance of positive APTs reactions is still to be proven by standardized provocation and avoidance tests and may also depend on the APTs model.

Conclusion

Cow's milk allergy rarely plays a role in the worsening of atopic dermatitis in adolescent and adult patients (1.1%). The majority of patients with positive results of specific IgE or skin prick tests (12%) to cow's milk appear to reflect sensitization only without clinical symptoms of allergy. We recommend that the confirmation of allergy should include an elimination diet and double blind placebo controlled food challenge.

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