Role of contact provoking factors in adult atopic dermatitis

Doctoral theses

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1. Introduction

1.1. The adult atopic dermatitis

Atopic dermatitis (AD) is a clinically well-defined, inflammatory, chronic-intermittant, genetically predisposed, itching skin disease elicited by various factors. In contrast to the more common IgE-mediated „extrinsic” form of AD, „intrinsic” AD patients are reported to show normal IgE levels, lack of sensitizations towards environmental allergens and absence of associated respiratory allergies.

Although AD is mainly considered to be a childhood disease, the number of adult cases is remarkable. Numerous studies discussed the occurrence of childhood AD and its prognostic factors. The adult form, however, has started to attract attention only recently.

The prevalence of childhood AD is 10-20% in developed countries, so one should expect the growing number of adult cases in the following years. The world-wide prevalence of adult AD is 1-3%, in some regions 10%.

Studies investigating the possibility of primary and secondary prevention of adult AD have revealed numerous factors playing a role in triggering and sustaining the disease. These studies already attribute a significant role to the environmental contact allergens (ECA) and aeroallergens that may flare up atopic skin symptoms. Discovering the genetical background (eg. fillagrin mutations) of the atopic barrier-defect, the agents passing the damaged barrier and causing sensitivity and inflammation obtained the focus of attention in the last years. The hypersensitivity to ECA and aeroallergens affects a lot of adult AD patient. The identification of the potential provoking allergens is considerable in terms of prevention and therapy.

1.2. Contact hypersensitivity and contact allergens in AD

Previously AD patients were thought to be less susceptible to contact allergic reactions. The low sensitization rate was explained by Th2 dominance, enhanced IL-4 and IgE production, and decreased IFNγ level. Thank to the discovery of the biphasic pathomechanism of AD (Th2→Th1) and to clinical experiences, it is known today that the prevalence of contact sensitivity among AD patients is concordant with data in the normal population. Haptens may provoke allergic reactions by penetrating the damaged epidermal barrier. There are only a few data in the literature about the hypersensitivity to ECA among adult AD patients. According to previous observations, 17-42% of the adult atopics are sensitized, typical allergens of them are nickel, chrome, cobalt, paraben, fragrance mix, lanalcolm, thiomersal, formaldehyde and balsam of Peru.

1.3. Aeroallergens and the atopy patch test

The IgE-mediated contact reaction elicited by aeroallergens is an important pathogenetic factor in AD. The skin symptoms of AD may be flared up by aeroallergen exposition: house dust mite, pollen, animal epithel. Atopy Patch Test (APT) - an epicutaneous test with allergens eliciting IgE-mediated reactions - may be regarded as a kind of „provocation test”, and „modell” of atopic reaction in these patients. APT has high sensitivity and specificity, so it is an important diagnostic tool in patients with an air-exposed AD distribution pattern.

The central role of the IL-4, IL-5, and IL-13 producing Th2 cells is known in the pathomechanism of AD. In patients with AD, IL-4 and IL-5 producing cells of Th0/Th2 type are dominant in acute skin symptoms. The immediate APT reaction is characterized by increased IL-4 production and Th2 infiltration for 24 hours, too. In chronic skin lesions, however, the majority of lymphocytes have a Th1 cytokine profile and produce IFNγ. The development of a late APT reaction is preceded by a switch from the original Th0/Th2 cytokine profile to Th1. The process is accompanied by increasing IFNγ production. Based on the comparison of the obtained results, the medical history, clinical symptoms and other tests (Prick test, specific IgE, total IgE), we can determine the relevance of any allergen’s capacity.
to elicit eczematous skin symptoms. One can observe strong correlation between the APT and specific IgE by most of the aeroallergens.

There are only few studies about the sensitization to aeroallergens among adult AD patients. Mostly house dust mites /Dermatophagoides pteronyssinus (D.p.) and Dermatophagoides farinae (D.f./ give positivity in APT, pollens and animal epithel more less frequently.

2. Aim of the study was to study the sensitivity rate and the common and relevant ECA and aeroallergens of adult AD patients divided into intrinsic and extrinsic groups, comparing the results with the current data in the literature.

3. Materials and methods

3.1. Patients

65 AD patients (47 women and 18 men) over 18 years of age from the Atopic Outpatient Unit of the Dermatology, Venerology and Dermato-oncology Department of the Semmelweis University have been studied. The mean age was 31 years.

Diagnosis of AD was based on the criteria of Hanifin and Rajka. All the patients were symptomfree at the time of testing. They did not take any antihistamin and they applied only indifferent topical treatment one week before the tests and at the time of testing. Pregnancy, breast-feeding, acute skin symptoms, active rhinitis, and UV radiation within 6 weeks before testing were drop-out criteria.

3.2. Methods

Epicutan environmental contact series (Brial-Allergen D-Greven Hungarian Panel), inhalative Atopy Patch Test (Stallergenes France), inhalative Prick test (Alk Abello Spain), total IgE (ELISA) and specific IgE (CLA-MAST) tests were performed, the medical history and clinical symptoms of the patients were related. Assessment of the Prick tests were done at 15-30 minutes, by environmental contact series and APT were done at 20, 40 (and 60) minutes, in 48,72,96 hours and on day 7.

4. Results

4.1. Hypersensitivity to ECA and to aeroallergens in 65 AD patients

4.1.1. Hypersensitivity to ECA in 65 AD patients

We observed hypersensitivity to ECA in 49% of the patients (women 51%, men 44%). The detected allergens were: nickel (20%), thiomersal (10.7%), mercury chloride (6%), mercury amidochloratum, lanalcol, wood tar and propolis (4.6%), iod chlorhydroxiquin and fragrance mix I. (3%), cobalt, benzoic acid, primin and paraben (1.5%). The detected allergen was relevant in 44% of the patients.

4.1.2. Aeroallergen- hypersensitivity in 65 AD patients

We observed late positivity in APT in 37% of the patients (women 36%, men 38%). The sensitivity rate of the adult atopics was to house dust mite 27% (relevant: 94%), to pollens 17% (relevant: 36%), to cat epithel 9.2% (relevant: 66.6%), to dog epithel 3% (relevant: 50%).

4.2. Intrinsic atopic patients

There were 10 female and 5 male patient (23% of the total patient number) without rhinitis, conjunctivitis, or asthma bronchiale in the personal medical history. Their total serum
IgE level was in the normal range (below 100 U/ml). They did not have any serum specific IgE positivity and their Prick testing remained negative.

4.2.1. Hypersensitivity to ECA in intrinsic AD
We observed contact hypersensitivity in 5 patients (33%) in the intrinsic group. The detected allergens were thiomersal, wood tar, propolis, fragrance mix I., mercury chloride and nickel. 40% of the intrinsic women and 20% of the men were sensitised. Two patients had relevant hypersensitivity. We observed the positive test-reactions in 48 and 72 hours.

4.2.2. Hypersensitivity to aeroallergens in intrinsic AD
We observed late APT positivity in one patient (7%) to D.p. (relevant) and to orchard grass (not relevant). We observed the positive test-reactions in 48 and 72 hours.

4.3. Extrinsic AD patients
50 AD patients (13 men and 37 women) were selected in the extrinsic group (77% of the total patient number). 64% of them had rhinitis and/or asthma bronchiale in the medical history. Total serum IgE was elevated in 34 patients. In the 16 AD patients with normal serum IgE levels specific IgE reactivity, rhinitis and/or asthma bronchiale was observed.

4.3.1. Hypersensitivity to ECA in extrinsic AD
In ECA series late positivity was seen in 27 patients (54%). The allergens causing positivity were nickel (24% of the extrinsic patients), thiomersal (12%), mercury-amidochlorate, mercury-chloride and lanalcolm (6%), iodine chlorhydroxyquin, wood tar and propolis (4%), cobalt, benzoic acid, primin, paraben and fragrance mix I. (2%). According to the patients’ report in 12 of them (44%) the detected allergens aggravated skin symptoms. We observed in 6 patients (22%) new positive test-reactions in 96 hours or on day 7.

4.3.2. Hypersensitivity to aeroallergens in extrinsic AD
Late positivity was observed in 23 patients (46%) in the extrinsic group by APT. 43% of the extrinsic women and 54% of the men were sensitised. We observed D.p. and/or D.f. positivity in 17 patients (13 of them had face and/or eyelids-symptoms, 11 of them hand-symptoms). All patients with eyelid-symptoms were positive to house dust mite by APT. APT positivity was relevant by 94% of the house dust mite-positive patients. 10 extrinsic patients were sensitized to one or more pollen allergens (40% of them were relevant). Six patients were positive to cat epithel and 4 of them (66.6%) reported the exacerbation of the skin symptoms upon contact with cats. We observed dog epithel positivity by 2 extrinsic patients (one was relevant). We observed by 39% of the APT–positive patients new positive test-reactions in 96 hours or on day 7.

4.3.3. Correlations of APT and specific IgE and/or Prick tests in extrinsic AD
We observed positivity by APT and specific IgE tests and/or Prick tests in 18 patients with extrinsic AD. We observed by 71% of the total APT positivity spec. IgE and /or Prick test positivity. 70% of APT house dust mite-positive patients had spec. IgE and/or Prick test positivity to the mites (according to the localisation, skin symptoms and medical history all of them were relevant). All patients with cat epithel positivity (100%) were positive with spec. IgE and/or with Prick test to cat epithel (4 cases – 66.6% were relevant). We observed by 11 pollen APT reactions spec. IgE and/or Prick test positivity, but the relevance could be proved clinically only by 5 APT positivity (3 patients).
One patient was positive to dog epithel by APT and special IgE jointly, and the symptoms flared up after this patient caressed the animal.
5. Conclusions

The increasing number of adult AD cases observed in the past years has turned the attention to ascertaining factors eliciting skin symptoms. Of these, great importance is attached to ECA and aeroallergens, but there are only a few investigations focusing on adult AD population.

The present study is the only one in the literature which examined the sensitivity rates, typical ECA and aeroallergens in adult atopics at the same time.

Studies presented in the literature report mostly about house dust mite hypersensitivity in AD, while about pollens and animal epithels more less frequently. This study presents the hypersensitivity rates of house dust mites, pollens and animal epithels in adult AD patients at the same time.

The number (10) of the tested aeroallergens is high compared to previous reports.

The present study gives unique or new data about the ECA and aeroallergen sensitivity rates in adult AD patients, in women and men, in intrinsic and extrinsic groups.

This study is unique in comparison of the environmental contact and aeroallergen sensitivity rate of intrinsic and extrinsic AD patients.

According to our results we suggest new recommendation in assessment of the APT.

Environmental contact allergens

1. The sensitivity rate (49%) to ECA reported in this study is higher than the previous results reported in general and adult AD populations.

2. 51% of the women, 44% of the men were sensitised to ECA in this study. These data are higher than previous results in the literature.

3. The most common detected allergens of the present study were nickel and mercury compounds. Sensitivity rate to nickel fits with the data of the general and adult AD populations. The data of thiomersal and mercury amidochloratum in the present study are higher, the values of wood tar and lanacolum among adult atopics are lower than the former data in the literature. The sensitivity rate of fragrance mix I., paraben and cobalt are lower than previously reported.

4. No data were found in the literature on the sensitivity rates of mercury chlorid propolis, iod chlorhydroxiquin, benzoic acid and primin that was evaluated in this study for the first time in adult AD patients.

5. To Balsam of Peru, chromate, formaldehyde, TMTD and cathon CG reported previously as typical for ECA in adult AD population, we couldn’t detect any positivity.

Aeroallergens

1. We detected in 37% of the patients APT positivity, the result is consistent with previous observations (30-75%).

2. The aeroallergen sensitivity rate in the adult AD patients is very similar by women and by men.

3. The sensitivity rates to aeroallergens in present study are lower than in previous publications.

4. There were no previous data in the literature about the sensitivity rate to dog epithel by adult atopics (present study: 3%).

5. The cat epithel is of greater importance than dog epithel.
6. We detected in 37% of the APT-positive patients new positive test reactions in 96 hours or on day 7. Actual recommendations suggest to read APT-s in 48 and 72 hours, however according to present data it should be done till day 7.

Comparison of intrinsic and extrinsic AD groups

1. According to previous data 23% of the patients belongs to the intrinsic, 77% belongs to the extrinsic AD group.
2. The sensitivity rate to ECA was higher in the extrinsic group (54%) than in intrinsic AD (33%). The sensitivity rates of the genders were higher in extrinsic than in intrinsic AD and were not different from each other (women 54%, men 54%). The allergological management and treatment of the intrinsic and extrinsic groups requires different approaches.
3. In extrinsic patients most common ECA were nickel, mercury compounds and lanalcolm.
4. The detected allergens proved to be relevant by 44% of the positive extrinsic patients.
5. We observed by 22% of the ECA positive extrinsic patients new positive reactions in 96 hours or on day 7, so it is necessary to read epicutan standard test till the day 7.
6. We detected APT positivity in higher rate in extrinsic AD (46%) than in intrinsic (7%).
7. In extrinsic AD men are sensitized to aeroallergens more likely.
8. In extrinsic AD more than 70% of the APT-positive patients are sensitized to house dust mite, more than 40% to pollen and more than 25% to cat epithel.
9. We detected correlation between APT and specific IgE and/or Prick tests by 71% of the APT reactions in extrinsic AD. The rate of correlation is allergen-specific: the highest rate (100%) could be proven by cat epithel.

In summary:
The sensitivity rate of environmental contact allergens and aeroallergens is remarkable in adult atopics. In case of an AD flare-up one should consider the role of some ECA or aeroallergen. Women are sensitized to ECA in higher rate than men, by aeroallergens the sensitivity rates are equal.
Adult extrinsic AD patients are sensitized to ECA in higher rate. Intrinsic AD women are sensitised to ECA, while extrinsic atopic men are more sensitised to aeroallergens. The most common ECA by adult AD patients are the nickel and mercury compounds, in extrinsic AD lanolin as well. Studying ECA sensitivity in AD patients, we suggest not to examine groups with mixed ages.
Among aeroallergens house dust mites are the most common ones in adult AD. The most relevant aeroallergens are house dust mites. Among animal epithels cat epithel was more significant.
One should read APT also on day 7.
The tests used for ECA and aeroallergen sensitivity in AD adult population are useful diagnostic tools.
6. Publications

Publications related to the dissertation:

**International journals:**


**National journals:**


**Publications not related to the dissertation:**

**International journals:**


**National journals:**


