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Original Article

CONTACT ALLERGY IN ATOPIC PATIENTS

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Summary

Atopic dermatitis (AD) is a chronic inflammatory disease based on genetic and immune alterations and is part of the atopic symptom complex, including allergic rhinitis, allergic conjunctivitis, and bronchial asthma. A disturbed barrier function facilitates antigen penetration through the skin, with the subsequent development of allergic contact dermatitis (ACD). The gold standard for diagnosing ACD is epicutaneous (patch) testing, also applied to objectify contact sensitization in AD. This study aimed to determine the frequency of contact allergy (CA) among individuals with atopic history and the allergens that caused ACD in those cases. We studied 453 individuals tested in the period 2009-2022. Of these, a subpopulation of 189 individuals with atopic diathesis was identified. A retrospective analysis was used. Using clinical and allergological methods, we divided the tested patients according to sex, age, professional occupation, and areas of the body affected by dermatitis and identified the most common contact allergens that cause positive reactions and ACD. In conclusion, our results highlight the possibility of developing ACD in people with atopic diathesis. As far as we know, our study is the first one in Bulgaria to examine the frequency of contact sensitization in AD patients.

Keywords: atopic dermatitis, allergens, allergic contact dermatitis, patch test

Introduction

Atopic dermatitis (AD) is a chronic-relapsing, itchy dermatosis, part of the atopic diathesis. AD manifests first among the other components of the atopic symptom complex, which also includes allergic rhinitis, allergic conjunctivitis, bronchial asthma, and atopic characteropathy [1]. At the heart of the disease are two defects - impaired skin barrier function and deviations in the immune response, caused by mutations in the genes encoding the filaggrin protein. This protein is essential in maintaining the normal skin structure and function. Impaired barrier function is a prerequisite for increased antigenic penetration and transepidermal water

loss (TEWL) [2,3]. In recent years, the incidence of AD has progressively increased, affecting 15 to 30% of children and 2 to 10% of adults worldwide. In 2050, every third newborn child is expected to have signs of atopy [4,5]. AD often begins in early childhood (early-onset AD). In 85% of all cases, the disease manifests in the first year, and in 95% - before five years of age, but never or extremely rarely before two months, seven years, and in puberty. In 25% of cases, AD persists after the 25th year. Bronchial asthma develops in 25% of patients, erythroderma in 3%, and atopic characteropathy in 90%. Although uncommon, the disease can also debut in adulthood (late-onset AD). Environmental, lifestyle, and occupational factors, as well as psycho-emotional episodes, can lead to a relapse or contact sensitization with clinical manifestation of ACD [6,7]. ACD is a disease resulting from contact allergy, which, in turn, is triggered by repeated exposure to antigens. Contact allergy can exist as an asymptomatic sensitization of the body, but upon repeated provocation, allergic contact dermatitis may develop, which has recently become increasingly common in connection with industrialization and increased exposure of individuals predisposed to allergenic factors [8,9].

Due to the growing number of patients with these complaints and the increasing relevance of the problem, we conducted a retrospective analysis of the tested patients from the regions of Pleven and Rouse within the framework of the Diagnosis and Prevention of Skin Allergic Diseases Annual National Campaign in the period 2009-2022. The study on the frequency of contact allergy among individuals with atopy is pioneering for the country.

The aim and tasks of the study are to determine the frequency of contact allergy in atopic patients by analyzing the structure of the tested patients by sex, age, and professional status, to determine which are the most affected areas of the skin, as well as the most common allergens, the cause of positive reactions among atopic persons.

Materials and Methods

In the period 2009-2022, 453 people were patch-tested with the European standard series S-1000. Of these, 222 (49%) had 362 positive reactions. Patch tests were not performed from March 2020 to March 2022 due to the restrictions imposed by the COVID-19 pandemic.

One hundred eighty-nine individuals (42%) of both sexes with a history of atopy, some with a clinical picture of mild to moderate atopic dermatitis, were selected from those examined. Eighty-three (44%) had contact allergies, with 173 positive reactions to various allergens. The patients are grouped by sex, age, profession, and location of the rash. They are also divided into two age ranges - up to 40 and 40 years and over.

For the purposes of the epidemiological analysis, a registration form valid in the country has been filled out, including a passport part, anamnestic data, topography of rashes in 23 areas, professional occupation of the patient, contact with possible irritants, hobbies of the patient, etc.

Clinical methods were used to collect anamnestic data for atopic diseases. Skin examinations were performed, and the clinical-morphological characteristics of ACD were investigated.

Patch testing was performed with the European standard series S-1000, with 30 and 36 allergens (European Baseline) to diagnose contact allergy. For application on the skin (for 48 hours on the back of the subject), aluminium disc cameras with a diameter of 8 mm (Thalloderma, Varna, Bulgaria) attached to a hypoallergenic patch (Micropore, 3M) were used. Results were reported at 48 and 72 hours and were interpreted according to ICDRG criteria [10,11].

The results were processed with the IBM SPSS Statistics 23.0.0 statistical package, applying descriptive statistics, dispersion, and correlation analysis. They are described by tables, graphs, and numerical values. A $p<0.05$ was chosen as the significance level at which the null hypothesis was rejected.

In an ethical aspect, the study complied with the national and international requirements for conducting clinical trials, including the anonymity of the participants and no information about personal data. Before the start of the study, each one signed an informed consent and was told that they could refuse to participate in the study without sharing reasons for doing so.

Results

During the indicated period, 453 persons were patch-tested, and 222 (49%) had 362 positive reactions. All of them saw a dermatologist for specific complaints during the national campaigns of the Bulgarian Dermatology Society for diagnosing and preventing allergic dermatoses in Bulgaria. Atopics among these were 189 cases (41.7%), of an average age of 37.71 ± 16.55 years; men were 46 (24.3%), and women were 143 (75.7%). There were 83 (43.9%) patients with positive patch tests, totaling 173 positive reactions. Forty-six patients had AD data in which 99 positive tests were reported, and in 37 individuals without AD, the reactions were 74. It was found that the risk of developing contact sensitization in individuals with atopy was 1.6, compared to that in the general population (OR= 1.6130; 95 % CI: 1.1601 - 2.2428; p = 0.0045), while the presence of AD in the atopic subpopulation was not a risk factor for contact sensitivity (OR=0.8823; 95% CI: 0.4939-1.5761; p = 0.67).

To track the ratio of the people with positive reactions concerning gender and age, they were divided into two age groups – under 40 years and over 40 years old. The result with the χ 2 -test showed that, among positive patients, a significant difference in the ratio was found between men and women under and over 40 years of age: 30% for men and 70% for women under the age of 40 and 60% for men and 40% for women over 40 (χ=5.602, df=4, p=0.018).

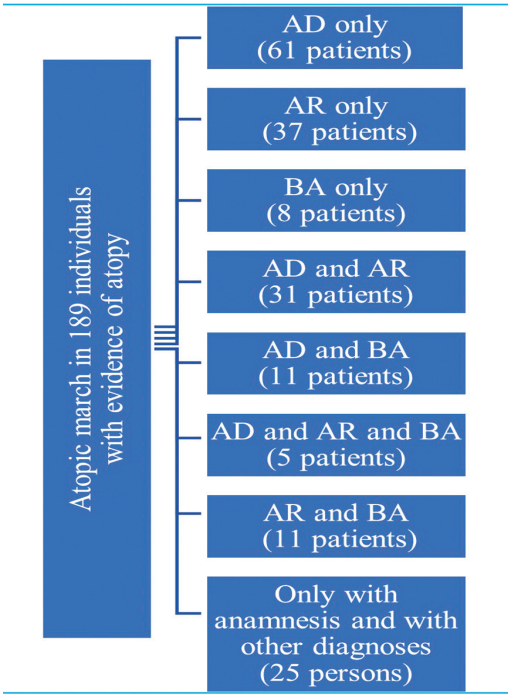
The anamnestic data showed that 61(32.2%) of the examined participants had personal and family history of atopic conditions, 97(51.3%) had only personal data, and 31(16.5%) had only family history (Table 1).

The simultaneous occurrence of more than one atopic disease and comorbidities with other allergic dermatoses shows the broad pathological spectrum of the atopic march. The occurrence in the studied subpopulation is presented in Figure 1.

Out of all 189 atopic cases, 108 (57%) suffered from AD with varying duration of complaints, 64 (59%) had manifestations of mild to moderately expressed dermatitis during the examination, and 44 (41%) had no complaints. The ANOVA analysis showed a statistically significant difference in the incidence of AD according to age – the average age for patients with AD was 35.25 ± 16.43 years, and for those without AD,

Table 1. Demographic and clinical characteristics of 189 individuals with evidence of atopy.

ATOPICS (n=189)	Mean ± SD	Number	Percent
SEX			
Men		46	24.3
Women		143	75.7
AGE	50.28 ± 14.56		
< 40 years	25.64 ± 9.932	106	56
>40 years	53.12 ± 8.57	83	44
PROFESSIONAL EMPLOYMENT			
Unemployed		60	31.7
Office workers		21	11.1
Doctors		24	12.7
Aesthetics		7	3.7
Others		77	40.7
ANAMNESTIC DATA ON ATOPIA			
Personal history		97	51.3
Family history		31	16.5
Personal and family		61	32.2
ATOPIC DIATHESIS			
Atopic dermatitis		108	57.1
Allergic rhinitis		74	39.1
Bronchial asthma		25	13.2



**AD-atopic dermatitis; AR-allergic rhinitis; BA – bronchial asthma*

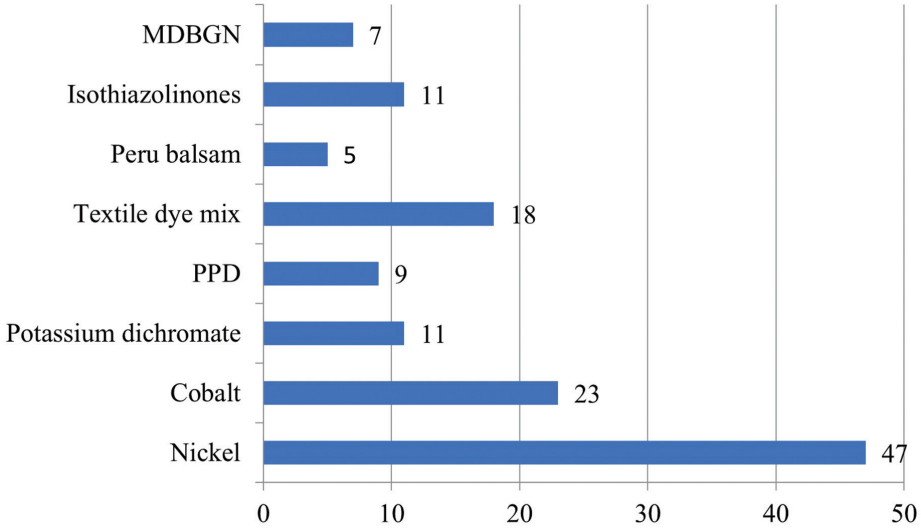
Figure 1: Atopic march in 189 individuals with atopic history

it was 40.99 ± 16.25 years (F=5.698, p=0.018).

The distribution by occupation shows that the highest share belonged to the group with diverse professions and education – 40.7%, followed by the unemployed – 31.7%, where women on maternity leave, housewives, and domestic helpers were included and had often been exposed to the action of aggressive cleaning products and detergents. Most often, pathological changes affected the palms (42.8%), upper limbs (29.6%), face (26.9%), trunk (47.2%) and lower limbs (16.4%).

The results of patch testing with S-1000 identified 83 patients (44% of all 189) – 20 men (24%) and 63 (76%) women. There were 173 positive reactions reported in 18 men (28%) and 47 women (72%). The number of positive responses to nickel (47 times) was the highest, followed by cobalt (23 times), textile dye mix (18 times), isothiazolinones (11 times), PPD (9 reactions), Balsam Peru (5 responses), methyldibromo glutaronitrile (7 responses), all of which were widely present in domestic and professional environment (Figure 2).

In nickel-positive individuals, a difference in the percentage distribution of cases with palm involvement was found between different occupations, with 81% of non-workers and 67% of healthcare workers having hand eczema (χ=9.852, df=4, p=0.043).



**PPD – para-phenilendiamin, MDBGN – methyl-dibromo-glutaronitril*

Figure 2: Frequency of the top allergens causing contact sensitization in the 189 subjects studied

Discussion

There are few epidemiological studies in the literature on the relationship between ACD and AD, while population studies do not show a significant relationship between AD and contact allergy, and the data is mixed. Our study found that in the general population, contact allergy in atopics was 18.3%, and in the subpopulation consisting of individuals with data on atopy, it was 43.9%. Mortz et al. reported that in 6-year-old children with AD, 37% had ACD, while in the entire study sample, this proportion was only 21.3% [12]. A study by Sharma (2005) on the prevalence of ACD in AD showed a frequency of 23%, against 19% in our study [13].

We found that the risk of developing contact allergy in individuals with atopy was 1.6 times higher than in the general population, while AD was not a risk factor for contact sensitivity. In the context of the divergent data on the issue after a meta-analysis of the relationship between AD and contact sensitization in individuals with and without AD, Hamann et al. (2017) reported an increased risk (OR 1.50, 95% CI 1.23-1.93) for CA patients with AD compared to the general population, and no significant association in the incidence of CA in individuals with and without AD, data close to ours [9]. Other authors have also reported the absence of a significant difference in the prevalence of CA between atopic and non-atopic populations [14-17].

Metals (nickel, chromium, cobalt) have been proven to be the most common allergens leading to ACD in patients with atopy [7, 18]. Worldwide, nickel has been shown as the most common contact allergen, consistent with our study data. The high number of affected patients is attributable to the nickel released in large quantities from the surfaces of mobile devices (phones, tablets, and laptops) as well as from piercings. This group of patients most often complain of eczema on their hands, which we also proved by employing $\chi 2$ -statistics [19, 20].

Preservatives are strong contact allergens. In our study, a total of 24 positive reactions to methylisothiazolinone (MI), Kathon CG®, methyldibromo glutaronitrile (MDBNH), formaldehyde, and quaternium-15 or 12.7% of contact hypersensitivity in atopics were found. According to Németh et al. (2022), in 639 patients with AD and ACD, contact sensitization to preservatives was 10.6%, with the most common concomitant combination being Kathon CG® + MI [21]. As early as 1990, A. C. de Groot reported a high incidence of positive reactions to nickel (18.8%), cobalt (6%), Kathon CG (4.8%), and Balsam of Peru (3.6%) in 214 atopic patients [22].

Textile dye mix allergen was added last to the standard European S-1000 series, but many positive reactions were reported in a short time, placing it among the most common allergens, which we also observed in our patch-test results. Textile dyes have proven essential in allergic skin pathology. The blue pigment used to color denim has been proven to be the most allergenic: achieving a blue colour requires a large amount of cobalt. This explains why patients with a positive reaction to textile dye mix often have one to cobalt as well [23, 24].

A widespread allergen is Peruvian balsam, widely used in producing mid-range cosmetics and PPD in hair dyes, henna, and temporary tattoo inks [20, 25].

Limitations

The study included individuals who actively sought help from a dermatologist who did not always provide information for current or past illnesses. It is not clear whether AD was correctly diagnosed by prick testing and/or according to the diagnostic criteria of JM. Hanifin and G. Rajka. At the same time, the patients with and without atopic dermatitis differ significantly by age. The study was conducted on a selected population, so the data can not be relevant to the general population in the country.

Conclusion

ACD is common among atopics, and epicutaneous (patch) testing is the gold standard for diagnosing CA. This study showed that 44% of a total of 189 individuals with atopy had a positive patch test response to various allergens. The most common was the contact allergy to nickel sulfate, followed by that to cobalt chloride, textile dye mix, and preservatives. Our data corresponded to those published in the literature. AD patients with suspected CA require a careful evaluation of the clinical status, anamnestic data on personal and family history for atopy, previous

allergies to detergents and disinfectants, hobbies and recreational activities, and information on medicinal and cosmetic products. Prevention remains the primary method of controlling all allergic dermatoses. Identifying the allergen and teaching the patient how to avoid it is the real solution to the problem.

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