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A cross-sectional study of allergic contact dermatitis in atopic dermatitis

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ABSTRACT

Objectives: Atopic dermatitis (AD) is a chronically relapsing dermatitis that occurs commonly during early infancy and childhood. Allergic contact dermatitis (ACD) is a type IV hypersensitivity reaction caused by re-exposure to a cutaneous contact allergen in a pre-sensitized individual. As previous findings have been conflicting, whether AD is associated with increased contact sensitization and ACD is still a controversial topic. The objective of this study was to estimate the prevalence of ACD among AD patients using a patch test.

Material and Methods: This was a cross-sectional study conducted in consecutive AD patients aged 6-16 years attending the outpatient department of dermatology in a tertiary care hospital in South India for 1.5 years. Consecutive sampling was done, and 71 patients who fulfilled the atopic diathesis criteria were recruited and patch-tested according to the study protocol. The data were coded and entered in Microsoft Excel and analyzed using the statistical software Statistical Package for the Social Sciences.

Results: The prevalence of patch test positivity in the study population was 54.9%. The most common allergen detected was neomycin (11 out of 71 participants; 15.5%), followed by cetrimide and nickel (7/71; 9.9% each), and thiomersal (5/71; 7%). A total of 32 different allergens were implicated. The presence of cetrimide ($P = 0.003$), neomycin ($P = 0.001$), nickel ($P = 0.011$), thiomersal ($P = 0.012$), cobalt, paraben mix, and butylated hydroxytoluene (BHT) ($P = 0.026$) in the study participants was found to be statistically significant.

Limitations: Sample size was limited; hence even though some associations were positive, they were not found to be statistically significant. A prevalence of ACD in the general population could not be elicited; hence it is not possible to make a statement that there is a higher prevalence of ACD in AD compared to the general population.

Conclusion: There is a remarkable prevalence of ACD in AD patients, especially to the allergens neomycin, cetrimide, nickel, thiomersal, cobalt, paraben mix, and BHT.

Keywords: Allergic contact dermatitis, Atopic dermatitis, Contact sensitivity, Patch test

INTRODUCTION

Atopic dermatitis (AD) is a prevalent chronic inflammatory skin condition marked by pruritus and a persistently relapsing course, typically commencing in infancy (early onset) but occasionally appearing in adulthood (late onset). It is a complex genetic disease, accompanied by other atopic diseases such as allergic rhino-conjunctivitis, asthma, and eosinophilic esophagitis.[1] The majority of patients will have a history of "atopic diathesis" in their families or personal lives.[2]

The prevalence of atopic eczema in different geographical areas varies from 1% to 20% in high-prevalence zones.[3] The worldwide prevalence was estimated as 7.9% and 7.3% in 6-7 years and

13-14 year age groups, respectively, and the prevalence in the Indian subcontinent is 3-4.2%.[4]

Atopic diseases significantly influence the mental as well as financial condition of those who are afflicted, as well as that of their families. Individuals with AD are affected both by the condition itself and by the stigma associated with visible skin lesions. Herein comes the importance of early and effective treatment.

AD is caused by genetically determined epidermal and immune alterations and modified by environmental factors. Lifestyle changes (hence gene-environment interactions) have led to the recent trend of an increase in the prevalence of AD.[5] It is here, in the environmental part of pathogenesis, that contact allergens come into play.

Re-exposure to a cutaneous contact allergen in a person who has already been sensitized can result in allergic contact dermatitis (ACD), a type IV hypersensitivity reaction. Patch testing is used to diagnose ACD. A patient must have contact sensitivity as well as dermatitis with clinically significant exposure to the allergen to be diagnosed with ACD.[6]

Identifying the contact allergen through patch testing would allow the patient to avoid flare-ups due to ACD and choose one's recreational activities and occupational activities accordingly, thus positively affecting quality of life and lowering economic burden.

However, as previous studies have been conflicting, whether AD is associated with increased contact sensitization and ACD is still a controversial topic, and hence, patch testing of atopic children is not commonly done.[5,6] While a reduced risk is suggested by the immunological profile, a higher risk is suggested by increased exposure to allergens found in topical products and compromised skin barrier function.[7]

Considering the rising prevalance of children with chronic, recurrent, and recalcitrant AD and the lack of safe and effective treatment strategies, further studies are needed focusing on potential triggers of AD, including contact allergens.

Studies to find an association between contact sensitization and AD in the 6-16-year-old age group especially to common allergens such as nickel and neomycin to avoid bias in the analysis (the bypass theory) are limited.[8,9]

MATERIALS AND METHODS

This is a cross-sectional study conducted in a tertiary care medical center in South Asia among consecutive AD patients aged 6-16 years attending the outpatient department of dermatology. The study was conducted for a period of 1½ years, using consecutive sampling, after approval by the Institutional Ethics Committee.

Seventy-one consecutive cases of AD attending the department of Dermatology were chosen (As per inclusion and exclusion criteria). Informed written consent from the patients' parents/guardians was taken. Patients were interviewed and examined to establish a clinical diagnosis of AD using the "Atopic skin diathesis" criteria validated by Diepgen *et al.*[10,11]Patients with more than 10 points were considered to have AD; patients with more than 6 points were suspected of having AD.

Severity was assessed using the SCORAD Index, which is a validated scoring system in AD.[12]

All patients of the study population were patch-tested. Testing was done using an Indian standard battery of allergens (General and cosmetic series, systopic laboratories-total 32 allergens). The results were read after 48 h and 72/96 h of application by the dermatologist. Recording of patch test reactions was done according to International Contact Dermatitis Research Group recommendations.[13]

The data were coded and entered in a Microsoft Excel sheet and analyzed using the statistical software, the Statistical Package for the Social Sciences. Appropriate statistical tests, such as the Fischer exact test, were done. The *P*-value for significance was taken to be 0.05.

RESULTS

The study comprised 71 individuals between the ages of 6-16. The study population's average age was 10.13 ± 2.7. The majority (38%) belonged to the 11-13 age group, while the lowest (8.5%) was in the 14-16 age group. There were 37 (52.1%) males and 34 (47.9%) females. AD lasted 8.44 ± 2.73 years on average. Patch test positivity and duration of AD did not significantly correlate ($P = 0.602$). The average age of onset of AD in the study population was 1.69 ± 1.66 years.

Out of the 71 study participants, 39 showed a positive patch test, that is, 54.9%. The most common allergen implicated was neomycin (11 out of 71 participants; 15.5%), followed by cetrimide and nickel (7/71; 9.9% each), and thiomersal (5/71; 7%). A total of 32 different allergens were implicated [Table 1].

The presence of sensitization to cetrimide ($P = 0.003$), neomycin ($P = 0.001$), nickel ($P = 0.003$), thiomersal (P value= 0.012), cobalt, paraben mix, and butylated hydroxytoluene (BHT) ($P = 0.026$) was found to be statistically significant [Table 1].

The majority (49/71; 69%) of the study participants had moderate AD. The lowest number of participants had severe AD- 6/71; 8.5%. Sixteen out of 71 (22.5%) had mild AD. In the study population, correlation between patch test positivity as well as increasing AD severity was insignificant ($P = 0.779$) [Table 2].

DISCUSSION

The prevalence of patch test positivity in AD has varied from 17% to 49.9% in various previous studies.[14-17] In this study, out of the 71 study participants, 39 showed a positive patch test, that is, the prevalence of patch test positivity was 54.9%, which is slightly higher than previous studies and consistent with our hypothesis.

Common allergens implicated by most studies are nickel (but considered irrelevant due to the bypass theory), chromium, composite mix, cobalt, paraphenylenediamine, neomycin, para-tertiary butylphenol formaldehyde resin, and isothiazolinones. In their meta-analysis, Hamann *et al.* found a statistically significant correlation between AD as well as contact sensitization to composite mix along with chromium.[7]

Recently, Wee *et al.,* found at least one positive reaction in 50.6% of AD individuals in their study with potassium dichromate, nickel sulfate, Myroxylon pereirae, fragrance mix I, and p-phenylenediamine.[18]

A recent study conducted in the United States also showed that after physical therapy, individuals with AD had a greater likelihood of ACD (54.8%) compared to non-AD individuals (47.3%).[19]

In our study, the most common allergen implicated was neomycin (11 out of 71 participants; 15.5%), followed by cetrimide and nickel (7/71; 9.9% each), and thiomersal (5/71; 7%). A total of 32 different allergens were implicated. Of this, the majority (19 out of 32) were from the cosmetic and fragrance series, and 13 out of 32 were from the general series [Table 1].

The presence of cetrimide ($P = 0.003$), neomycin ($P = 0.001$), nickel ($P = 0.011$), thiomersal ($P = 0.012$), cobalt and paraben mix, and BHT ($P = 0.026$) sensitization in the study participants was found to be significant [Table 1].

The fact that contact sensitization to neomycin and cetrimide was significant could be due to the increase in the use of over-the-counter antiseptics and creams that are prevalent in the Indian scenario. This finding highlights the importance of judicious use of such medications.

Nickel and cobalt sensitivity is also prevalent in this population and underlies patterns of dermatitis, such as posterior thigh dermatitis and dermatitis associated with ornaments/watches. Thus, such patterned dermatitis in AD patients should alert the treating physician about the possibility of ACD and proceed with thorough history taking about triggers and patch testing.

Thiomersal is another commonly implicated allergen that we found in our study. It is found widely as a preservative in medications, vaccines especially. Hence, its relevance as a contact allergen is controversial.

Table 1: Frequency and *P*-value of positive patch tests.

Allergen	Positive patch test		*P*-value
	Frequency	Percentage	
Neomycin	11	15.5	0.001
Cetrimide	7	9.9	0.003
Nickel	7	9.9	0.003
Thiomersal	5	7.0	0.012
Paraben Mix	4	5.6	0.026
BHT	4	5.6	0.026
Cobalt	4	5.6	0.026
4-PTBP	3	4.2	0.054
Colophony	3	4.2	0.054
Pot. Dichromate	3	4.2	0.054
Phenyl salicylate	2	2.8	0.118
Parthenium	2	2.8	0.118
BHA	2	2.8	0.118
Wood alcohol	2	2.8	0.118
Fragrance mix	2	2.8	0.118
Benzyl alcohol	2	2.8	0.118
Benzocaine	2	2.8	0.118
Cetyl alcohol	1	1.4	0.271
Chloroacetamide	1	1.4	0.271
Geranium oil bourbon	1	1.4	0.271
Imidazolidinyl urea	1	1.4	0.271
2-OH-4 MBP	1	1.4	0.271
PCMC	1	1.4	0.271
Hexamine	1	1.4	0.271
Black rubber mix	1	1.4	0.271
Propylene glycol	1	1.4	0.271
Lavender absolute	1	1.4	0.271
Musk mix	1	1.4	0.271
Triethanolaminme	1	1.4	0.271
Kathon CG	1	1.4	0.271
Benzyl salicylate	1	1.4	0.271
Bronopiol	1	1.4	0.271

BHT: Butylated hydroxytoluene, 4-PTBP: 4-para tertiary butylphenol, BHA: Butylated hydroxyanisole, 2-OH-4 MBP: 2-hydroxy 4-methoxybenzophenone, PCMC: Parachlorometacresol, CG: Cosmetic grade

Table 2: Association between severity of atopic dermatitis and patch test positivity.

Severity	Patch test positivity		Total	Fisher exact (*P*-value)
	0	1		
Mild	8	8	16	0.779
Moderate	22	27	49	
Severe	2	4	6	
Total	32	39	71	

Paraben mix and BHT were not previously found to be commonly associated with ACD in AD but were found significant in our study.

Methyl-, ethyl-, propyl-, butyl-, and benzyl-parahydroxybenzoate are the five distinct paraben esters that make up the paraben mix. These preservatives are most frequently found in topical pharmaceutical preparations, skin care products, pharmaceuticals, foods, cosmetics, and industrial items such as oils, fats, fabrics, adhesives, and shoe polish. While rare, given its ubiquitous use, allergic hypersensitivity to paraben is not uncommon. Contact sensitivity to paraben mix is not commonly seen in AD, but it was seen in our study in statistically significant proportions. This is probably due to the wide variety of topical preparations used to treat AD, both prescription and over-the-counter, that use paraben as a preservative. Previous studies have also shown that parabens are more likely to cause ACD when applied on damaged skin (for example - that of an AD patient).[20] When found to be sensitized, patients need to be counseled in reading labels to avoid exposure to this widely seen allergen.

BHT is widely used in cosmaseuticals and as an antioxidant in food, petrol products, animal feed, synthetic rubbers, as well as plastics. Contact sensitization to BHT is not commonly associated with AD, but our study found a significant association. This can probably be explained by the increasing use of cosmetics in the child and adolescent population in general.[21]

Our study had its limitations - due to the COVID-19 pandemic, it was not possible to fulfill the initial proposed sample size of 104; instead, only 71 participants could be recruited till February 2020. Hence, some of the findings, though they show a positive association, were not found to be statistically significant. As it was not a comparative study, it is not possible to say whether the prevalence of AD is more than that of general population. Instead, it was only possible to compare it with previously found data.

CONCLUSION

From the study, we can see that there is an increased prevalence of patch test positivity in AD patients. The allergens neomycin, cetrimide, nickel, cobalt, thiomersal, paraben mix, and BHT were the commonest allergens implicated, and clinicians should have a high suspicion of ACD caused by these in AD patients. They should be prepared to perform appropriate patch testing and comprehensive, intuitive history-taking to detect ACD in individuals with AD.

Ethical approval: The research/study was approved by the Institutional Review Board at Amala Institute of Medical Sciences, Thrissur, number ECR/653/Inst/KL/2014/RR-17, dated October 19, 2018.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent.

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