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ORIGINAL ARTICLE

Relationship between Concomitant Atopic Diseases with Atopic Dermatitis Severity and Persistence

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ABSTRACT

Introduction: The atopic march consists of atopic dermatitis (AD), allergic rhinitis or sinusitis (AR), allergic conjunctivitis (AC) and bronchial asthma (BA). The influence of concomitant atopic diseases on AD is under-explored. We determined the relationship between personal and family history of atopic diseases with AD severity and persistence. **Methods:** A cross sectional study involving AD patients was performed at dermatology clinics of two tertiary hospitals. Inclusion criterion was all patients diagnosed with AD. Demographic data, personal and family history of atopy (BA, AR and AC) were obtained by face-to-face interview. AD severity was evaluated using Investigator's Global Assessment (IGA). AD was considered persistent if continued beyond age 12 years. **Results:** Sixty patients aged 21.6±17.2 participated. There were 25(41.7%) with concomitant AR, 16(26.7%) BA and 12(20%) AC. Forty seven (78.3%) patients had family history of atopy, 25(41.7%) had eczema, 24(40%) AR, 19(31.7%) BA and 2(3.3%) AC. Patients with BA [OR=3.8, 95%CI 1.04 to 14.4)], BA and AR [OR=9.74, 95%CI 1.13 to 83.67) and family history of BA [OR= 4.00, 95%CI 1.20 to 13.27) were more likely to exhibit moderate-severe AD. Personal AR, AC and family history of AD and BA were significantly more prevalent in patients with persistent AD. **Conclusions:** AR was the most common atopic disease associated with AD. Family history of eczema and AR were common. Personal BA, BA with AR and family history of BA were predictors of severe AD. Personal AR, AC and family history of AD and BA were associated with AD persistence.

KEYWORDS: Atopic march; atopic dermatitis; risk factors; severity

INTRODUCTION

AD results from a complex interaction between genetic predisposition, impaired skin barrier integrity, immune system dysregulation, sensitization to environmental and food allergens and mechanical scratching. The prevalence of atopic dermatitis (AD) is increasing over the past few decades in both developing and developed countries [1]. AD commonly occurs concomitantly with allergic rhinitis/ sinusitis (AR), bronchial asthma (BA) and allergic conjunctivitis (AC) or in association with family history of these diseases.

The atopic march is classically described with AD as the first disease manifestation, followed by IgE-mediated food allergy (FA), BA and AR [2,3]. The peak age at diagnosis of AD is between 0 to 5 months, 12 to 17 months for BA and FA, and 24 to 29 months for AR [2.] About 85% of patients with AD developed the disease before the age of 5 years, 45% of them before the age of 6 months and 60% between 0 to 12 months of life [3]. Between 50–80% patients with AD developed AR or BA later in childhood as part of the atopic march [4]. These atopic diseases are thought to share the same process of allergen sensitization and reaction as a common element in their pathophysiology. Epicutaneous sensitization to environmental, aero and food allergens through defective skin barrier triggers Th2 pathways that include systemic responses [5]. However, the influence of an atopic disease on other diseases once a patient has developed more than one

atopic disease is largely unclear. Concomitant BA and AR have been suggested to occur more frequently in patients with moderate to severe AD compared to those with mild disease [6,7,8].

Our study objectives were to determine the relationship between personal and family history of atopy with AD disease severity and persistence of AD. This information could aid in AD prognostication and guide patients' expectations in disease association and progression.

MATERIALS AND METHODS

A cross sectional study was conducted at Dermatology Clinics of two tertiary centers between 2017 to 2018. Inclusion criterion was patients diagnosed with AD according to the Hanifin-Radjka Criteria [9]. Demographic data, personal and family history of atopy (BA, AR and AC) were obtained by interviewing the patients or the parents of children with AD. Presence of BA, AR and AC were based on history of any previous physician's diagnosis and treatment of these conditions. Physical examination was performed to determine AD disease severity, the Investigator's Global Assessment (IGA) scoring was used [9]. The IGA score ranged from 0 to 5: 0 denotes clear, no inflammatory signs of AD, 2 for almost clear, just perceptible erythema and just perceptible papulation/ infiltration, 3 for mild disease, mild erythema, and mild papulation/ infiltration, 4 for moderate disease, moderate erythema, and moderate papulation/ infiltration, 5 for severe disease, severe erythema, and severe papulation/ infiltration, and 5 for very severe disease, severe erythema, and severe papulation/ infiltration with oozing/crusting. SPSS version 25 statistical software was used for statistical analyses. Chi-square test with Yates's correction where applicable, was used to compare the prevalence of other atopic diseases in patients aged less than 12 years with patients aged 12 years and older. AD severity was categorized into 2 groups ie mild and moderate to severe according to IGA scores. Patients with severe AD were grouped together with patients with moderate disease as there were only 2 patients (3.3%) with severe disease. Logistic regression analyses were performed to ascertain the effects of concomitant presence of BA, AR, AC on the likelihood of the study subjects having more severe AD. The odds ratios were adjusted for age, gender and ethnicity. A p-value of <0.05 was considered significant.

RESULTS

Sixty patients with AD participated in the study. Forty-four (73.3%) patients were females while 16(26.7%) were males. The mean age was 21.57±17.21 years old. There were 37(61.7%) Malays, 16(26.7%) Chinese, 5(8.3%) Indians, an Iban and a Kadazan 2 (3.3%). Twenty-five (41.7%) patients had AR, 16(26.7%) had BA, and 12(20%) had AC. Forty-seven (78.3%) patients had family history of atopy. Twenty-five (41.7%) had family history of eczema, 24(40%) had family history of AR, 19(31.7%) had family history of BA, and 2(3.3%) had family history of AC. AD severity assessments revealed 2(3.3%) patients with severe disease, while 29(48.3%) patients had mild and moderate disease respectively. Forty-nine (81.7%) patients used moisturizers, 50(83.3%) were on topical corticosteroids while 39(65%) required antihistamines. Mean body surface area (BSA) affected was 6.36±12.98, itch score was 4.83±2.36 and DLQI was 6.58 ± 4.16. Characteristics of the study population are summarized in Table 1.

Table 1 Characteristics of study population

Characteristics	n (%) or mean ± SD
Age, years	21.57 ± 17.21
Gender	
Male	16 (26.7%)
Female	44 (73.3%)
Ethnicity	
Malay	37 (61.7%)
Chinese	16 (26.7%)
Indian	5 (8.3%)
Others	2 (3.3%)
Co-morbidities	
Allergic rhinitis/sinusitis	25 (41.7%)
Bronchial asthma	16 (26.7%)
Allergic conjunctivitis	12 (20%)
Family history of atopy	47 (78.3%)
Eczema	25 (41.7%)
Allergic rhinitis/sinusitis	24 (40%)
Bronchial asthma	19 (31.7%)
Allergic conjunctivitis	2 (3.3%)
Atopic dermatitis severity	
Investigator's Global Assessment (IGA)	
Mild	29 (48.3%)
Moderate	29 (48.3%)
Severe	2 (3.3%)

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We used the age 12 years as the cut off point to define AD persistence. Both AR and AC were significantly more prevalent in ≥12 years age group than <12 age group (p=0.001, p=0.003). In the 12-65 age group, a significant proportion of them had AR (57.9 %), 31.6% had AC, 23.7% had BA. Family history of AD was significant in ≥12 years age group compared to <12 years age group (p= 0.001). Both personal and family history of atopy were more prevalent in ≥12 years group compared to <12 age group (Table 2).

Table 2 Prevalence of other atopic diseases in patients with persistent AD

Atopy	< 12 years old, n (%)	12 – 65 years old, n (%)	p-value
Personal history of			
Bronchial asthma (BA)	7 (31.8)	9 (23.6)	0.50
Allergic rhinitis/ sinusitis	3 (13.6)	22 (57.9)	**0.00**
Allergic conjunctivitis	0	12 (31.6)	**0.00**
Family history of			
Atopic eczema	3 (13.6)	22 (57.9)	**0.00**
Bronchial asthma	4 (18.2)	15 (39.5)	**0.01**
Allergic rhinitis/ sinusitis	7 (31.8)	17 (44.7)	0.33
Allergic conjunctivitis	1 (4.5)	1(2.6)	0.69

Patients with BA were more likely to exhibit moderate-severe AD with OR=3.88, 95%CI 1.04 to 14.44. Presence of AR was significant in determining severity of AD if there is concurrent BA, with OR=9.74, 95%CI 1.13 to 83.67. The odds of having moderate to severe AD is non-significant with AR alone OR=1.76, 95%CI 0.53 to 5.84. Presence of AC, albeit being part of the atopy march, has no predictive value in AD disease severity, OR= 0.28, 95%CI 0.16 to 1.31 (Table 3).

Table 3 Odds of moderate-severe AD with presence of other atopic diseases

Personal history of atopy	AD severity, n (%)		Adjusted OR (95%CI)
	Mild	Moderate-severe	
Bronchial asthma (BA)	4 (13.8)	12 (38.7)	**3.88 (1.04-14.44)**
Allergic rhinitis/sinusitis (AR)	11 (37.9)	14 (45.2)	1.76 (0.53-5.84)
Allergic conjunctivitis (AC)	8 (27.6)	4 (12.9)	0.28 (0.16-1.31)
2 atopic diseases			
BA + AR	1 (3.4)	8 (25.8)	**9.74 (1.13-83.67)**
BA + AC	1 (3.4)	2 (6.5)	0.52 (0.04-6.04)
AR + AC	5 (17.2)	4 (12.9)	1.41 (0.34-5.85)
3 concurrent atopic diseases	1 (3.4)	2 (6.5)	0.52 (0.04-6.04)

Analyses on family history of atopy revealed that BA has significant predictive value on AD disease severity with OR=4, 95%CI 1.20 to 13.27. Family history of eczema, AC, AR and the presence or 2 or more atopic diseases is not significantly associated with AD severity (Table 4).

Table 4 Odds of moderate-severe AD severity with presence of family history of other atopic diseases.

Family history of atopy	AD severity, n (%)		Adjusted OR (95%CI)
	Mild	Moderate-severe	
Atopic dermatitis (AD)	11 (37.9)	14 (45.2)	1.372 (0.465-4.042)
Bronchial asthma (BA)	5 (17.4)	14 (45.2)	**4.00 (1.20-13.27)**
Allergic rhinitis/sinusitis (AR)	12 (41.4)	12 (41.4)	0.86 (0.29-2.55)
Allergic conjunctivitis (AC)	0	2 (6.5)	N/A**
2 concurrent atopic diseases			
AD + BA	1 (3.4)	7 (22.6)	8.167 (0.94-71.2)
AD + AR	3 (10.7)	7 (22.6)	2.53 (0.6-10.9)
AD + AC	0	1 (3.2)	N/A**
BA + AR	2 (6.9)	6 (19.4)	3.24 (0.6-17.6)
BA & AC	0	1 (3.2)	N/A**
3 or 4 concurrent atopic diseases	0	5 (16.1)	N/A**

*Ref: ** - cannot be computed, cells with zero subjects*

DISCUSSION

Dysfunctional skin barrier in AD serves as the site of transcutaneous food and aero allergens exposure which activates systemic Th2 immune responses leading to food allergy, allergic rhinitis and allergic conjunctivitis [2,3]. AR was the commonest concomitant atopy observed in our study population followed by about equal numbers of patients with BA and AC. BA developed in 43% of AD children up to the age of 7 years while 45% developed allergic rhinitis [10]. In AD children aged 2 months to 15 years, the prevalence of AR was 36.6% and BA 9.3% [11]. About 31.6% patients with AD developed BA while 28.9% developed AR during a 5-year prospective study [12]. Age is an important factor in comparing and interpreting the prevalence of atopic diseases. In the atopic march, eczema was most commonly diagnosed at age 5 months, BA and food allergy at 12 and 17 months, while the peak age of AR diagnosis was 24 and 29 months [2]. Reports showed different or similar prevalence depending on the ages of the population studied. However, the order of progression from one atopy to the next remained similar.

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We found personal history of BA, both BA and AR, along with family history of BA to be independent predictors of AD severity. Interestingly, concurrent presence of all four atopy; AD, BA, AR and AC in the same patient did not appear to predispose to more severe AD. AR and BA has been observed to be more prevalent in moderate to severe AD [6,7]. Presence of food allergy and family history of atopy were identified as risk factors for severity in children aged 0- 2 years [8]. We did not observe significant association between personal and family history of AR alone and AC with AD severity. Aeroallergen sensitivity, increased serum IgE and increased peripheral eosinophil count were identified risks for older children aged 2 to 7.5 years old [6]. Another cohort of children aged 5-10 years old showed BA, AR, and AD onset in the first year of life as predictors of disease severity [7]. History of infected AD [12] and FLG mutation carrier status [15] were additional factors identified to be associated with AD severity. BA and AR were concomitant atopic diseases consistently reported to be associated with more severe AD. The association appeared to be more prevalent with AR [6,7,8]. We did not include food allergy in our study as it was very difficult to confirm food allergy in our cohort due to various factors especially unreliable reporting of symptoms by the patients.

Prognosis of AD is good in most patients. Complete remission of AD was observed in 49.8% children by the age of 3.5 years (range 1.5- 7.8 years) [10], and 76% by age 13 years [16]. AD has been reported to persist in 24.1% to 47.6% of adolescents [16,17]. A meta-analysis of 45 studies found 20% of children had AD that persisted beyond the age of 8 years [18]. In terms of atopic diseases, family history of AR and AD has been associated with AD persistence [17]. Paternal history of BA and AD were factors identified in children with AD persisting after age 13 years, however personal history of BA was not a significant predictor [16]. In our cohort of patients, personal history of AR, AC and family history of AD and BA were observed in those with AD at age 12 to 65 years.

Limitations to the interpretation of our results were the majority of the study population had mild or moderate AD and existence of BA, AR and AC were based on history of physician's diagnosis. Although there were statistically significant results, the confidence intervals were wide. Further investigation should include a bigger sample size, more patients with severe disease and standard criteria for diagnosis of BA, AR and AC. It would be interesting to study if optimizing BA and AR control reduces severity of AD and vice versa.

CONCLUSIONS

Personal history of BA, family history of BA and concomitant BA/ AR/ AD in an individual are risks for more severe AD. Concomitant AR and AC are not significant in predictors of disease severity. Persistence of AD beyond the age of 12 years is associated with personal history of AR, AC and family history of AD, BA.

Conflict of Interest

Authors declare none.

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