CIA Update – Review Article

International Archives of Allergy and Immunology

Int Arch Allergy Immunol 2020;181:1–10
DOI: 10.1159/000502958

Received: August 6, 2019
Accepted: August 27, 2019
Published online: October 8, 2019

Atopic March: Collegium Internationale Allergologicum Update 2020

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Keywords
Atopic march · Atopic dermatitis · Asthma · Rhinitis

Abstract
In recent decades, the worldwide prevalence of allergic disease has increased considerably. The atopic march is a model aimed at explaining the apparent progression of allergic diseases from atopic dermatitis (AD) to allergic asthma (AA) and to allergic rhinitis (AR). It hypothesizes that allergic disease begins, typically in children, with the development of AD, then AA, and finally progresses to AR. This theory has been widely studied in cross-sectional and long-term longitudinal studies and it has been found that as prevalence of AD declines, prevalence of AA increases. A similar relationship is reported between AA and AR. The legitimacy of the atopic march model is, however, currently debated. Epidemiological evidence and criticism of longitudinal studies point to an overstatement of the atopic march's prevalence and incorrect mechanisms, opening a discussion for alternative models to better explain the pathophysiological and epidemiological processes that promote this progression of allergic diseases. Albeit, risk factors for the development and progression of allergic disease, particularly AD, are critical in identifying disease progression. Investigating the role of age, severity, family history, phenotype, and genetic traits may give a better indication into the progression of allergic diseases. In addition, studies following patients from infancy into adulthood and a general increase in longitudinal studies would help broaden the knowledge of allergic disease progression and the atopic march.

Introduction

Regarded as the first moral philosopher and founder of Western ethical thought, Socrates was often called ἀτοπία, which means out of place [1]. Two millennia later, the term atopy (derived from ἀτοπία) was used to describe the atopic family of diseases: allergic asthma (AA), hay fever, food allergy, atopic dermatitis (AD), and allergic rhinitis (AR) [2]. The relationship between allergic diseases and progression from AD to AA, and AR is characterized as the atopic march [2, 3]. The atopic march is driven by both genetic and environmental factors resulting in type 2 immune responses and sometimes elevated

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IgE levels [3, 4]. These conditions frequently occur in childhood, although this succession of diseases has been observed later in life [5–7]. The aim of this review is to investigate the substantiality of that atopic march and progression of allergic disease from AD to AA, and finally to AR.

Epidemiology of the Atopic March

The progression of the atopic march is supported by a body of epidemiological evidence investigating the temporal relationship among AD, AA, and AR development [8].

Epidemiology of the Atopic March: Linking Childhood AD with Asthma

The International Study of Asthma and Allergies in Childhood project estimates that the prevalence of AD in children aged 6–7 years ranges from 0.9 to 22.5% and that childhood AD has increased globally over the past decade, particularly in developing countries [9, 10]. A number of longitudinal and cross-sectional studies have explored the relationship between childhood AD and AA and provide meaningful insight into the development of the atopic march [7, 11–30]. These results are summarized in Table 1. In the population-based birth cohort, Tucson Children's Respiratory Study (TCRS), AD manifesting before 1.5 years of age was associated with persistent wheezing at 6 years (OR 2.4; 95% CI 1.3–4.6) [19]. Similarly, the population-based Prevention of Allergy among Children in Trondheim (PACT) and Tasmanian Longitudinal Health Study studies found that that early-onset AD (onset within first 2 years of life) increased the odds of developing childhood AA (OR 2.06, 95% CI 1.09–3.90 and OR 1.74, 95% CI 1.30–2.34, for PACT and Tasmanian Longitudinal Health Study respectively) [20, 29]. This data suggests a temporal association between AD and AA.

Epidemiology of the Atopic March: Linking AD with AR

Progression of AD to AR has been reported in a number of retrospective analyses, prospective, longitudinal, and cohort studies [12, 14, 16, 17, 24, 26, 27, 31]. The Swedish population-based birth cohort BAMSE (Barn [children], Allergy, Milieu, Stockholm, Epidemiological Study), which followed infants over 12 years (n = 810), indicated that infantile physician-diagnosed AD was associated with AR development at age 12 (OR 4.32; 95% CI 2.04–9.12) [31]. Similarly, in the Dampness in Building and Health (DBH) study, which followed 3,124 children (aged 1–2 years) over 5 years, children with physician diagnosed AD had a near threefold increased OR of developing AR (aOR 2.63; 95% CI 1.85–3.73) [24]. However, given the general late onset of AR in relation to AD, there is less longitudinal empirical evidence directly comparing AD and the onset of AR compared to AD and AA development.

Epidemiology of the Atopic March: Linking AA with AR

Within the context of the atopic march, AA and AR are strongly associated with one another [14, 16, 17, 20, 24, 26, 27]. In the DBH study, childhood AA was associated with an increased OR of developing AR (OR 4.10, 95% CI 2.57–6.54) compared to non-asthmatic children [24]. In the long-term retrospective follow-up study, Ricci et al. [16] observed an increased risk of AR onset in AA patients compared to non-asthmatics (OR 3.448, 95% CI 1.741–6.847). Additionally, as part of the Pediatric Eczema Elective Registry, a cross-sectional study of physician-confirmed AD (n = 2,270), indicated an increased risk in AR development in children with AA (OR 4.8, 95% CI 4.0–5.8). Conversely, in the birth cohort BAMSE, AA before the age of 2 was not significantly associated with AR (OR 1.48, 95% CI 0.93–2.36), suggesting that AA before 2 is unlikely to be linked with the atopic march [31]. This evidence implicates AA and AR as commonly associated diseases that share a temporal link. As such, this may suggest these allergic diseases are causally related, and thus fit with the atopic march model.

Epidemiology of the Atopic March: The Whole March

A select number of studies have described the progression of all 3 atopic diseases in succession from AD, to AA, and AR and provide strong evidence to validate the atopic march theory [16, 17, 32, 33]. Ricci et al. [16] identified that patients with moderate and severe AD were at a greater risk of developing AA compared to those with mild AD (OR 2.855, 95% CI 1.084–6.176, OR 4.770, 95% CI 2.063–11.032 respectively). They then identified an increased risk of AR onset in patients with AA (OR 3.229, 95% CI 1.668–6.252) but observed no increased risk for AR development in patients with persistent AD (OR 0.951, 95% CI 0.911–0.994).

The German mass allergen study studied 942 infants over 17 years [32–34]. In patients with allergic family history, the prevalence of AD, AA, and AR comorbidity increased from age 3 to 7 in both males and females (3.9 and 2.6% respectively) [33, 34]. Over the same period, AD in

Table 1. Studies exploring childhood AD progression to AA and AR

Author, year; country	Study design	Patient population	Duration of observation	Key findings
Gustafsson et al. [17], 2000; Sweden	Prospective cohort	94 children from Uppsala (45) and Örebro (49), Sweden. Mean eczema score 5.4±1.3 (median 6.0) Aged 4–35 months (median of 17.0 months)	Up to 7 years reported	Initially elevated eczema severity (6–8 eczema score) was associated with childhood AA prevalence (OR 2.6, 95% CI 1.1–6.1)
Amat et al. [13], 2015; France	Prospective cohort; ORCA	214 infants with physician-diagnosed early-onset AD	Children ≤1–6 years of age	MS and FHA phenotypes had highest levels of AA at 6 years of age compared to LS cluster 36.1 and 33.3% versus 14.9% respectively, $p < 0.01$
Carlsten et al. [12], 2013; Canada	Prospective follow-up	373 high-risk infants who had undergone a randomized control trial with intervention measures for primary prevention of asthma applied during the first year of life	Assessments at 1, 2, and 7 years of age	Non-persistent early-onset AD was not associated with AA at 2 years, but was associated with AA at 7 years of age (OR 2.88, 95% CI 1.07–7.74). Persistent early-onset AD was significantly associated with AA at 7 years (OR 7.48, 95% CI 2.53–22.2)
Roduit et al. [47], 2017; Austria, Finland, France, Germany, and Switzerland	Birth cohort; PASTURE	1,038 were recruited from birth (503 females, 532 males) from farming and non-farming families	Assessments from 1 to 6 years of age	Early persistent AD was associated with AA development in the first 6 years of life (adjusted OR 2.87, 95% CI 1.31–6.31)
Burgess et al. [29], 2008; Australia	Prospective cohort; TAHS data	5,729 participants with lifetime history of eczema self-reported in 2004 or parent reported in 1968	Study population selected independent of atopy; 7–44 years	Early-onset eczema was significantly associated with childhood AA (OR 1.74, 95% CI 1.30–2.34)
Wan et al. [18], 2017; USA	Observational cohort; PEER	3,966 children aged 2–17 with physician-diagnosed AD	Mean 7.5-year follow-up	No significant difference in AA incidence between different AD onsets (early-onset vs. mid-onset vs. late-onset)
Martinez et al. [27], 1995; USA	Birth cohort; TCRS	826 children with follow-up data recruited independent of atopy	Data collected at 3 and 6 years of age	Early-onset eczema (within 1 year of life) independently associated with persistent wheeze (OR 2.4, 95% CI 1.3–4.6). Eczema prevalence greatest in persistent wheezers (18%) compared to non-wheezers (7.7%)
von Kobyletzki et al. [24], 2012; Sweden	Prospective cohort; DBH study	3,124 children aged 1–2 in Värmland county, Sweden	Children were followed up for 5 years	Children with AD had increased odds of developing AA (aOR 3.07; 95% CI 1.79–5.27) and AR (aOR 2.63; 1.85–3.73) at follow-up compared to children without AD
Gough et al. [33], 2015; Germany	Birth cohort; allergen study MAS	High-risk allergy enriched population of 942 newborns across Germany	Follow-up assessments from 1–20 years of age (19 years)	Prevalence of AD + AA + AR increased in males and females with family history of atopy (3.9, 2.6%); no increase in males and 1% increase in females with no family history of atopy
Mortz et al. [30], 2015; Denmark	Prospective cohort; TOACS	1,206 8th grade students in Odense, Denmark, were recruited in 1995 having AD, inhaled allergy, contact allergy, or control	15 year follow-up until the age of 30	Persistent AD observed in 50% of children diagnosed in 8th grade. Lifetime prevalence of having AD, AA, and AR given having just one was 9.8%
Tran et al. [28], 2018; Canada	Longitudinal study: CHILD	3,495 Canadians recruited during pregnancy with 2,311 children who had complete data	3 years	AD increased risk of AA (aRR, 2.23; 95% CI 1.36–3.67) and AR (aRR 4.44; 95% CI 2.59–7.63) at 3 years
Abo-Zaid et al. [39], 2018; England, Wales, and Scotland	Analysis of birth cohort study (1958); NCDS	18,500 babies recruited with data collected on asthma and wheezing	Followed at year 11,16, 23, 33, 42, 46, 50, and 55	Self-reported AA prevalence decreased 11–50 years from 9.0 to 5.1%. Risk of AA given AD also decreased between 11 and 50 years by 1.11 (OR 4.17; 95% CI 3.30–5.29; OR 3.06; 95% CI 2.25–4.16)

Table 1 (continued)

Author, year; country	Study design	Patient population	Duration of observation	Key findings
Machluf et al. [15], 2019; Israel	Cross-sectional study	113,671 adolescents from northern Israel in the IDF. Participants had valid medical baseline records	NA	Mild and moderate-severe AA significantly associated with AR in males and females (males: OR 6.9, 9.0, and females: OR 8.2, 10.2)

ORCA, Observations of Respiratory risks linked to Cutaneous Atopy; TAHS, Tasmanian Longitudinal Health Study; PEER, Pediatric Eczema Elective Registry; TCRS, Tucson Children's Respiratory Study; DBH, Dampness in Building and Health; MAS, mass allergen study; TOACS, The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis; CHILD, Canadian Healthy Infant Longitudinal Development; NCDS, National Child Development Study; IDF, Israeli Defense Force; PASTURE, Protection against Allergy Study in Rural Environments; NA, not applicable; AD, atopic dermatitis; AA, allergic asthma; AR, allergic rhinitis.

males decreased from 12 to 3.6%, while AA increased by 3.4% [33]. A delayed increase in AR and AR + AA was also observed in males over 17 years (13.2 and 10%, respectively). In females, a similar increase in AA, AR, and AA + AR was observed although there was a small increase in AD-only patients that peaked from ages 9 to 15 [33]. It is likely that the persistence of AD in females may be due to increased female sex hormones during puberty, resulting in a greater prevalence compared to males [35–37]. These data support the temporal progression from AD to AA, and then to AR with a concurrent decline in the prevalence of the preceding atopic disease.

A prospective follow-up of children with AD over 3 visits (average ages in years: 1.5, 3.5, 7.1) investigated a change in Eczema Area and Severity Index (EASI) [17]. Over the 3 visits, a drop in EASI score from 5.4 to 2.4 coincided with an increase in physician diagnosed bronchial obstruction in the past year (26, 33, and 43% respectively). AR development in the last year followed the same trend as bronchial obstruction but was initially delayed with a greater increase toward the third visit (14, 37, and 45% respectively) [17]. The delay in AR progression compared to AA coincided with a decrease in the EASI score. This may suggest a progression of AD to AA, and from AA to AR while AD prevalence declines. Epidemiological evidence demonstrates that the allergic diseases AD, AA, and AR are unlikely independent diseases; rather, they are temporally associated to each other and may be causally related.

Overstatement of Universality

Understanding the atopic march hypothesis maintains a clinical benefit because it creates a framework to predict whether those with early atopic symptoms are likely to follow the traditional atopic march. While there is substantial evidence for the presence of the atopic march, its prevalence may be overemphasized. In a 2018 editorial, Busse [38] argued that while the atopic march exists, the prevalence of patients following the classic pathway (AD to AA, to AR) is largely overstated.

Overstatement of Universality: Identification of Allergic Disease

Methods of data collection and disease identification in studies that evaluate the atopic march are a major point of dispute when discussing study validity. Cross-sectional and longitudinal studies investigating allergic diseases and the atopic march can recruit thousands of patients, reaching up of 100,000 [15]. Large patient numbers increase both the cost and time required to make physician diagnoses, and thus allergic disease identification is often based on "yes" or "no" questions. A number of longitudinal studies that have supported the atopic march theory have utilized simple "yes" or "no" questionnaires for AD, AA, and AR diagnoses, some even without further physician confirmation [13, 17, 18, 24, 27, 29, 33, 39]. The use of questionnaires may also introduce recall bias in self-reported data. Moreover, lay individuals often over-report disease, resulting in an overestimation of true disease prevalence [40]. Consequently, major population cohort studies that employ these screening methods may overestimate the prevalence of the atopic march, indicating that a lower true prevalence with fewer individuals progressing through the classic model exists.

The Childhood Origins of Asthma cohort study investigated the effects of virus-induced wheezing episodes in patients with AA where participants were followed from

birth to age 6 (n = 259) [41]. AA diagnosis at 6 years was based on the presence of >1 of 5 criteria within the last year: (1) physician diagnosis of asthma, (2) use of albuterol for coughing or wheezing episodes, (3) use of a daily controller medication, (4) step-up plan including use of albuterol or short-term use of inhaled corticosteroids during illness, and (5) use of prednisone for asthma exacerbation [41]. AA diagnosis was confirmed based on the 5 criteria by 4 separate investigators who were blinded to any prior histories of viral illnesses or patterns of aeroallergen sensitization [41]. With this strenuous AA diagnosis, Jackson et al. [41] found that AD within the first year of life was not associated with AA at 6 years (multivariate OR 1.2, 95% CI 0.5–2.5, p = 0.08). In addition, when evaluated at 13 years of age, AD within the first year was not found to be significantly associated with AA development (multivariate OR 2.2, 95% CI 1.0–4.7, p = 0.06) [42]. The data from this study indicate that the process of an atopic march may not hold true when rigorous criteria for allergic diseases identification are employed and may be a result of inadequate disease diagnosis.

Overstatement of Universality: Phenotypic Importance, a Question of Causality

A critical issue when investigating the atopic march is the use of umbrella terminology and failure to recognize disease heterogeneity. AD, AA, and AR are often used as umbrella terms for allergic diseases, which ignore disease expression, underlying mechanisms, and severity. The importance of recognizing distinct patterns in allergic disease is evident in the population-based birth cohort TCRS, where early life wheeze-patterns were associated with different long-term asthma diagnoses [27]. Subdivided into transient early, late-onset, and persistent wheezers, Martinez et al. [27] observed that AD was a risk factor for only transient early wheezers and persistent wheezers, not late onset wheezers (OR 0.7, 95% CI 0.3–1.6). This suggests that if AD is a risk factor for AA, it may be restricted to AA subpopulations and is not universal. The Observatory of Respiratory risks linked with Cutaneous Atopy prospective cohort study utilized a cluster analysis to investigate the effect of early-onset AD phenotypes on AA development [13, 43]. Their analyses indicated that the phenotypes "multiple sensitizations" (39%) and "family history of asthma" (17%) were associated with AA development (39 and 17%, respectively), whereas 44% of children did not develop AA or other allergic diseases [13, 43]. Therefore, nearly half of children with early-onset AD did not develop further allergic diseases associated with the atopic march. The restriction of AD and AA interconnectedness to subpopulations may be further evidence toward an overstated prevalence and oversimplification of the atopic march.

In the Avon Longitudinal Study of Parents and Children (ALSPAC) Cohort and the Manchester Asthma and Allergy Study (MAAS) Cohort, Belgrave et al. [43] investigated the presence of the atopic march at an individual level in contrast to many studies that at large-scale population prevalence [38]. By processing data on AD, wheeze, and AR data from cohorts at ages 1, 3, 5, 8, and 11, the authors used machine learning to identify 8 distinct subpopulations describing the progression of AD, AA, and AR [43]. The subgroups identified were as follows: no-disease, atopic march, AD-only, AR-only, persistent AD and wheeze, transient wheeze, persistent AD with late-onset AR [43]. Within the individual-level analysis, 3.1% of children followed the classically hypothesis atopic march model (AD first, followed by AA, and then AR), and over 90% of children with atopic symptoms did not follow the typical progression [43]. Although AD, AA, and AR often develop as comorbidities, these conditions may exist as independent allergic diseases whose association with atopic sensitization differs. Therefore, the classic atopic march pathway may represent only a small fraction of allergic disease patients.

Overstatement Response

While criticism of the atopic march model has mounted, so have counter-arguments, which often aim to rebut the criticism or propose alternative models to the atopic march.

Overstatement Responses: A Different Model

A chief criticism of the atopic march is that relatively few children (3.1%) follow the typical model (AD first, followed by AA, and then AR) [43]. Hill et al. [44] argue that although this may be true, the traditional atopic march model is an overly restrictive definition. Instead, a model whereby the atopic march is defined by initial AD development followed by any other allergic manifestation or disease is proposed [44]. This indicates that a patient may progress through the atopic march without ever developing AA or AR. Using this alternative model and the data from ALSPAC and MAAS, the prevalence of the

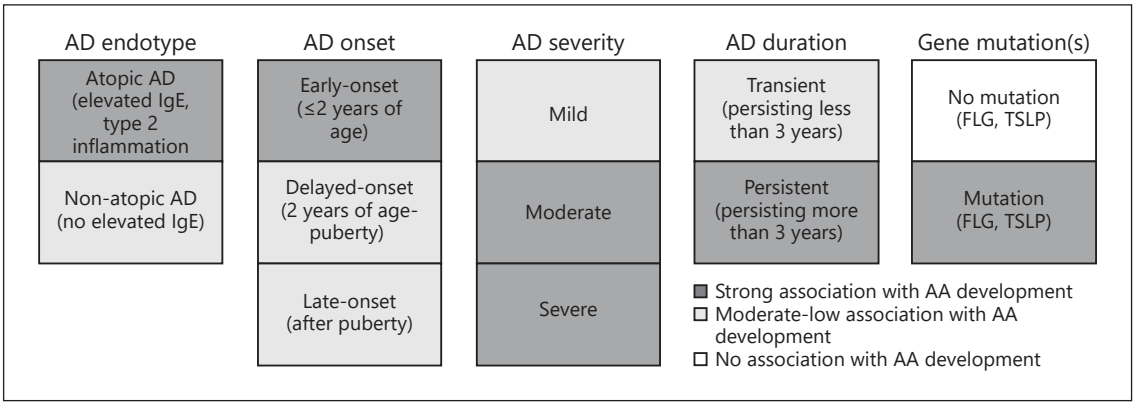

Fig. 1. Notable features of AD and associations with AA. Atopic endotype of AD, early onset-AD, moderate and severe AD, persistent AD and gene mutations (e.g., *FLG, TSLP*) are strongly associated with AA development. Non-atopic AD, delayed-onset and late-onset, mild AD and transient AD are moderately associated with AA development. No gene mutations are associated with subsequent AA development. AD, atopic dermatitis; AA, allergic asthma; FLG, filaggrin; TSLP, thymic stromal lymphopoietin.

atopic march increases to 10.5%, which represents nearly half of all patients with AD in these studied populations. Broadening the definition of the atopic march may help explain allergic disease progression for a greater proportion of patients.

However, Hill et al. [44] appear to overestimate the atopic march's prevalence (16.2%) with their alternative model incorporating the ALSPAC and MAAS cohorts. This is a result of including "persistent wheeze with later-onset rhinitis" patients (5.7%) into their new estimation, a group who should not be included, as they do not fit their criteria of the alternative atopic march model (developing AD first) [43, 44].

Overstatement Response: Adult AA

Another rebutted criticism of the atopic march is that adult onset AA appears to be independent of the atopic march. In the TCRS, early-onset AD was associated with inactive and chronic AA at an age of 22 (OR 3.8, 95% CI 1.9–7.8; OR 2.0, 95% CI 1.0–4.1 respectively), but not with adult onset AA [19]. This suggests that there is a discrepancy in the traditional atopic march model, since the diseases may persist beyond childhood or manifest in an adult population. Since it is widely accepted that childhood AD and adult-onset AA are distinct, some have proposed a non-allergic pathophysiological mechanism for adult-onset AA may exist, which is induced by age-related changes to the lungs and immune system and drives this "mature atopic march" [44, 45].

Risk Factors for AD

Although the evidence surrounding the prevalence of the atopic march among patients with atopic disease are disputed, identifying risk factors for AD remains critical in the context of the atopic march and the development of subsequent allergic disease. AD risk factors are summarized in Figure 1.

Risk Factors for the Atopic March: Age-Dependent Onset and Severity

Time-line of AD onset and severity appear to increase the risk of AA development and contribute toward the atopic match. Data from the mass allergen study indicated a positive association between AD within the first 2 years of life and wheeze at 7 years (OR 1.93, 95% CI 1.22–3.06) compared to those without AD or AD without scratching [22, 34]. The DBH project further discerned a strong association between early-onset AD and the risk of developing AA during a 5 year follow-up (OR 3.44, 95% CI 1.94–6.09) but no association between late-onset AD and AA [24]. Evidence by Wan et al. [18] shows no significant differences in reported AA over a median 7.5 follow-up period between different early-onset, mid-onset, and late onset AD groups (≤2, 3–7, 8–17 years respectively). Children taking immunosuppressants were however, excluded from the study. These patients may represent children with severe AD, which are most prone to subsequent AA development [11, 12, 16]. Within the PACT study, early-onset AD was subdivided into 3

groups (0–3, 4–12 and 13–24 months) [20]. Those who presented with the earliest AD (0–3 months) were most likely to have AA at 6 years of age (OR 4.51, 95% CI 1.73–11.72) [20]. Interestingly, adult onset AA appears to be independent of the atopic march. In the TCRS, early-onset AD was associated with inactive and chronic AA at an age of 22 (OR 3.8, 95% CI 1.9–7.8; OR 2.0, 95% CI 1.0–4.1 respectively) but not with adult onset AA [27]. Given the impact of AD onset on the development of diseases in the atopic march, it is important to distinguish between pediatric and adult onset-AD, particularly when considering immunological characteristics.

Czarnowicki et al. [46] found that childhood AD is characterized by skin-honing T_H2 cells and a T_H1/T_H2 imbalance, whereas adult AD extends to systemic and interleukin (IL)-22 producing T cells. T_H22 activation may be a consequence of disease chronicity, recurring skin infections or immune development [46]. As the atopic march is predominately observed in children, imbalance of the T_H1/T_H2 paradigm may be a critical feature mediating the progression of systemic atopy. Future longitudinal studies should evaluate the T-cell profile changes of children who present with early-onset AD and subsequently develop AA.

Persistent AD is generally defined as having chronic AD for 3 or more years and increases the risk for childhood AA. In 2 birth cohort studies, a strong association was found between early-onset persistent AD and childhood AA [12, 47]. In a prospective Canadian birth study investigating children at risk of atopy, the odds of developing AA and AR by the age of 7 were significantly greater for children with early-onset persistent AD [12]. The Protection against Allergy Study in Rural Environments study was an international European initiative to explore the AD phenotypes in rural communities [47]. AD onset was characterized as early transient (≤ first 2 years), early persistent (≤ first 2 years), late onset (≥2 years), and infrequent/never. The risk of AA within the first 6 years of life was associated with early persistent AD (aOR 2.87, 95% CI 1.31–6.31) [47]. An association between AA and early transient AD was observed, but it was not significant [47]. Similar findings indicate that persistent AD at an early age increases the likelihood of presenting with doctor-diagnosed AA and or AR later in life [48].

Risk Factors for the Atopic March: Endotypes Predict Asthma Severity

There is evidence to support numerous AD endotypes, whereby only some of them are associated with the development of subsequent allergic diseases [13, 48, 49]. In population-based studies, only a third of patients with eczema have any allergen-specific IgE sensitization [49]. A number of longitudinal studies have found a strong relationship between IgE-associated AD and AA [48, 50, 51]. In an Australian birth cohort study of children with at least one atopic parent, children with atopic eczema had a greater risk for developing AA (OR 3.2, 95% CI 1.5–6.9, $p < 0.003$), food allergies (OR 4.2, 95% CI 1.7–10.4, $p < 0.001$), and AR (OR 3.5, 95% CI 1.7–7.1, $p < 0.0005$), compared to children with non-atopic eczema [48].

This atopic eczema endotype generally manifested itself at a younger age, typically within the first 6 months of life (OR 9.3, 95% CI 3.7–23.1, $p < 0.005$) [48]. Additionally, the atopic eczema endotype is positively associated with serum IgE levels [13, 48, 49]. The Observatory of Respiratory risks linked with Cutaneous Atopy cohort study describes 3 unique AD phenotypes: "low sensitization," "multiple sensitizations," and "familial history of asthma" [13]. At age 6, the prevalence of AA was elevated in the latter 2 groups relative to the low sensitization group (36.1 and 33.3 vs. 14.9% respectively, $p < 0.01$). A similar trend was seen in the total number of cases of AA observed throughout the study (30.5 and 27.3 vs. 12.6%, respectively, $p = 0.01$) [13]. Since high serum food, or aeroallergen specific IgE levels distinguish AD with multiple sensitizations, it is likely that this endotype is a subset of atopic eczema [13]. These results implicate allergic eczema with the atopic march.

Risk Factors for the Atopic March: Genetic Factors

It is evident that the atopic march is hereditary. Children whose parents are both atopic are 5.35 times more likely to develop early-persistent AD, a phenotype associated with the atopic march [12, 47, 48]. Within the PACT study, children who had a family history of atopy were at a greater risk of developing early-onset AD and AA at 6 years compared subjects from non-atopic families (aOR 2.46, 95% CI 1.08–5.62) [20]. Furthermore, there is a genetic association between AD and AA. In a population-based study of 1,480 Swedish twins aged 7–9 years, a 0.3 phenotypic correlation between AD and AA was identified, with the majority of the observed correlation (85%) linked to genetic factors [52]. The Danish Twin Registry reported a 0.4 phenotypic correlation between AD and AA, of which 81% of the correlation was ascribable to genetic pleiotropy and observed a significant association between AA and AD within the same individual (OR 4.82, 95% CI 4.01–5.79) [53]. This information provides strong evidence to support the genetic relatedness of AD and AA.

Filaggrin

One of the prevailing theories explaining AD development is the "outside-in" hypothesis, which postulates that skin barrier defects facilitate allergen, pathogen entry, and subsequently stimulates inflammation [4]. Filaggrin (FLG) is an integral epidermal protein that regulates barrier formation by facilitating the compaction of keratin filaments. Additionally, it plays a role in epidermal hydration by forming an insoluble barrier in the stratum corneum [54]. FLG expression is downregulated in AD, and individuals with loss-of-function FLG mutations are at greater risk for AD because of greater epithelial barrier dysfunction [55, 56]. Rodríguez et al. [56] explored the relationship between loss-of-function *FLG* mutations, AD, and AA in a meta-analysis of 24 human studies. An overall OR of 1.48 (95% CI 1.32–1.66) for asthma occurrence and *FLG* mutations without AD was established from a sub-analysis of 29 studies analyzing AA or AA + AD [56]. A stronger effect was observed for the asthma plus eczema phenotype in the context of an *FLG* mutation, with an overall OR of 3.29 (95% CI 2.84–3.82) [56]. Henderson et al. [57] analyzed the relationship between 2 common *FLG* mutations (*R501X* and *2282del4*), in the context of the atopic march from within ALSPAC population-based birth cohort. Overall, *R501X* and *2282del4* alleles predispose affected individuals to asthma (OR 1.80, 95% CI 1.34–2.41) [57]. In the absence of AD, loss-of-function *FLG* alleles had no association with asthma (OR 0.80, 95% CI 0.46–1.41), but *FLG* genes were strongly associated with the comorbid AA and AD phenotype (OR 3.42, 95% CI 2.38–4.90) [57]. The statistical relationships indicate that *FLG* mutations predispose individuals for AD, which then predisposes for AA, but not AA directly.

Thymic Stromal lymphopoietin

Thymic stromal lymphopoietin (TSLP), an IL-7-like cytokine, is a critical immunological regulator of allergic responses. It is an alarmin that stimulates type 2 immune responses and is linked with AD, AA, food allergies, and AR [58]. Genome-wide association studies and specific gene association studies have identified that SNPs for TSLP cytokine and its canonical receptor (IL-7Rα) are positively associated with AD [59, 60]. TSLP polymorphisms and TSLP overexpression are associated with asthma [61, 62]. In an AD mouse model, Demehri et al. [63] found TSLP-overexpression stimulated bronchial hyper-responsiveness to inhaled allergen, despite the absence of cutaneous allergen sensitization. These outcomes infer TSLP influences an atopic phenotype in a fashion independent of traditional epicutaneous sensitization. The potential high systemic availability of skin-derived TSLP in individuals with AD has led many to investigate its importance in subsequent asthma development. Demehri et al. [63] used mice deficient in notch signaling, an important mechanism for forming the granular and spinous epidermal layers. These mice had increased trans-epidermal water loss and consequently over-expressed TSLP [63]. These mice were epidermally sensitized to ovalbumin (OVA) and then giving an inhalation OVA challenge. Compared to wild-type mice, the OVA-sensitized notch-deficient mice had significantly more profound lung inflammation. These mice had a sevenfold increase in lung eosinophil infiltration, extensive goblet hyperplasia, and more severe AHR. In an IL-7Rα knockout model, notch signaling-deficient mice did not appear to develop AHR. Most interestingly, Demehri et al. [63] found that epithelial-derived TSLP in the absence of epicutaneous sensitization was sufficient to facilitate the sensitization of the lungs to inhaled allergens. In a similar mouse model, TSLP –/– mice did not present with AD-like symptoms nor did they exhibit asthmatic-like responses to inhaled OVA [64]. These results showcase the important role of TSLP in the development of asthma in the context of the atopic march. Given the experimental evidence and the fact that TSLP variations are independently affiliated with asthma and AD, it is possible that this is a linking genetic factor between these diseases. However, further research is needed to investigate the association between TSLP variations and AD with subsequent asthma in humans.

Conclusion

As the global prevalence of allergic disease rises, so does its impact on population health. Epidemiological evidence supports the progression of allergic disease as seen through comorbidity and temporal prevalence changes. However, additional evidence exists to rebut the claims of the atopic march. While evidence does exist to support the existence of the atopic march, its prevalence may be overstated. Instead, alternative hypotheses that incorporate various perspectives of the atopic march may develop as increased understanding of the progression of allergic disease continues. Identifying the risk factors associated with the atopic march, particularly AD, is important in the early recognition of allergic diseases. Understanding the role of age, severity, family history, phenotype, and genetic traits all give a clearer picture as to how AD and may progress into AA and AR.

Disclosure Statement

All authors declare no conflict of interest with respect to the scientific information presented in this publication.

Funding Sources

J.P. and M.A. were funded by summer scholarships from the McMaster Bachelor of Health Sciences Program.

Author Contributions

M.A. and J.P. conducted the primary literature research organizing and writing of the paper. G.M.G., H.L., and R.S. provided overall supervisorial and editing support in the development of this article.

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