Atopic dermatitis and atopic march: which link?

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Abstract. There is a long standing debate on the atopic march in childhood. The natural progression of allergic manifestations may be considered as comorbidities, which occur more frequently in a specific evolutive age. On the other hand, the natural history of allergies in children may follow trajectories that may be heterogeneous. The effects of atopic march in clinical practice have also been reported. (www.actabiomedica.it)

Key words: atopic march, atopic dermatitis, food allergy, asthma, T helper 2 lymphocytes, eosinophilic esophagitis

Introduction

Atopic dermatitis (AD) is a chronic recurrent inflammatory disease with a multifactorial etiology and complex pathophysiology. Its relevant heterogeneity of clinical phenotypes results in different progression trajectories, concerning severity, persistence and risk of developing atopic comorbidities. Therefore, it would be very important to determine, for each affected child, the pathways that will be followed over time. Indeed, in addition to peculiar skin manifestations, AD can predispose young patients to other atopic diseases, a phenomenon known as atopic march (1).

Historical Background

We report a summary of the works that have contributed to identifying this atopic pathway, where dermatitis is in most cases the first step. In 1978 the group of Atherton and Soothil (2), composed of dermatologists and pediatricians, published a work on the link between severe atopic dermatitis and food allergy. This publication represented an important reference for the management of the disease but, unfortunately, their conclusions on severe forms have been erroneously extended to all pictures, creating a tendency to consider all cases of atopic dermatitis caused by food allergy.

Several years later, in 1980 Hanifin and Rajka (dermatologists) published the diagnostic criteria for AD, highlighting the link with atopy but without defining the pathogenetic mechanisms (3). Until the 2000s, numerous epidemiological and clinical works were published, clearly showing the presence of a pathogenetic link between the two conditions, but not yet demonstrable (4,5).

The discovery of T helper 2 (Th2) lymphocytes in blood paved the way for the definition of the al-
ergic response. Then, the progression of immunology science would let the identification of the exact pathogenetic basis of atopic disease. Donald Leung published in 2000 a synthesis of histopathology studies on pathogenetic mechanisms in AD, where he showed that during the acute phase of the disease, a Th2 cytokine pattern can be found in the skin while in the chronic phase, Th1 elements are also observed (6).

In the same years, the Berlin group studying the MAS (Multicenter Allergy Study) cohort (the first longitudinal birth cohort to examine multimorbidity of asthma, allergic rhinitis and eczema up to 20 years of age) contributed to outlining the concept of atopic march (4). Term atopic march was pronounced for the first time by Jonathan Spergel and, since then, it has been used to define the progression of atopic manifestations (5).

A further aspect of the allergic march was demonstrated by genetic studies by Palmer and collaborators in 2006 (7). However a genetic-based alteration in the production of filaggrin (FLG), later shown do not exist in all patients (8), but was a possible cause of the skin barrier alteration, through which atopic response can be generated. Several papers thereafter supported the concept that the alteration of the skin barrier in AD may be the primum movens of atopy. However, it was shown that the Th2 cytokine pattern mediated by IL-4 and IL-13 can reduce the production of filaggrin and other barrier proteins, thus the alteration of the skin barrier can be determined by an atopic condition (9). These data show how the alteration of the barrier in AD may represent a possible trigger of the allergic response, but also that allergy itself may modulate the skin barrier, especially the skin of infants whose corneocytes are less adherent and in fewer layers. The difficulty in defining the IgE-mediated disease pathway is increased by the fact that the cellular mechanism is the main pathogenetic condition not only in AD but also in other diseases, such as eosinophilic esophagitis (EoE). In fact, recently EoE has been considered one of the disorders included in the atopic progression (10). Indeed, a cellular pathogenetic mechanism may underlie different food allergy-related diseases, such as allergic proctitis and food protein induced enteropathy syndrome (11), but currently clinical and laboratory data support this evidence only for EoE. Moreover, data from a genome-wide association study reported EoE sharing some specific genetic loci with other manifestations of the atopic march, including signal transducer and activator of transcription 6 gene (STAT 6) and Thymic Stromal Lymphopoietin (TSLP) polymorphisms (12).

Also epidemiological studies have shown the association between EoE and allergic diseases. Mohamad et al. analyzed 449 patients with EoE and described prevalence rates of allergic rhinitis, asthma and AD of 61.9%, 39%, and 46.1% respectively, and the development of these 3 atopic diseases in up to 21.6% of patients with EoE (13).

Another study involving 35,528 subjects reported that subjects with IgE-mediated food allergy were at higher risk for EoE (14). A cohort study of 130,435 infants found a positive association between EoE and other allergic manifestations (15).

The above studies, therefore, suggest that EoE may be the fifth “member” of the atopic march, although this hypothesis is controversial because EoE occurs not only during childhood but also at later ages. Furthermore, EoE can occur in individuals without a history of atopy. Therefore, larger cohorts are needed to analyze the epidemiological connection between EoE and other manifestations of the atopic march and the mechanisms involved (10).

**Developmental trajectories or comorbidities?**

Atopic march can be considered an important paradigm to understand the natural progression of allergic diseases mediated by Th2 lymphocytes. Therefore, the various studies that hypothesized a stereotyped progression of the allergic manifestations, with AD as the first step, have not been confirmed since, in clinical practice, there is usually a considerable variability in the number and sequences of allergic diseases encountered.

One could assume that these allergic manifestations are only comorbidities, which occur more frequently in a specific evolutive age. There is a heterogeneity in the trajectories followed, not all of which are yet known, and which are the result of a complex interaction between environmental, genetic (primarily
loss of function mutations of the FLG gene or mutations of other genes encoding skin barrier proteins or in genes of the innate or adaptive immunity) and psycho-social factors (16).

These trajectories share allergen-specific Th2 responses and are characterized by a “type 2” effector phase that includes the generation of specific IgE production, granulocyte activation, and other features such as mucus production and edema. Importantly, the presence of one allergic condition increases the risk of developing the others, resulting in the additional clinical features of the atopic march (11).

Prevention

The term atopic march means atopic progression, involving AD as the first obligatory stage. Features of AD (i.e. barrier defects and inflammation of the skin and/or alterations of the microbiome (17) could be the basis for the development of sensitization (18) and the subsequent appearance of other allergic diseases. From this perspective, the prevention of AD may also prevent subsequent stages of the march.

Very recent data suggest that a genetic predisposition for more than one atopic disorder, together with early environmental exposures (i.e. exposure to irritants/allergenic air pollutants or certain microbes, cesarean delivery or dysbiosis of the skin microbiome with prevalent colonization by staphylococcus aureus) could contribute to the development of the atopic march.

On the contrary, early environmental factors like a vaginal delivery, breast milk feeding, avoidance of antibiotics and antacids may protect against allergic morbidity during childhood (19).

Another recent study including 1,637 children from the Cohort for Childhood Origin of Asthma and Allergic Diseases (COCOA) study reports that antibiotic exposure within the first 6 months of life correlates with the incidence of early persistent AD and a dose-dependent increase in the incidence of AD in childhood, an effect modified by IL-13 (20).

IL-13 significantly impacts the alteration of the skin microbiome, causing a deterioration of the skin barrier function and could therefore be the most important mediator, of the Th2 response in the skin, compared to IL-4 (21).

The recent reformulation of “The Epithelial Barrier Hypothesis” further clarifies this phenomenon (22). It postulates that environmental exposure to toxic substances introduced by the modern lifestyle affects the skin epithelial barrier and that of the upper and lower airways and intestinal mucosa.

These toxic substances include detergents, cleaning products (particularly enzymes and surfactants), microplastics, nanoparticles, ozone and particulate matter in increased concentrations, cigarette smoke and food additives (enzymes and emulsifiers).

Exposure to these harmful agents leads to the development of inefficient epithelial barriers, microbial dysbiosis, translocation of bacteria to inter- and sub-epithelial areas and microinflammation of tissues in and around the skin epithelium.

Microbial dysbiosis and the translocation of commensals and opportunistic pathogens a cross epithelial barriers is typically followed by a type 2 immune response, characterized by a predominance of T helper 2 cells, type 2 innate lymphoidcells (ILC2s) and eosinophils. Mastcells, macrophages and antibody-producing B cells can also be involved in this response. The epithelium cannot fully repair and close the barrier (23).

Therefore, this theory assumes that barrier damage caused by environmental changes is not only responsible for the development of allergic and autoimmune diseases, but also for a wide range of diseases in which immune responses to bacteria may have systemic effects (22).

To summarize, “The epithelial barrier hypothesis” considers five points: a) the consistent increase in allergic and autoimmune diseases, b) the evidence of epithelial barrier breakdown in these conditions, c) the microbial dysbiosis and bacterial translocation, d) the immune response to commensals and opportunistic pathogens, and finally, f) the changes in environmental exposure due to urbanization and industrialization.

AD and asthma

The link between AD and asthma has always
been of special interest. Although AD is considered an important risk factor for subsequent allergies the progression from AD to asthma represents only one of the pathways for the development of asthma (23). In fact, only a percentage of children with early eczema proceed to develop asthma (24) and only a few cases of asthma are preceded by eczema (25,26). For example, in the Tucson Children’s Respiratory Study, only 18% of children with wheezing at 6 years of age had eczema before age 2 (27).

Another important well-known risk factor for asthma is allergic sensitization (28). Evidence suggests that the development of asthma may be related to the number and type of sensitizing allergens and the timing of sensitization (29). Early sensitization to aeroallergens, particularly to multiple aeroallergens, increases the risk of asthma in school-aged children (30).

Food sensitization in early childhood and co-sensitization to both tropho and aeroallergens have also been associated with asthma (31).

The current scientific position is that the risk of developing asthma appears to be due to a combination of factors rather than to any single factor, such as AD or allergic sensitization. Childhood asthma is defined by a history of respiratory symptoms, such as wheezing, coughing, shortness of breath, and chest tightness along with variable airflow limitation. Moreover, the same clinical manifestations are present in patients with heterogeneous asthma traits, such as the presence or absence of atopy, normal or impaired lung function, and persistent or intermittent disease course. This observation suggests that the clinical manifestations observed in asthma are common endpoints of a variety of underlying diseases. Indeed, such non-specificity of the clinical presentation is common to many diseases.

First consideration

In recent years, thanks to the advances in the field of immunology and genetics, the knowledge of pathogenetic mechanisms of allergic disease have been incredibly increased but we cannot still define the different temporal and causal relationships between them.

Different phenotypes of AD, allergic rhinitis and asthma are associated with several endotypes, but they are still difficult to define and identify in cohort studies and/or epidemiological studies, due to the lack of univocal markers. Thus, it has become difficult and perhaps incorrect to speak of atopic dermatitis or asthma in generic terms, at least when one has to predict the possible evolution.

The temporal sequence of the classic atopic march could reflect a tissue-specific time of onset of each disease, so it would be appropriate to speak of a cluster with precise peculiarities more than of atopic march. In other words, the “classic marchers” would represent a specific cluster rather than a real progression or march.

The reported clinical case confirms what was reported by the various cohort studies that evaluated atopic march in children with AD. Certainly the cluster in which children with AD at very early onset (3 months or earlier) are grouped, with a positive family history in both parents, poly- and co-sensitized for food and inhalants, possibly with mutations with loss of function of the FLG or mutations of the TSLP, who live in an urbanized environment (lack of protective factors related to life on farms) is the one who will most likely encounter atopic march, even complete, for which it must be identified and followed over time.

Case report

We describe the case of an 18 months-old child, firstborn, suffering from moderate-severe atopic dermatitis (SCORAD 75) since the first months of life. She also presented with recurrent episodes of impetigo and was not responsive to topical anti-inflammatory corticosteroid therapy.

Her family history was positive for allergies in both parents (father with AD and asthma, mother with food allergy and asthma). She was breastfed from birth to 18 months of life. The little girl was sent to an allergist because, according to her mother, she had a skin rash after the intake of vegetable soup containing lentils. She presented also urticaria, diarrhea and cough apparently related to the intake of food contaminated with peanuts. Also, other episodes of urticaria were reported presumably after amoxicillin oral intake, direct contact with dog hair and also after
contact with kiwi. At around 2 years of age (February 2020), her AD worsened and extended to the whole body. Moreover, in the same year, she manifested hives when outdoor in a park, probably related to contact with grasses. In October 2020 she had her first episode of wheezing treated with Fluticasone propionate 50 mcg spray (1 puff 2 times a day) for three months with a good response. The patient also complained of allergic rhinitis, diagnosed by the otorlaryngologist, and the following month she had her second episode of otitis (first around 12 months).

Thus, total and specific IgE dosage, as well as ISAC 112 allergens test (ThermoFisher Scientific, Uppsala, Sweden) were performed (see table 1 and 2). The total IgE was 453 kUa/L in February and 817 kUa/L in March.

The girl resulted poly-sensitized to major food allergens and inhalers (olive tree, cypress, mugwort). In addition, the presence of Phl p 4 suggested an early sensitization to grasses that paved the way for sensitization to primary allergenic components such as Phl p 1 and 5. Moreover, sensitization to a panallergen food that is the deposit protein of the seeds, the 2s albumin, is currently detectable. The evaluation of total and specific IgE (CAP system and ISAC) after about one year is shown in Table 1 and 2. The appearance of specific IgE for major allergenic determinants of grasses, namely Phl p 1 and 5, and the initial appearance of specific IgE for LTP peach, Pru p 3, detectable at ISAC test, provides a global picture of the allergic sensitization.

To note that at CAP, the presence of mite-specific IgE

Table 1. Dosage specific IgE (ImmunoCAP)

| Allergen                  | February 2020, value (kUA/l) | March 2021, value (kUA/l) |
|---------------------------|------------------------------|---------------------------|
| *Dermatophagoides*       |                              |                           |
| *pteronyssinus*           |                              |                           |
| Dermatophagoides          | 0.15                         | 0.22                      |
| farinae                   |                              |                           |
| Cathair                   | 0.09                         |                           |
| Dog hair                  | 6.98                         | 12.5                      |
| Peas                      | 8.26                         | 9.53                      |
| Lentils                   | 8.03                         | 8.56                      |
| *Anthoxanthum odoratum*   | 10.0                         | 39.5                      |
| *Parietaria judaica*      | 22.5                         | 66.7                      |
| Amoxicillin               | 0.17                         | 0.15                      |
| nGald d 1                 | 0.09                         | 0.09                      |
| nGald d 2                 | 0.40                         | 0.15                      |
| nGald d 4                 | 0.19                         | 0.09                      |
| rAra h 9                  | 0.06                         | 0.32                      |
| rAra h 1                  | 5.30                         | 3.46                      |
| rAra h 2                  | 20.9                         | 23.6                      |
| rAra h 3                  | 0.52                         | 0.43                      |
| Mushrooms (champignon)    | 0.07                         | 0.09                      |
| Alternaria                | 0.09                         | 0.11                      |
| Staphylococcal A          | 0.08                         |                           |
| Staphylococcal B          | 0.24                         |                           |
| Staphylococcal C          | 0.27                         |                           |
| Malassezia ssp            | 2.56                         |                           |

Table 2. Dosage specific IgE (ISAC).

| Allergen | February 2020, value (ISU-E) | March 2021, value (ISU-E) |
|----------|------------------------------|---------------------------|
| Ana o 2  | 0.4                          |                           |
| Cor a 9  | 0.5                          |                           |
| Cor a 14 | 0.5                          |                           |
| Ses i 1  | 6                            | 4.8                       |
| Ara h 1  | 3.8                          | 5.5                       |
| rAra h 2 | 36                           | 28                        |
| rAra h 6 | 4.6                          | 9.9                       |
| Gly m 5  | 0.3                          |                           |
| Gly m 6  | 0.3                          | 0.3                       |
| Jug r 2  | 1.6                          |                           |
| Act d 1  | 1.2                          | 1.3                       |
| Cyn d 1  | 5.1                          | 11                        |
| Phl p 4  | 3.9                          | 5                         |
| Phl p 5  | 7.1                          |                           |
| Phl p 6  | 0.8                          |                           |
| Cry j 1  | 3.6                          | 2.5                       |
| Cup a 1  | 3.5                          | 3.9                       |
| Ole e 1  | 2                            | 38                        |
| Art v 1  | 70                           | 5.5                       |
| Pla a 2  | 2.4                          |                           |
| Par j 2  | 22                           | 40                        |
| Sal k 1  | 0.3                          |                           |
| Can f 1  | 11                           | 15                        |
| Can f 4  | 12                           |                           |
| Art v 3  | 0.4                          |                           |
| Pru p 3  | 0.5                          |                           |
| MUXF3 CCD | 1.5                          | 1.5                      |
is detectable, while ISAC does not report it, being less sensitive in detecting the molecular components of the dust mite. Regarding the relevant markers of AD severity, malassezia IgE was detectable, while the levels of specific IgE for Staphylococcus aureus toxins were borderline. Serum eosinophils levels were 9% and 25 OH vitamin D levels were 14.4 ng/mL.

**Last consideration**

Fitzpatrick AM et al. distinguished four latent classes of recurrent preschool wheezing, based on type 2 inflammatory features including blood eosinophils, atopic eczema, sensitization to aeroallergens and food and/or pet exposure. The likelihood of exacerbation according to these authors was greater in children with exposure and sensitization to indoor pet allergens (latent class 2) and children with polysensitization and eczema (latent class 4) (32).

As suggested by the MPAACH (Mechanisms of Progression of Atopic Dermatitis to Asthma in Children) study, in our patient co-sensitization (sensitization to at least 1 aeroallergen and 1 food allergen) seems associated with the severity of AD more than and beyond polysensitization (sensitization to 2 aeroallergens or 2 food allergens), and this appears to be independent of the total number of sensitizations (33).

Higher SCORAD in children are associated with barrier defects such as high transepidermal water loss (TEWL) and low FLG expression (genetically defined or induced by Th2 cytokines, IL-4 and IL-13). This suggests that skin sensitization occurs not only against food allergens but also against aeroallergens. Non-lesioned skin in MPAACH study subjects is similar to the affected skin, in terms of low FLG levels and high alarmin expression, and increased colonization with Staphylococcus aureus.

Treatment of pediatric AD should involve both lesioned and non-lesioned skin because subclinical inflammation in apparently normal areas can predispose to allergic comorbidities and more severe disease.

In our case, dermatitis improved considerably with the proactive therapy pimecrolimus applied on the face and topical steroids at moderate potency, but lesions persisted on the face and hands.

Currently, the patient complains of intense allergic rhinoconjunctivitis and sneezing when exposed to pollens of Parietaria, olive and grasses in parks or gardens.

**Conflict of Interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Received: 1 September 2021
Accepted: 30 September 2021
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