

Atopic dermatitis and asthma

Elena Galli, M.D., Ph.D.,* Simona Gianni, M.D.,* Giovanni Auricchio, Ph.D.,* Ercole Brunetti, M.D.,* Giorgio Mancino, Ph.D.,* and Paolo Rossi, M.D., Ph.D.#

ABSTRACT

Atopic dermatitis (AD), a chronic inflammatory skin disease, frequently associated with respiratory allergy, is one of the most common skin disorders observed in children. The prevalence of AD and other allergic diseases is increasing in industrialized countries, representing a major burden on health care cost. AD has been proposed as an "entry point" for subsequent allergic diseases, suggesting the possibility that effective management of AD could prevent the development of respiratory allergy or at least reduce the severity of asthma and allergic rhinitis. AD and asthma share a common genetic and pathogenic basis, and several longitudinal studies provided evidence for the atopic march from AD to allergic rhinitis and asthma. However, because only a few prospective studies starting at children's births and having a sufficiently long follow-up have been developed, little is known about the natural course of AD and the potential succession of atopic phenotypes in childhood. Finally, recent genetic and epidemiological data raised the question whether AD may either develop to asthma or be part of a syndrome consisting of both diseases.

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Key words: Asthma, atopic dermatitis, atopy, dermatitis, entry point, phenotypes, respiratory allergy

Atopic dermatitis (AD), a chronic relapsing inflammatory skin syndrome depicted by typically distributed eczematous skin lesions with lichenification, pruritic excoriations, severely dry skin, and susceptibility to cutaneous infections, is a complex genetic disorder with variable phenotypes.^{1–4} The onset of AD, which is one of the most common skin disorders found in infants and children, appears during the first 6 months of life in 45% of affected individuals, the 1st year of life in 60% of affected individuals, and before 5 years of age in at least 85% of affected individuals.

AD is characterized by a set of immunologic aberrations, concerning interactions between IgE-bearing antigen-presenting cells, T cells, mast cells, keratinocytes, and eosinophils, as well as a combination of innate and cell-mediated immune responses. During the acute phase, there is an overexpression of Th2 cytokines with a predominance of IL-4 and IL-13, whereas the maintenance of chronic inflammation is associated with a Th1-biased response with IL-5, granulocyte-macrophage colony-stimulating factor, IL-12, and Interferon

(IFN)- γ expression accompanied by the infiltration of eosinophils and macrophages. The increased expression of IL-12 in chronic AD skin lesions is crucial, because its secretion by eosinophils, macrophages, or intraepithelial dendritic cells (IDECs) plays a key role in initiating the switch to Th1.^{2,4}

The prevalence of AD in the U.S. childhood population is 17.2%, similar to the 15.6% prevalence described among European children and the 24% prevalence in 5- to 6-years-old Japanese children.⁵ The appearance of AD in such a sizable proportion of the pediatric population underwent a marked increase during the past decades. In fact, studies performed before 1960 estimated the prevalence to be up to 3%. AD occurs more frequently in smaller families, in higher socioeconomic classes, and in urban rather than in rural areas, suggesting that exposure to antigenic pollutants as well as lack of exposure to infectious Th1-triggering agents early in life might favor the establishment of the disease.

Asthma, an inflammatory disease concerning the small airways of the lung with bronchial hyperresponsiveness, is a complex genetic disorder with variable phenotypes, largely attributed to the interactions between multiple genes and the environment.^{6–8} Similar to AD, asthma has reached epidemic proportions, with >10% of children being affected in many westernized societies, even if recent reports indicate that its rate of mortality and morbidity has reached a plateau.⁷

From the *Research Center, AFaR, "S. Pietro" Hospital, Fatebenefratelli, Roma, Italy, and #Department of Pediatrics, University of Tor Vergata, Roma, Italy

Address correspondence and reprint requests to Elena Galli, M.D., Ph.D., Research Center, AFaR, "S. Pietro" Hospital, Fatebenefratelli, Via Cassia 600, 00189 Roma, Italy

E-mail address: galli.elena@fbfrn.it

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Table 1 AD and asthma: Common relevant points

Complex Polygenic Disorder
Inflammatory diseases with interaction between genes and environment
Shared several immunologic findings
Shared common loci and candidate genes
↑ Prevalence after 1960: reached epidemic proportions
↑ Prevalence has been linked to progressive westernization of lifestyle
↑ Bronchial hyperresponsiveness in AD to methacholine

THERAPEUTIC APPROACHES

Recently, the American Academy of Dermatology has published evidence-based guidelines for AD.⁹ For maintenance, therapy emollients are widely used because they improve appearance and symptoms of the dry skin, whereas topical steroids represent the first therapeutic choice in the acute phase of disease.¹⁰ Topical calcineurin inhibitors (tacrolimus and pimecrolimus) have been shown to be effective in vehicle-controlled studies. Secondary infection with *Staphylococcus aureus* is common and usually is treated with short courses of antibiotics, such as amoxicillin-clavulanate, floxacillin, and cephalexin. Finally, AD associated with food allergy is, as a rule, responsive to a specific avoidance diet, mainly when the patients are very young. Furthermore, indoor allergen avoidance measurements can reduce the severity score for AD children suffering from house mite allergy.^{3,4}

Asthma guidelines¹¹ recommend several intervention approaches, such as bronchodilators for treating symptoms, with the addition of systemic glucocorticoids for significant exacerbations or inhaled corticosteroids, long-acting β -agonists, theophylline, and leukotriene antagonists for long-term control therapy in cases of persistent asthma. Other approaches modulating IgE-associated immunologically mediated inflammatory responses are in use when an associated allergy is documented.

THE ATOPIC MARCH

Early manifestation of AD has been associated with an increased risk of asthma, suggesting that AD can be a starting point for the so-called "atopic march."^{5,12,13} This is characterized by a typical progression sequence of clinical signs of AD, asthma, and allergic rhinitis with some symptoms becoming more prominent while others subside.

Actually, many common features between AD and asthma emerged in the last years, suggesting that the conception of atopic march is true (Table 1). Of course, there is a deep clinical interest about this theory. In this

context, it could be a useful early therapeutical control of AD to reduce the onset of asthma. Because AD may be considered as the entry point for the development of subsequent allergic diseases, it is essential that clinicians from a spectrum of disciplines recognize that AD management must include comprehensive concerns about asthma, allergic rhinitis, and food allergy. Therefore, therapies aiming at modifying the severity of AD in young children may decrease the risk for the development of asthma.

PROPOSED MOLECULAR MECHANISM OF THE ATOPIC MARCH

Severe AD patients tend to have exaggerated airway responses to inhalation challenge with methacholine and allergens, as well as experience the development of respiratory allergy.¹³ Experimental data in animal AD models suggest that the impaired barrier function of the AD epidermis allows epicutaneous sensitization, enhanced by rubbing and scratching of inflamed atopic skin, and can lead to systemic allergic responses and airway sensitization.¹⁴

How does the local sensitization lead to systemic effects? The epidermis of AD patients contains an increased number of IgE-bearing Langerhans cells, expressing the high-affinity receptor for IgE, which contribute to the capture and internalization of allergens before their processing and antigen presentation to T cells.¹⁵ Langerhans cells bearing IgE migrate from inflamed skin to the lymph nodes and stimulate naive T cells inducing expansion of Th2 cells. Subsequently, migration of this pool of Th2 cells from draining lymph nodes through the circulatory system to various sites, including nasal and lung mucosa and bone marrow, would contribute in maintaining a systemic Th2 environment, promoting an allergic response in the airways on inhalation of allergens. In fact, systemic elevated levels of IL-4, IL-5, and IL-13 promote a systemic Th2 environment. Later, inhalation of allergens results in presentation within local dendritic cells and interaction with these Th2 cells. These interactions activate eosinophils and promote their infiltration into inflamed tissues, inducing IgE production, epithelial cell activation, mast cells, and smooth muscle cells proliferation that are observed in asthma.^{13,14} The high spontaneous resolution of AD by the age of 5 years could be caused by the loss of the cutaneous lymphocyte antigen receptor on Th2 cells, which then could find their way to the atopic respiratory tract.

EPIDEMIOLOGICAL STUDIES AND NEW CONCEPT

During the last 20 years, several longitudinal and prospective studies¹⁶⁻²⁰ provided evidences for the

Table 2 AD and asthma: Risk factors

AD Risk Factors	Correlated Diseases
Parental history (asthma, AD); OR, 2.9	Asthma and/or rhinitis
Severity onset OR 2.6	Asthma
Atopic sensitizations <2 yr; OR, 5	Asthma and/or rhinitis
Early onset 3 mo–2 yr	Sensitization (inhalants)
OR = odds ratio.	

atopic march from AD to the development of allergic rhinitis and asthma. The comprehensive analysis of such data allowed the identification of some specific risk factors for the succeeding appearance of asthma (Table 2), indicating which fraction of AD that affected children should be subjected to a primary intervention. Very few surveys have systematically investigated the clinical predictive value of IgE levels during AD. Recently reported data, concerning studies that differentiate between IgE⁺ and IgE-AD children, show that the risk of development of allergic respiratory disease appears to be increased in patients with IgE-associated versus non-IgE-associated AD.^{21–23} Nevertheless, the analysis performed in these studies was not adjusted for a family history of allergic disease. However, because only few prospective studies exist so far, starting at birth and having a long follow-up, little is known about the real natural course of AD and the potential succession of atopic phenotypes in childhood.

Recently, some authors expressed the idea that the allergic march could oversimplify the true natural history of atopic sensitization and allergic disease, thus needing some modifications.^{24,25} The Multicenter Allergy Study (1314 children in a 7-year follow-up) proposed a revisionist theory to the atopic march. In this study, Illi and coworkers²⁴ noted that childhood wheezing often began before, or concurrently with, AD in early life rather than as a consequence. Children with AD without wheezing or early sensitization did not have an increased risk for developing current wheezing or bronchial hyperresponsiveness at 7 years of age. In 87 patients with early AD and early wheezing, AD preceded wheezing in 56%, was concomitant in 11%, and wheezing preceded AD in 33%. It is also important to note that early wheezing is not necessarily asthma because many of these wheezing episodes are virus induced and transient.

Rather than early AD being a risk factor for subsequent asthma in a progressive atopic march, it seems more likely that a certain phenotype exists as a coexpression of asthma and AD. This phenotype probably is characterized, in early life, by AD plus either wheezing or a specific pattern of atopic sensitization and a

more severe course, resulting in significant impairment of lung function. Instead of “cause and effect,” might food sensitization, food allergy, and eczema be similar “end organ” expressions to asthma and rhinitis that arise from shared genetic and environmental triggers? However, there is a need for additional larger population studies to confirm these latter findings, because the debate about atopic march is still open.

GENETIC STUDIES

Although the change in environmental and lifestyle factors is likely to be responsible for the recent rise in the prevalence of atopic diseases, it is clear that interaction between both genes and environment contributes to the genesis of atopy. A genetic background for AD as well as other allergic disorders has long been proposed, because such diseases tend to cluster in families genomewide screens for AD. Genetic studies using modern techniques of molecular biology are expected to advance our understanding of atopic diseases and refine our approaches to their management. They may provide improved definitions of disease, identify subgroups, and reveal new targets for treatment. In addition, if genetic studies can identify individuals who are at risk of atopic diseases, rational strategies for prevention can be potentially developed.

Studies developed during the last 10 years showed that AD and other atopic disorders, such as asthma, share some common genetic basis.^{26–28} Numerous loci and candidate genes (alleles of microsatellite markers and single nucleotide polymorphisms within specific cytokine/chemokine and IgE regulating genes) have been reported to show linkage and association between asthma and asthma-associated phenotypes, atopy, elevated IgE levels, and bronchial hyperresponsiveness. However, only a few genes conferring significant risk have been mapped.²⁹ Focused linkage studies have identified some common chromosomal linkages between AD and asthma on chromosomes 5q31-33, 11q13, and 13q12-14.³⁰

More recently, genomewide screens for AD were completed in four different populations. Results from genomewide screens for AD have been compared with genomewide linkage results for related diseases. Interestingly, of the four major regions identified for AD (3q, 3p, 17q, and 18q), only two (3p and 17q) have shown suggestive evidence for linkage to asthma or related phenotypes in more than one study.²⁸

Furthermore, the regions most consistently linked to asthma or related phenotypes, including the cytokine cluster region on chromosome 5q, the major histocompatibility complex region on chromosome 6p, and regions on 13q and 12q, did not show substantial evidence for linkage to AD in the four genomic screens, indicating that separate genes might be important for

susceptibility to AD. In fact, some of the regions relevant for AD overlap with regions showing linkage to psoriasis, another chronic inflammatory skin disorder.

Thus, genes that are expressed in the skin might play an important role in AD pathogenesis, in addition to genes influencing atopic diathesis. Accordingly, Hoffjan and Epplen²⁸ propose a changing concept for AD pathophysiology. AD was previously mainly classified as a part of the spectrum of allergic disorders with IgE-mediated sensitization and Th2-titled immune dysregulation as major characteristics. Nevertheless, results from genetic studies suggest that AD is partly also a local skin disease that shares important features, such as abnormal epidermal differentiation and defective skin defense mechanisms, with other skin diseases, *e.g.*, psoriasis. Thus, two different sets of possible candidate genes for AD can be evaluated.

There is initial evidence for the genetic background of AD and asthma to be less similar than expected and for genes expressed locally in the skin (*e.g.*, genes encoding proteins for cornified envelopment and local defense mechanism) to be crucial for AD development. These new genetic data are crucial for a better characterization of the atopic march and could partially account for the recent data, expressed by some authors, that seem to contrast with the classic idea of AD. Identifying genetic variation that influences the development of AD could have important clinical implications. Particularly, knowledge about genetic susceptibility could allow us to identify real at-risk individuals very early in life and to develop specific prevention strategies.

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