



Atopic dermatitis as a systemic disease

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Abstract Atopic dermatitis (AD) is a chronic inflammatory disease that seriously affects the quality of life of these patients. Both immune deviations and epidermal barrier deficiency have been defined as pathophysiologic mechanisms in the disease development. The atopic march, or the natural progression from atopic dermatitis in infancy to asthma and allergic rhinitis, is a classic example for the multiorgan involvement in atopy. It has been hypothesized that epidermal barrier impairment is the primary pathologic condition responsible for the atopic march. In recent decades, a growing body of evidence has accumulated that AD can be accompanied by a variety of systemic diseases, such as autoimmune disorders, ophthalmologic involvement, eosinophilic gastroenteritis, inflammatory bowel disease, nephritic syndrome, and metabolic diseases. This contribution reviews these associations and focuses on the possible common underlying mechanisms of AD and the associated syndromes. We present a concept on AD as a multiorgan systemic disease.

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Introduction

Atopic dermatitis (AD), also known as atopic eczema, is a chronic, inflammatory, clinically defined disease with predominant affection of the skin that seriously disturbs the quality of life of these patients.^{1,2} It affects around 20% of the pediatric population and up to 3% of the adults in western societies.³ Beyond affection of the individual due to the chronic pruritus, insomnia, attention concentration disturbances, and absence from work, the economic burden of AD has tremendously increased in the past decades.³

Historical perspective

Although descriptions of chronic pruritic skin conditions exist in ancient and Hippocrates's texts, the first known AD mentioned in the literature was made by Suetonius for the case of the Emperor Augustus suffering from an itchy skin condition together with seasonal respiratory complaints.⁴

In the medical literature, AD was mentioned first in the *De morbis cutaneis* (1572) by Girolamo Mercurialis, the first textbook of dermatology.⁵ Willan and Bateman were the first describing the morphologic basis of eczema/dermatitis, and their approach was dominant for almost two centuries until the work of Hebra, who showed that the disease can be dominated by different lesions in its different stages, and then Besnier, who focused on the subjective manifestations of AD.⁴ Systemic involvement in AD was disclosed in the classic descriptions of Hebra, who stated that axillary and inguinal lymphadenopathy

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were present and that in children urticarial lesions were often observed.

The term “atopy” was coined by the allergists Arthur Coca and Robert Cooke in 1923 for abnormal hypersensitivity against environmental triggers that tended to occur within families and required obvious prior sensitization.⁶ The term “atopic dermatitis” was introduced by Fred Wise and Marion Sulzberger the 1930s to describe the classic flexural skin involvement of the disease.

Pathophysiology in the light of systemic involvement

Immune disturbances

In its classic description, AD is only part of the so-called atopic complex or atopic syndrome that comprises beyond skin changes allergic rhinoconjunctivitis and asthma and is accompanied by typical psychologic trait. One of the key hypotheses for the disease pathogenesis is that all diseases in this group are organ-specific manifestations of a systemic disorder. In consistency, peripheral eosinophilia and elevated IgE are often observed in these conditions.³ Immune dysregulation is one of the key components in AD pathogenesis (Figures 1 and 2), ie, inside-out concept. According to it, AD is a systemic immunologic disorder with increased propensity toward inflammatory response. Certain genetic predisposition to such phenotypes has been witnessed.⁷ Antigen stimulation of Langerhans cells (LC), mast cells, and keratinocytes results in increased populations of eosinophils and inflammatory dendritic epidermal cells, which in turn are capable of switching to the predominant Th₂-response in chronic AD.⁸

IgE is responsible for the antigen presentation. There is evidence that in both lesional and nonlesional skin of AD patients overexpress IgE receptor is on the surface of LC in comparison to healthy subjects.⁹ Subclinical inflammation in nonlesional AD skin is also characterized by Th₂-infiltrates and increased Th₂-originating cytokines, such as interleukin (IL)-4

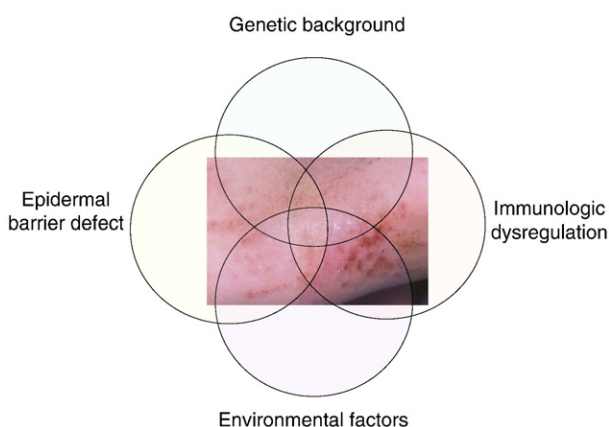


Fig. 1 Ethopathogenetic factors in atopic dermatitis.

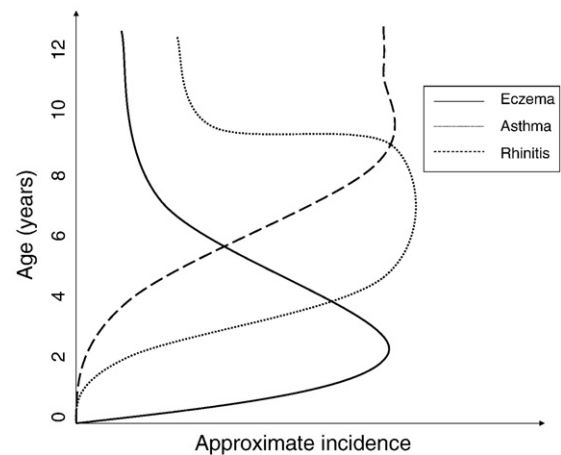


Fig. 2 Schematic overview on the approximate incidence of the disease from the atopic spectrum throughout life.

and IL-13.^{2,10} Both elevated IgE and Th₂-cytokine profile have been witnessed in patients with asthma and allergic rhinitis.¹¹

Epidermal barrier defects

The outside-in concept focuses on epidermal barrier dysfunction as the milestone in AD pathogenesis. A decrease in all three major extracellular stratum corneum (SC) lipids, especially ceramides, was disclosed in both lesional and nonlesional skin of AD patients.^{12,13} Epidermal barrier impediment is witnessed even in uninvolved skin of AD patients, characterized by decreased SC hydration, increased transepidermal water loss (TEWL), and specific structural deficits.⁸ Mutations in the gene encoding for filaggrin, a structural protein of the cornified envelope of the SC, are found in 15% to 50% (severe cases) of AD.¹⁴ In addition, the impeded degradation of filaggrin to the major constituents of the natural moisturizing factor results in diffusely xerotic skin of AD patients. Filaggrin mutations have been associated with asthma, food allergies, nickel sensitization, and allergic rhinitis.¹⁵⁻¹⁸ This mutation was not prevalent in asthma without dermatitis, however, suggesting the role of epidermal barrier impairment for the penetration of allergens through the skin.^{17,18} These findings confirm the role of the skin for the development of lifetime prevalent systemic inflammatory disease; however, not all AD patients and not all severe AD cases show the filaggrin mutation indicating that other relevant mechanisms, as yet undiscovered, play a major role in the development of AD.

Clinical evidence for systemic involvement in AD

The atopic march

The most explicit evidence that AD can be regarded as a systemic disease is the so-called “atopic march.” It is defined

as the progression through the atopic individual's life-form atopic dermatitis in infancy to asthma and allergic rhinitis in childhood. There is a growing body of evidence that dermatitis precedes the sensitization to aeroallergens.¹⁹ Up to 50% of AD patients will develop asthma and even more are prone to get allergic rhinitis later in life according to different studies (reviewed in Ref 3). Probably, the risk is overestimated, as the majority of studies recruit inpatients hospitalized at specialized clinics, favoring severe disease forms. Indisputably, the atopic, also called the allergic march, can be detected in many AD patients, suggesting the complex systematic nature of AD.

Disease associations

Skin disorders

The list of commonly associated skin diseases with AD is long, and some nosology associations have been addressed by multiple studies. Table 1 summarizes the dermatologic diseases (in alphabetic order) reported to be associated with AD. Some of them are barrier driven; others are more related to known immunological factors.

Eye involvement

Ocular involvement is seen in many AD patients. The most common eye disorder is allergic belfaroconjunctivitis. Atopic or vernal keratoconjunctivitis is a distinct, self-limited disease with seasonal exacerbation and is more prevalent in climatic hot regions.²⁰ Findings include stinging, lacrimation, and mild photophobia. Keratoconus, characterized by conical transformation of the cornea, is common in AD patients. A multivariate analysis disclosed atopy as a risk factor for keratoconus development.²¹ The disease is characterized by vision distortion (multiple

images) and exaggerated photosensitivity. Posterior and anterior subcapsular cataracts have been described in AD. Although posterior forms are more common, anterior subcapsular cataract is more specific to AD.²² A decreased inducibility of superoxide dismutase was registered in the disease, suggesting oxidative damage of the lens related to chronic inflammation in AD.²²

Gastrointestinal involvement

Involvement of the digestive system is known in AD patients. The most specific one is eosinophilic gastroenteritis—a relatively rare condition characterized by prominent eosinophilic infiltration of the stomach or small intestine.²³ Clinical findings vary with abdominal pain, nausea, vomiting, diarrhea, weight loss, malabsorption, protein-losing enteropathy, anemia, and nutritional deficiencies being the most common. Atopy was found to be highly prevalent in inflammatory bowel disease by most of the studies.²⁴ A potential sharing of Th₂ cytokine-related pathways in the pathogenesis of these two disorders of barrier dysfunction was suggested.²⁵

Renal involvement

Approximately 48% of pediatric patients with idiopathic nephritic syndrome have a history of atopy and/or elevated serum IgE, and 40% had clinical sign of an atopic disease.²⁶ Steroid-responsive nephrotic syndrome can be exacerbated by reaction to aero and food allergens and atopy is highly prevalent in this disease.^{27,28}

Autoimmunity and AD

A connection between atopy and autoimmunity has been suspected. An increased incidence of autoimmune disorders was observed in atopic children, especially in those with gastrointestinal symptoms after milk ingestion.²⁹ More recently, atopy was disclosed as risk factor for thyroid autoimmunity in children.³⁰ A review of epidemiologic data on rheumatoid arthritis, multiple sclerosis, and type I diabetes mellitus suggested that Th₁-mediated inflammation can protect against atopy, and atopy could reduce the severity but not necessarily the onset of autoimmunity.³¹ It has been shown that AD patients exhibit IgE autoreactivity to human proteins in a variety of cell and tissue types.³² The level of IgE autoantibodies are associated with severity of disease. These findings suggest autoimmunity as a mechanism in the pathogenesis in AD.

Metabolic syndrome

Obesity was linked to asthma; however, no association between insulin resistance and atopy was witnessed.³³ A possible explanation for this phenomenon is the secretion of proinflammatory mediators from the adipose tissue and their effects on mast cells.³⁴ Greater maternal adiposity is associated with transient wheeze in offsprings but not asthma or atopy.³⁵ A significant positive association between total and low-density lipoprotein cholesterol levels and atopy

Table 1 Associations of atopic dermatitis and other skin disorders

Allergic and irritant contact dermatitis
Alopecia areata
Cutaneous amyloidosis
Cutaneous lymphomas
Dermatitis herpetiformis
Exfoliative erythroderma
Lichen sclerosus et atrophicus
Netherton's syndrome
Palmo-plantar keratoderma of Thost-Unna
Pityriasis rosea
Psoriasis (especially inverted)
Skin infections
- Bacterial (Staphylococci and Streptococci)
- Fungal (Dermatophytes, Candida, Malassezia)
- Viral (Molluscum contagiosum, Herpes simplex, HPV)
- Parasitic (<i>Sarcoptes scabiei</i>)
Urticaria
Vitiligo

was found suggesting a link between atopy and hyperlipidemia in schoolchildren.³⁶

Psychological profile of AD patients and psychiatric comorbidities: AD can be regarded as a psychosomatic disease

Psychological factors are considered serious eliciting factors in AD. In past decades, a great number of studies showed that AD patients have impaired quality of life, accompanied by coping problems, sleep disturbance, and impeded interpartner relationships.^{37,38} Hostility, neuroticism, and problems in dealing with anger are typical for the psychological profile of the patients.^{39,40} Personality features of AD patients include temperaments of depression, feelings of inferiority, nervousness, and lack of objectivity in a Japanese cohort.⁴¹

The most common psychiatric comorbidities of atopy patients are anxiety and depression.⁴² Having both asthma and rhinitis strengthens the association with anxiety in comparison to having either disease alone. Attention deficit hyperactivity disorder is observed in AD children.⁴³ The same study found increased risk for depression, anxiety, conduct disorder, and autism among the pediatric AD patients. Restless legs syndrome, characterized by an unpleasant sensation in the legs, which produces an urge to frequently move the legs, was more common in AD than in psoriasis patients and healthy controls.⁴⁴ A recent study linked schizophrenia to atopic diseases and asthma in particular suggesting common immunologic mechanisms.⁴⁵

Stress is considered as a major eliciting factor in AD. Psychologic stress has the potential to induce systemic inflammation and enhancement of dendritic cell migration from the skin and recruitment of CD8⁺T lymphocytes upon antigen stimulation.⁴⁶ In addition, psychologic stress may interfere with epidermal barrier permeability and homeostasis, a key pathomechanism in AD.⁴⁷

Other disorder

A variety of systemic diseases have been reported to be associated with AD among which are cystic fibrosis, endometriosis, hypoproteinaemia, Down syndrome, hearing loss, insect venom allergy, and drug hypersensitivity, which are beyond the scope of this paper, and the reader is referred to the extensive review by Vieluf et al for further details.⁴⁸

Unifying concept

We are practicing in the era of evidence-based medicine. It is recognized as the process of acquiring and applying into practice the best available research findings in a defined field.⁴⁹ In this paper, we have tried to summarize the knowledge on AD not simply as a skin condition but as a disorder affecting the whole organism with its multiple organs and systems. Evidence exists that epidermal barrier

impairment is a major driver for the subsequent sensitization and respiratory symptoms.¹⁹ Systemic inflammation in AD can be witnessed by the so-called subclinical inflammatory changes of clinically uninvolved skin. Finally, the numerous associations of AD with multiple disorders can be accepted as coincidence, but we think that they are intimately linked. The plethora of clinical findings and comorbidity along with discovering distinct altered pathways will lead to a diagnostic stratification of AD and subsequently to more specific treatments. The near future will disclose the intimate mechanism of systemic involvement in AD.

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