Atopic dermatitis. A clinical challenge

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SUMMARY

Atopic dermatitis has a significant impact on both the pediatric and adult population worldwide, which has triggered extensive research on the topic. However, various limitations have created difficulties both in making accurate diagnoses and effectively managing atopic dermatitis patients. This review summarizes the current knowledge in the field, providing an overview of the pathophysiology, disease progression, clinical presentation, and diagnosis and treatment of atopic dermatitis.

KEY WORDS

dermatitis, atopic, immunology, clinical evaluation, diagnosis, management

Introduction

Atopic dermatitis (AD) - also known as atopic eczema - is a chronically relapsing, highly pruritic, inflammatory skin disease that affects 2-5% of the general population. AD has the largest impact on infants and children, affecting an estimated 10-20% or more, but is also believed to affect 1-3% of adults (1). The mechanisms underlying the pathogenesis of AD remain unclear, but numerous studies have demonstrated the integral involvement of immunopathology, genetic predisposition, and emotional and environmental stimuli in AD development and progression.

The term "atopy" was introduced by Coca and Cooke in 1923 as a broad term for a collection of diseases, particularly asthma and allergic conjunctivitis (hay fever) (2). Its precise definition, in relationship to other immunologic terms such as "allergy" and "hypersensitivity", has been the source of and remains unresolved. The ambiguity in its current definition has contributed to difficulty in reaching a consensus in the diagnosis of AD (3-5). The diagnostic criteria recommended by the American Academy of Dermatology at the 2003 consensus conference is currently used by many clinicians, and will be employed for the purposes of this paper (6).

Etiology

Genetic predisposition

Inheritance has been recognized as an important risk factor in the development of allergic diseases since the early 1900s (7). Later, more sophisticated epidemiological studies provided convincing evidence supporting genetic predisposition for atopic dermatitis (8). Over recent years, genome-wide screens have been used in an effort to determine the specific genes that may underlie atopic illness. Such studies have linked atopic dermatitis with several chromosomal loci, including 3q21, 5q31-33, and 11q13. Candidate genes found in these regions code for various immunomodulators including costimulatory proteins (CD80 and CD86) in-

volved in T-cell activation (3q21), interleukins 3,4,5, 11 and GM-CSF (5q31-33), and the beta-subunit of the high affinity IgE receptors (11q13). Such genetic linkage has contributed to the universally accepted role of immunologic abnormalities as central to AD pathogenesis (9-13). A better understanding of the structural and functional alterations of these and other relevant gene products will help to delineate the underlying mechanisms of such genetic susceptibilities.

Pathophysiology

Immune dysfunction

Clinically, AD progresses as two distinct phases: an early, acute phase with intensely pruritic, erythematous, papular lesions, followed by a chronic phase characterized by dry, fibrotic lichenified papular lesions (14). Consistent with the available genetic evidence, immunologic abnormalities have been demonstrated as a core feature in both phases of AD and have been investigated extensively. A variety of studies have analyzed immune cell distribution and cytokine expression patterns in unaffected atopic skin, acute skin lesions, and chronic skin lesions in order to better understand immune dysfunction in AD. A well-accepted immunologic model describes the acute phase as a T-helper cell, type 2 (Th2)-mediated process with high expression levels of interleukin 4 (IL-4), IL-5, and IL-13, and the subsequent chronic phase as primarily T-helper cell, type 1 (Th1)- mediated with high interferon-gamma and IL-12 cytokine expression (15,16).

Increased levels of circulating eosinophils is a characteristic feature of AD and has been shown to correlate with disease severity.(17-19) Studies have also demonstrated infiltration of eosinophils into the sites of active lesions (20,21). Further, there are increases in the levels of interleukin-5, eosinophil chemotactic factors, and eosinophil-derived products (i.e. ECP, EDN, EPX, and MBP) in both the serum and the affected skin (19,21-23). Taken together, there is clear evidence for the infiltration and activation of eosinophils in symptomatic AD.

AD has been associated with elevated levels of total and allergen-specific IgE for many years. However, in the 1980s, a common variant of AD was discovered in which IgE levels remain within normal limits (24). Today, AD is subdivided into two distinct subtypes: an allergic subtype ("extrinsic" AD), and a nonallergic subtype ("intrinsic" AD). This distinction has been elusive, at least in part, due to similar clinical presentations (25). However, further investigation has revealed specific clinical and immunologic differences which have enabled the differentiation between these two subtypes. Important clinical differences of the intrinsic subtype include a lower frequency of cases, a female predominance, and a negative skin prick test (26). Diagnostically, intrinsic AD patients can be identified with normal levels of total serum IgE (<150 kU/L), and the absence of allergen-specific IgE(25). Other differences in cytokine levels, receptor expression, and frequencies of genetic polymorphisms have also been described (27-32), and help contribute to an overall understanding of the complex immunopathology involved in AD.

Elevated levels of IgE specific for exogenous allergens are a common feature of extrinsic AD. However, studies have also revealed elevated IgE antibodies against various autoallergens in the skin, most frequently seen in severe and chronic forms of the disease (33,34). Currently, five IgE-autoallergens have been described: 1) Hom s 1, which has sequence homology with an antigen recognized by cytotoxic T cells in carcinoma patients, 2) Hom s 2, which is involved in sorting and translocation of intracellular proteins, 3) Hom s 3, which has sequence homology with a possible oncogene, 4) Hom s 4, which is a calium-binding protein, and

Table 1. Diagnostic criteria. The diagnostic criteria established at the 2003 "Consensus Conference on Pediatric Atopic Dermatitis" (with minor modification) (6).

I. Essential features (must be present)
- A. Pruritus
- B. Eczema (acute, subacute, chronic)
  1. Typical morphology and age-specific patterns
     - a. scalp in infants
     - b. facial, neck, and extensor involvement in children
     - c. current or prior flexural lesions in any age group
     - d. sparing of groin and axillary regions
  2. Chronic or relapsing history

II. Important features (seen in most cases, adding support to the diagnosis)
- A. Early age at onset
- B. Atopy
  1. Personal and/or family history
  2. IgE reactivity
- C. Xerosis

III. Associated features (nonspecific clinical associations that help in the diagnosis of AD)
- A. Atypical vascular responses (eg, facial pallor, white dermographism, delayed blanch response)
- B. Keratosis pilaris/hyperlinear palms/ichthyosis
- C. Ocular/periorbital changes
- D. Other regional findings (eg, perioral changes/ periauricular lesions)
- E. Perifollicular accentuation/lichenification/ prurigo lesions

Exclusionary conditions: It should be noted that a diagnosis of AD depends on first excluding other potential diagnoses, as listed in Table 2.

Table 2. Differential diagnosis for atopic dermatitis (13,53,97,119).

Pediatric	Adult
· Acrodermatitis enteropathica · Agammaglobulinemia · Ataxia telangiectasia · Atopic dermatitis · Carboxylase deficiency · Dermatitis herpetiformis · Dermatomyositis · Dermatophytosis · Hartnup's syndrome · Hurler's Syndrome · Hyperimmunoglobulin E syndrome · Ichthyoses · Infection · Letterer-Siwe disease · Netherton's syndrome · Phenylketonuria · Scabies · Seborrheic dermatitis · Severe combined immunodeficiency · Wiskott-Aldrich syndrome	· Allergic contact dermatitis · Alopecia areata · Atopic dermatitis · Biotin deficiency · Celiac disease · Cutaneous T-cell lymphoma · Dermatitis herpetiformis · Dermatomyositis · Ichthyoses · Infecton · Irritant contact dermatitis · Pellagra · Pityriasis rubra pilaris · Psoriasis · Scabies · Seborrheic dermatitis · Zinc deficiency

5) Hom s 5, a cytoskeletal protein(35). Mitterman et al. (35) suggest that IgE autoreactivity may contribute to disease by two potential mechanisms: 1) triggering a type I hypersensitivity response, or 2) through the activation of autoreactive T cells. Further investigation is needed to better understand the importance of autoreactivity in AD.

Pathophysiology

Barrier dysfunction

Among other important functions, the skin serves as the principal barrier between the environment and the body, in order to limit the loss of water and important nutrients, and exposure to harmful substances. The mechanical damage that results from the severe scratching is the most obvious cause of barrier dysfunction in AD patients (36,37). However, over recent years, other important factors have been suggested to play important roles. It has been demonstrated that the composition of the skin is altered in affected and unaffected skin of AD patients, and that such alterations cause xerosis and increased susceptibility to allergens and other irritants (38). Several studies have shown that reduction in both hydration state and lipid content of the stratum corneum are significantly reduced in skin of AD patients as compared to normal skin (39-44). Ceramide deficiencies likely contribute to the observed transepidermal water loss (TEWL) and reduction of lipid content in AD patients (45). In support of this theory, in 2003, Loden(46) reported that administration of high-ceramide topical ointments decreased TEWL and improved atopic dermatitis in children, which provides additional support for the importance of ceramide in barrier dysfunction. Bacterial colonization, changes in enzymatic activities, and alkalinization of the skin have all been suggested as contributors to AD ceramide deficiencies (46-49).

Because of such barrier dysfunction and related immunopathology, the relationship between AD and allergic contact dermatitis (ACD) has been of great interest for many years. However, there has been controversy surrounding the nature of that relationship. There may be a decreased prevalence of contact dermatitis in atopic patients, possibly related to a defect in delayed-type hypersensitivity. Other studies suggest that AD may in fact be a predisposing factor to ACD and that the compromised barrier may be responsible for such predisposition (50-52). Further investigation may unravel the relationship between AD and ACD.

Stimuli

A wide spectrum of factors has been reported to trigger flares of atopic dermatitis. Triggers include contact- and aero-allergens (dust mites, pet dander, molds), food allergens, irritants (soaps, disinfectants), microbial agents (*Staphylococcus aureus*, viruses, fungi), emotional stress, and climate (53-65). However, few objective, scientific studies have confirmed the relative importance of these triggers in the exacerbation of AD (64-67).

Infection

Of the various triggers of AD, microbial colonization has proven to have an important role in AD pathogenesis and consequently impacts effective treatment and management of AD symptoms and progression. *S. aureus* is one of the predominant organisms found in patients with AD and for this reason has been studied extensively in relation to AD. Skin colonization with *S. aureus* can be found in 64-100% of AD patients (68-70). *S. aureus* has a prevalence of approximately 5% on skin of healthy individuals (71). Various factors may contribute to the high incidence of *S. aureus* infections in AD, including altered lipid composition in the stratum corneum increased availability of adhesins in the extracellular matrix (73), and an impaired local immune response (48,49,72), including decreased expression of endogenous antimicrobial peptides (74,75).

The bacterial superantigens (so called because of their potent polyclonal activation of T cells) generated by *S. aureus* have been demonstrated in AD lesions and have been implicated in AD-related pathology (70,76-79). It has recently been postulated that these superantigens may contribute to the disease process through the inhibition of the immunosuppressive activity of T regulatory lymphocytes.(49) In a separate study, it was suggested that superantigens contribute to the observed decrease in glucocorticosteroid sensitivity in *S. aureus*-infected AD patients (79). However, there is still debate on the importance of superantigens in AD pathogenesis (80).

The lipophilic yeast *Malassezia furfur* (*Pityrosporum ovale*) is commonly found in seborrheic areas of the body such as the head and neck. However, unlike infections with *S. aureus*, *M. furfur* skin colonization does not appear to be any more common in patients with AD than in healthy individuals. However, this organism generated a lot of interest with the discovery of IgE specific to various *M. furfur* antigens in patients with AD (81). Studies have stressed the importance of antifungal agents in treating severe cases of AD patients with *M. furfur*-specific IgE (82,60).

In addition to increased frequency of bacterial and fungal infections, AD patients have also been found to be at greater risk for viral infection. Two major families of viruses, herpesvirus and poxvirus, have attracted the most attention for their involvement in three widespread disseminated viral infections designated as eczema herpeticum (EH), eczema molluscatum (EM), and eczema vaccinatum (EV). EH, also known as Kaposi's varicelliform eruption, is the diagnosis that refers to a disseminated herpesvirus infection associated with any form of dermatitis, including AD (60,83). EH is perhaps the most important of the secondary viral infections, due to its severity and potentially life-threatening nature (13,83). For this reason, early diagnosis and prompt systemic antiviral intervention is essential to limit EH morbidity and mortality. Though not as dangerous as EH, the poxvirus infections responsible for EM and EV are also important to note because of their increased propensity in AD. AD patients are found to be more susceptible to both localized molluscum contagiosum virus (MCV) infections, presenting as isolated papulonodules, and disseminated MCV infections (referred to as EM), which leads to generalized cutaneous lesions. In immunologically compromised patients, such as those with AD, vaccination with vaccinia can lead to disseminated vaccinia infection and is an important contraindication to smallpox vaccination (13,83).

Altered vascular and neurocutaneous reactivity

It is well-known that vascular reactivity is altered in AD. White dermographism, nicotinic acid blanching, and delayed blanch with methacholine are all phenomena that have long been associated with their eczematous skin (84-88). These observations have initiated a wide array of studies on the neurocutaneous and microvascular systems in AD (84-89). However, the relative importance of these observations in the underlying pathophysiology is still unclear, and their usefulness in the diagnosis of the disease remains limited.

Clinical course

Three phases

AD progresses with specific age-dependent presentations and for this reason is often described by three phases: 1) an infantile phase (birth to 2 years of age), 2) a childhood phase (2 years of age to puberty), and 3) an adult phase (puberty through adulthood) (90). In the infantile phase, highly puritic erythematous papules and vesicles most commonly begin on the cheeks, forehead, or scalp and often develop on the extensor surfaces of the arms and legs by 8 to 10 months of age. Generalized xerosis is common and affected areas are often edematous which can lead to exudative, crusted lesions. The childhood phase is characterized by more chronic, lichenified lesions without exudation, and typically involve the hands, feet, wrists, ankles, antecubital, and popliteal regions and less commonly involve extensor surfaces. Patients in the chronic adult phase demonstrate chronic, lichenified lesions most commonly on flexural folds, the face, the neck, the upper arms and back, and the dorsa of the hands, feet, fingers, and toes. Adult patients may develop exudation and crusting as the result of *S. aureus* superinfections (90).

Atopic march

The term "atopy" most often refers to a syndrome comprising a triad of diseases: AD, asthma, and allergic rhinitis. The "atopic march" is term given to the progression of symptoms that is typically seen with atopic patients. AD usually manifests first and is subsequently followed by allergic rhinitis and asthma (90-92). In a 1992

study of forty patients with infantile AD, approximately 75% went on to develop allergic rhinitis and more than 50% developed asthma (93). Consistent with these findings, many reports have demonstrated that epicutaneous testing with allergens can ultimately lead to sensitization and to a systemic allergic response (94-96), which may explain the order of progression seen with the atopic march. Further studies suggest a potential Th2-mediated mechanism that may be responsible for this systemic sensitization (90).

Diagnosis

Diagnostic criteria

Establishing reliable criteria for the diagnosis of AD has historically been a major clinical challenge. Until recently, clinicians most commonly used the diagnostic criteria published in 1980 by Hanifin and Rajka for diagnosis of AD (25). The major features for the Hanifin and Rajka classification include: 1) pruritus, 2) facial and extensor eczema in infants and children; flexural eczema in adults, 3) chronic or relapsing dermatitis, and 4) a personal or family history of atopic illness (1,25). However, due to continued lack of standardization in AD diagnosis and treatment, in January 2001 the American Academy of Dermatology convened a consensus conference to address various AD-related issues. Table 1 summarizes the recommended diagnostic criteria for AD as established at the 2003 consensus conference (6). Adherence to these guidelines will likely prove to be helpful in standardizing AD diagnosis and treatment.

Differential diagnosis

Because the skin lesions in AD can present in many different forms, including papules, vesicles, plaques, nodules and excoriations, the differential diagnosis for AD is extensive, as illustrated in Table 2. In addition to a thorough physical examination and personal and family history, exclusion of these other conditions is critical to reaching an accurate diagnosis of AD.

Diagnostic tests

To date, there are no specific laboratory tests that can be used to define AD. However, some of the typical features of AD can be helpful in confirming or ruling out a diagnosis of AD. Histologically, acute lesions display spongiosis, hyperkeratosis, parakeratosis, acanthosis, and leukocyte infiltration (exocytosis). Chronic lesions are typically hyperkeratotic with areas of parakeratosis and papillomatosis (97). Once a diagnosis of AD has been made, various tests can be used to identify patient sensitivity to specific allergens. *In vitro* tests, such as the radioallergosorbent test (RAST) and enzyme-linked immunosorbent assay, have been used to identify serum IgE reactivity to specific allergens. Skin tests, such as the atopy patch test (APT) and skin prick test (SPT), are other means for determining sensitivity to various allergens. APT has been described as the most specific of these tests, and as a result has become increasingly popular for allergen sensitivity determination (97-99).

Treatment and management

Treatment options

There are three primary levels for management of AD: 1) skin care, 2) avoidance of triggers, and 3) medical intervention. Skin care for the atopic patient must first begin with proper bathing in order to help maintain proper hydration of the stratum corneum. Patients should bathe in lukewarm (not hot) water for 20-30 minutes and wash with a mild, unscented, pH-balanced moisturizing cleanser. After the bath, the surface should be patted dry with a soft towel, immediately followed with the application of topical medication and emollient or an emollient alone. Emollients should be reapplied frequently to maintain optimal hydration, since most have a maximum duration of six hours (6,97,100).

There are several, guidelines that should be followed to minimize exposure to some of the most common triggers of AD. Patients should 1) avoid wearing clothing that may irritate the skin (cotton clothing is preferred), 2) avoid overheating, 3) keep the skin covered by clothing to protect the skin from various environmental triggers, 4) specifically avoid exposure to known allergens as determined by allergic testing.

When acute exacerbation occurs, the first-line, mainstay medical treatment is topical corticosteroids, which is effective in the majority of cases due to their antiinflammatory and immunosuppressant activity. Corticosteroid potency should be adjusted with disease severity, and because side-effects are directly related to drug potency, treatment should be tapered once control is achieved (6,13,97). Use of systemic corticosteroids should be limited to the most severe, chronic cases and should be discontinued upon relief of the main symptoms. Other systemic drugs, that may be considered include antihistamines, interferon, cyclosporine, and antimetabolites (13).

The nonsteroidal topical immunomodulators (TIMs), tacrolimus and pimecrolimus, have attracted a lot of attention over recent years for their efficacy in treating AD. TIMs are calcineurin inhibitors, effectively functioning as immunosuppressants, and have proven to be effective in managing AD in numerous studies (101-111). However, as a relatively new class, the potential long-term adverse effects of calcineurin inhibitors are unknown and remain a concern. For this reason, topical corticosteroids remain as the first-line in treatment, and TIMs are only recommended for use under specific circumstances, as detailed in the 2003 report from consensus conference by the American Academy of Dermatology.(6)

In order to treat the secondary infections that are rather frequent in AD patients, antimicrobials are an important adjunct to therapy. An antistaphylococcal regimen must be followed to treat the common *S. aureus* infections seen in AD (112,113). In addition, antiviral and antifungal therapy must also be considered to control the various viral and fungal infections (13,60,82,83).

Other approved therapies that should also be considered for managing AD include phototherapy (114-116), application of tar/coal tar solutions (117), and psychotherapy to eliminate help in treating emotional triggers (118), and various alternative/complementary therapies e.g. Chinese herbal therapy, hypnotherapy, etc. (112,117).

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