

Atopic dermatitis and the atopic march

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Atopic dermatitis (AD), one of the most common skin disorders seen in infants and children, usually has its onset during the first 6 months of life. The prevalence of AD is similar in the United States, Europe, and Japan and is increasing, similar to that of other atopic disorders, particularly asthma. AD has been classified into 3 sequential phases: infantile, childhood, and adult, each with characteristic physical findings. AD has a tremendously negative effect on the quality of life of patients as well as family, most commonly disturbing sleep. The condition also creates a great financial burden for both the family and society. The cutaneous manifestations of atopy often represent the beginning of the atopic march. On the basis of several longitudinal studies, approximately half of AD patients will develop asthma, particularly with severe AD, and two thirds will develop allergic rhinitis. Epicutaneous sensitization has been thought to be responsible, with subsequent migration of sensitized T cells into the nose and airways, causing upper and lower airway disease. Animal models and human observation concur with this theory. Preliminary prevention studies with oral antihistamines provide evidence that early intervention might slow the atopic march. (*J Allergy Clin Immunol* 2003;112:S118-27.)

Key words: Atopic dermatitis, atopic march, quality of life, asthma, skin sensitization

Atopic dermatitis (AD), one of the most common skin disorders seen in infants and children, has its onset during the first 6 months of life in 45% of children, the first year of life in 60% of affected individuals, and before 5 years of age in at least 85% of affected individuals.¹ Although the term *eczema* is frequently used, AD is a more precise term to describe this subset of dermatitis. The concept of “atopy” (derived from the Greek *atopia*, meaning “different” or “out of place”) originally was proposed in 1923 to include asthma and allergic rhinitis, but AD was added to the group of atopic disorders in 1933 on the basis of association of this form of eczema with asthma and allergic rhinitis. In fact, AD is most often the first manifestation of this atopic triad.

The prevalence of AD in the US childhood population is 17.2%² and is similar to the 15.6% prevalence described in European children³ and the 24% prevalence

Abbreviations used

AD: Atopic dermatitis
BAL: Bronchoalveolar lavage
ETAC: Early Treatment of the Atopic Child
ISAAC: International Study of Asthma and Allergies in Children
MAS: Multicenter Atopy Study

in 5- to 6-year-old children in Japan.⁴ The manifestation of AD in such a sizable proportion of the pediatric population represents a marked increase during the past several decades. Studies performed before 1960 estimated the prevalence to be up to 3%.⁵ The subsequent steady increase has paralleled the increase seen in children with asthma, suggesting shared triggers and consistent with the frequency of development of other atopic disorders in children with AD.⁶ AD occurs more frequently in urban areas than in rural areas, in smaller families, and in higher socioeconomic classes, suggesting that exposure to antigenic pollutants and lack of exposure to infectious agents or other antigenic triggers (particularly that favor a T_H1 helper T-cell response) early in life might play a role in the development of the dermatitis. The prognosis of AD for an individual child is unpredictable. Recent studies have shown complete clearing of the disorder at puberty or shortly after puberty in 40% to 60% of patients, although patients who do not show clearance might show improvement with advancing age.^{7,8}

The clinical features of AD that allow diagnosis are the chronicity of the disorder, its associated pruritus, and the age-specific morphology and distribution of lesions (Table I).⁹ Extent of involvement might range from mild and limited, for example, mild flexural area involvement only, to generalized and severe. AD has been divided into 3 phases on the basis of the age of the patient and the distribution of lesions: the infantile phase, the childhood phase, and the adult phase.

THREE PHASES OF ATOPIC DERMATITIS

The infantile phase of AD reflects the manifestations of AD from birth to 2 years of age (Fig 1). The erythematous papules and vesicles typically begin on the cheeks, forehead, or scalp and are intensely pruritic. Lesions might remain localized to the face or might extend to the trunk or particularly the extensor aspects of the extremities in scattered, ill-defined, often symmetrical patches. Exacerbation of facial dermatitis on the medial cheeks and chin is often seen concomitant with teething and initiating solid foods, probably because of the exposure to irritating saliva and foods, although contact urticaria might contribute to the localized reactivity. Characteristic of this

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FIG 1. Facial involvement in affected infants with AD. The cheeks and chin often show edema and erythema, exacerbated by exposure to saliva and foods.

TABLE I. Clinical criteria for AD in pediatric patients

Essential features
Pruritus
Eczematous changes
Chronic or relapsing course
Typical and age-specific patterns: face, neck, and extensor involvement in infants and children; flexural lesions, especially in older children and adolescents; sparing of the groin and axillae
Important features (support the diagnosis but do not occur in all patients)
Early age of onset
Xerosis
Atopy (IgE reactivity)
Exclusions: The diagnosis of AD depends on the exclusion of conditions such as scabies, allergic contact dermatitis, seborrheic dermatitis, psoriasis, and ichthyosis.

infantile phase is the tendency to show significant edema of affected areas, leading to oozing and crusting unrelated to secondary infection. Generalized xerosis is common. By 8 to 10 months the extensor surfaces of the arms and legs often show dermatitis, perhaps because of the role of friction associated with crawling and the exposure of these sites to irritant and allergenic triggers such as in carpets. Although dermatitis of the antecubital and popliteal fossae, periorbital areas, and neck is more commonly involved in older children and adolescents, these sites might also be affected in infants and young children. Typically, lesions of AD spare the diaper area during

infancy, which aids in the diagnosis. This sparing likely reflects the combination of increased hydration in the diaper area, protection from triggers by the diaper, and inaccessibility to scratching and rubbing.

Not uncommonly, infants present with an initial pattern suggestive of seborrheic dermatitis, particularly during the first month or two of life. The associated pruritus and the dry character of the scaling either support the diagnosis of AD rather than seborrheic dermatitis or suggest the combination of both disorders. The skin changes of infants who exhibit this combination of features usually evolve into a more classic picture of AD as the seb-



FIG 2. Fold areas are typically affected in the childhood phase, particularly antecubital and popliteal areas.

orrheic component clears. In children 1 year of age or older, nummular lesions (“coin-shaped,” sharply defined scaling erythematous plaques) might accompany the more typical dry scaling erythematous patches of AD. Nummular lesions tend to be more recalcitrant to topical therapy and are frequently secondarily infected.

The childhood phase of AD might follow the infantile stage without interruption and usually occurs during the period from 2 years of age to puberty. Children are less likely to have the exudative lesions of infancy and instead exhibit more lichenified papules and plaques representing more chronic disease. The classic areas of involvement in children are the hands, feet, wrists, ankles, and antecubital and popliteal regions (Fig 2). Although localization at flexural areas is more common, some children show an “inverse” pattern with primarily involvement of extensor areas. Facial involvement, when present, tends to localize to periorbital and perioral areas, in contrast to the relative sparing of these facial localizations in the infantile face. In African American children the lesions of AD are often more papular (follicular AD). Pruritus is frequently severe, leading to sleep disturbances. Lymphadenopathy might be a prominent feature in affected children, reflecting the role of lymph nodes in handling local infection and inflammation.

The adult phase of AD begins at puberty and frequently continues into adulthood. Predominant areas of involvement include the flexural folds, the face and neck, the upper arms and back, and the dorsa of the

hands, feet, fingers, and toes. The eruption is characterized by dry scaling erythematous papules and plaques and the formation of large lichenified plaques from lesional chronicity. Weeping, crusting, and exudation might occur but usually as the result of superimposed staphylococcal infection.

Regardless of the phase of AD, postinflammatory hypopigmentation or hyperpigmentation might be seen, especially in darker skinned children. The pigmentary changes are transient and are reversible when the underlying inflammation is controlled; however, 6 months or more might be required for repigmentation, and sun exposure will accentuate the differences between uninvolved and dyspigmented skin areas. Parents might mistake the postinflammatory pigment change for scarring and need reassurance. AD is not usually a scarring disorder, unless secondary infection or deep gouging of lesions occurs. Hyperpigmentation is predominantly noted at sites of lichenification, because the thickened epidermis, especially in darker skinned children, accumulates epidermal melanin pigment.

INFECTIONS AND OTHER CLINICAL MANIFESTATIONS ASSOCIATED WITH AD

Several other clinical signs are seen with increased frequency in children with AD (Table II), although they might appear in children without AD as well. Children with AD also have an increased risk of developing cuta-



FIG 3. Staphylococcal superinfection occurs frequently in children with AD, characterized by exudative papules and pustules that rapidly crust and erode.

TABLE II. Clinical features seen with increased frequency in children with AD

Associated disorder	Manifestations
Keratosis pilaris	Follicular-based keratotic papules; lateral aspects of face, extensor aspects of arms, and anterior thighs
Lichen spinulosus	Round collections of numerous, tiny, skin-colored to hypopigmented dry spiny papules
Pityriasis alba	≥ 1 cm hypopigmented patches, sometimes with fine scale; especially on face, upper arms
Hyperlinear palms	Accentuated markings on the palms and soles; distinguish from ichthyosis vulgaris
Atopic pleats	Groove of the lower eyelid; often present from infancy
Allergic shiners	Slate-gray to violaceous infraorbital discoloration with or without swelling

neous *Staphylococcus aureus* infection and cutaneous dissemination of the viral organisms herpes simplex and molluscum contagiosum. *S aureus* can be cultured from 93% of dermatitis lesions and 76% of uninvolved (normal-appearing) skin of patients with AD.^{10,11} The increased adherence of *S aureus* to the epidermal cells of individuals with AD¹² and a failure to produce endogenous antimicrobial peptides in the inflamed skin of patients with AD¹³ might account for the high rate of *S aureus* and infection. The pyoderma associated with AD is usually manifested by erythema with exudation and crusting and occasionally by small pustules in the advancing edge (Fig 3). This complication must be considered whenever a flare of chronic AD develops or fails to respond to appropriate therapy. *S aureus* exacerbates the AD, because *S aureus* itself is a trigger for AD with heightened IgE and T-cell responses to staphylococcal antigens and superantigens.¹⁴ The higher risk of cutaneous spread of molluscum and herpetic lesions has been attributed to defects in T_H1 cytokine generation and cytotoxic T-cell function. Molluscum, a common cutaneous viral infection, usually affects the trunk, axillae, antecubital and popliteal fossae, and crural areas, manifesting as small, dome-shaped papules that often show a central umbilication. The molluscum lesions tend to be most

numerous at sites of active dermatitis and can induce pruritus as well as dermatitis around the molluscum papules. Eczema herpeticum describes the extension of the typical clustered vesiculopustules of herpes simplex virus in an atopic individual and also tends to involve sites of active dermatitis more readily.

QUALITY OF LIFE IN ATOPIC DERMATITIS

Whereas physicians note changes in the clinical signs of AD to gauge severity and response to therapy, patients and their families are equally concerned about their quality of life. When the dermatitis is active, the quality of life in infants, children, and adolescents has clearly been shown to be reduced, particularly in patients with moderate and severe disease. The resultant psychologic stress, as well as other stresses such as concurrent infectious illness, can clearly provoke AD. Recent studies have shown that stress can induce immunologic changes in patients with AD, including increases in the levels of eosinophils, subpopulations of T lymphocytes, and natural killer cells. These increases are not seen in healthy control subjects or individuals with psoriasis.¹⁵

By using the Children's Dermatology Life Quality Index as a tool to assess the psychosocial effects of cutaneous

neous disorders in children between the ages of 5 and 16 years, AD was second only to scabies among dermatologic disorders in its adverse effect on quality of life.¹⁶ In particular, the AD in children led to distress, anxiety, embarrassment, poor self-esteem, and lack of self-confidence. The discomfort led to sleep disruptions and a reduced functional capacity, including as related to sports activities and social relationships. A more recent survey of families through the National Eczema Association for Science and Education (<http://www.nationaleczema.org>) showed impairment in the performance of daily activities in nearly 60% of school-age children with AD, impairment in performance at school (50% in children with moderate disease and 80% in children with severe disease), and adverse effects on sports and outdoor activities (40% of children with mild disease, 64% with moderate disease, and 84% with severe disease).¹⁷ Formal psychologic testing has also shown abnormalities in 53% of school-age children with moderate disease and 80% with severe AD, in comparison with 27% of control subjects. Testing in children with mild disease was not significantly different from that of control subjects. Affected children showed tears on arrival to school, excessive worrying, stomach aches, and sleeping problems. The high percentage of psychologic disturbances in children with moderate and severe AD was similar or greater to that seen in patients with hemiplegia (55%) or brainstem lesions with seizures (59%) but was significantly greater than in children with other disorders such as leukemia (38%) or uncomplicated seizures (29%).¹⁸

As many as 66% of children complained that the itching disrupts sleep, including greater difficulty in falling asleep, frequent night waking, less total sleep, greater difficulty in awakening for school, and daytime irritability.^{19,20} Sleep disturbance occurs in children without visibly active dermatitis as well. Sleep studies have shown that the sleep disturbances might not relate to the scratching per se, with arousals and awakening observed without evidence of active scratching. Peer and teacher acceptance might be affected by the disfigurement of AD, the tendency to show hyperactive behavior and chronic scratching, the inability to participate actively in sports activities, and the concern that AD could be contagious.

The quality of life in preschool children is also impaired. Infants with AD exhibit chronic itching and scratching, mood changes, and sleep disturbance.²¹ Preschool children have been shown to be excessively dependent, shy, and fearful. More behavioral problems have been noted in comparison with preschool children without AD (50% vs 12%).

Having a child at home with AD also impacts family life, parenting, and spousal relationships.²² Mothers of affected preschool children exhibit more distress (85% vs 31% of mothers of control children) and do not feel supported socially (34% vs 65%). Overall, fewer mothers of preschool children with AD work (27% vs 65%), leading to greater financial burdens and social isolation.²³ Siblings and the spouse who is not the primary caretaker might resent the time spent taking care of the affected

child, leading to family dysfunction. Familial dysfunction has been shown to correlate with poor treatment compliance and inadequate control of symptoms.²⁴ Su et al²⁵ have shown that caring for a child with AD is more stressful than caring for a child with insulin-dependent diabetes. Sleep interruption plays a major factor in this stress.^{22,26,27} Parents of children with AD get on average 1 to 2 hours less sleep than parents of normal children.²⁵ As a chronic disorder that requires frequent attention, the family carries a high financial burden of parental missed days from work for doctor visits and home care, lost wages as a result of interruption of employment, expensive medications, and the costs of special or additional bedding, clothes, and food.

Recent investigations of oral and new topical medications for AD have considered the effect of medications on the quality of life in affected infants and children, not just on the physical signs of dermatitis.²⁷⁻³⁰ Attention to the effects of intervention on quality of life has also demonstrated the significant impact of a nurse-led specialist eczema clinic and of a parental training program.³¹

The financial costs of AD impact not only families but society as a whole. More than a decade ago Lapidus et al³² estimated an annual cost of \$364 million to treat children with AD. A 1995 study from Scotland estimated that £465 million pounds (\$767 million US equivalent) were spent annually in the United Kingdom in treating individuals with AD, with more than half of that cost being paid by the families.³³ In an Australian study the direct cost to families for the care of a child with moderate to severe AD was comparable with that of a child with insulin-dependent diabetes and substantially higher than the direct financial cost to the family for care of a child with asthma.²⁵

THE ATOPIC MARCH

The atopic march is the natural history of atopic manifestations, characterized by a typical sequence of progression of clinical signs of atopic disease, with some signs becoming more prominent while others subside. In general, the clinical signs of AD predate the development of asthma and allergic rhinitis, suggesting that AD is an "entry point" for subsequent allergic disease (Fig 4).

Several longitudinal studies provide evidence for the atopic march from AD to the development of allergic rhinitis and asthma. Rhodes et al^{34,35} studied 100 infants from atopic families during a 22-year period in the United Kingdom. The prevalence of AD peaked at 20% of children by 1 year of age and declined to approximately 5% of patients at the end of the study. Meanwhile, the prevalence of allergic rhinitis slowly increased over time from 3% to 15%. The percentage of patients with parents reporting wheezing during the year increased from 5% in the first year of life to 40% of the remaining 60 patients in the last year of the study at 22 years of age. In addition, sensitization to allergen by skin prick test to 1 of 6 allergens (*Dermatophagoides pteronyssinus*, mixed grass, dog, cat, egg, and milk) increased to a peak of 36% at 22 years of age. The major risk factor for asthma as an

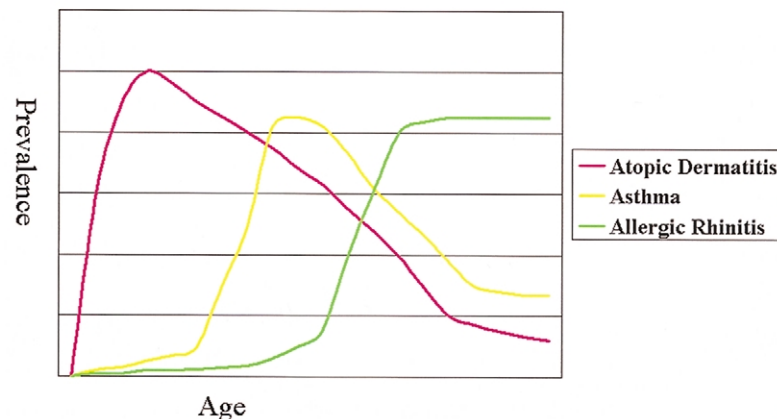


FIG 4. Incidence of different types of atopy. AD peaks in the first years of life and declines after that time. Asthma and allergic rhinitis increase over time as sensitization develops.

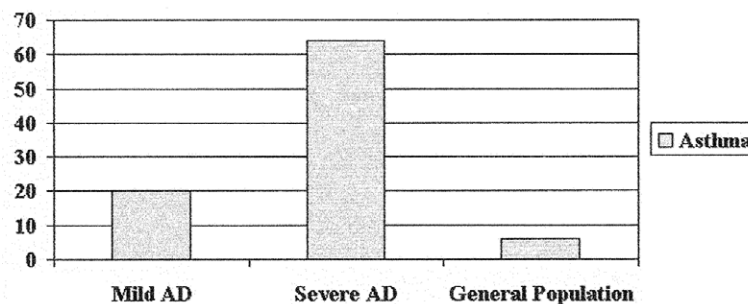


FIG 5. Percentage of patients developing asthma. Risk for developing asthma at 8 years of age increases with AD severity.³⁶ The diagnosis of asthma in the general population is based on the ISAAC study in Sweden.⁴⁴

adult was early sensitization to either foods in first year (odds ratio, 12.3) or aeroallergens (odds ratio, 4.6) in the first 2 years of life.³⁴

A second longitudinal study examined 94 children with AD for 8 years.³⁶ AD improved in 84 of 92 children, consistent with the atopic march; 43% of the patients developed asthma during the 8 years and 45% developed allergic rhinitis. Only children with the mildest AD¹⁴ did not develop either allergic rhinitis or asthma. Their severity of AD was a risk factor for subsequent development of asthma. Seventy percent of the patients with severe AD developed asthma compared with 30% of the patients with mild AD and approximately 8% in the general population (Fig 5). Similarly, the severity of AD correlated with the risk of developing allergic rhinitis and with elevated levels of total and specific serum IgE.³⁷⁻³⁹ Elevation of IgE levels has also been correlated with the risk of developing asthma.⁴⁰ The linkage of high IgE and AD and the risk of developing asthma might be a marker or part of the pathogenesis.

The larger German Multicenter Atopy Study (MAS) showed the atopic march in 1314 children during a 7-year

study period. Thirty-eight percent of the children were in a high risk group with at least 2 family members with atopy or a cord blood IgE greater than 0.9 kU/L. In this population, MAS found that 69% of infants who had developed AD by 3 months of age were sensitized against aeroallergens by 5 years of age.^{41,42} The rate of aeroallergen sensitization increased to 77% in all high-risk children. By 5 years of age, 50% of children with early AD and a strong family history of allergy had allergic airway disease or asthma compared with 12% in patients without AD or a family history of atopy, further verifying the relationship between AD, early sensitization, and the subsequent development of allergic airways disease.

Ohshima et al⁴³ also noted a greater risk for developing signs of asthma during a 4-year period of follow-up in 169 Japanese children with AD. Although the AD had improved in 51% and disappeared in 34% of the patients, 15% of patients with persistent AD had a greater risk for developing asthma. Similar to previous studies, earlier sensitization led to a greater risk for developing asthma. Overall, 45% of the children developed evidence of asthma and 35% were given a diagnosis of asthma by a physi-

cian, compared with the 10% prevalence of asthma in Japan in the International Study of Asthma and Allergies in Children (ISAAC) study.⁴⁴ The ISAAC study, which examined the prevalence of AD, allergic rhinitis, and asthma worldwide by validated questionnaire, showed a strong correlation in a given country between the prevalence of AD and the prevalence of allergic rhinitis and asthma.⁴⁴ In addition, the prognosis of asthma is better in children without a history of AD. In a 10-year evaluation of the natural course of their asthma, 41% of patients without AD were well, 52% had mild asthma, and 5% had severe asthma. In contrast, 34% of patients with asthma and a history of AD were well, 54% had mild asthma, and 11% had severe asthma or had died of the disease.⁴⁵

AD and other atopic disorders share a common pathogenesis and genetic basis. Seven linkage studies have identified 9 different chromosomal regions linked to asthma.⁴⁶ A number of these regions contain genes that encode proteins involved in immune function, including ILs, MHC proteins, and a component of the high-affinity IgE receptor. Common chromosomal linkages between AD and asthma have been identified on chromosomes 5q31-33, 11q13, and 13q 12-14.⁴⁷ In addition, both disorders share common immunologic features, including elevated IgE, peripheral and lesional eosinophilia, T_H2 cytokines and epithelial dysfunction, and similar allergenic triggers.⁶

ROLE OF EPICUTANEOUS SENSITIZATION IN THE RELATION BETWEEN AD AND OTHER ALLERGIC DISORDERS

Several additional studies have suggested that skin sensitization precedes airway sensitization. Dohi et al⁴⁸ examined 8 patients with asthma and no AD and 8 patients with AD and no asthma for dust mite sensitization. Both groups had inhalation challenges to acetylcholine, a nonspecific bronchodilator, and to dust mites. Both groups showed airway hypersensitivity to dust mites, and the response of the AD patients to acetylcholine ranged from normal to the asthmatic range. These findings indicate that patients with skin sensitization to dust mites can develop airway sensitization to same allergen.

These studies suggest that epicutaneous allergen sensitization might evoke a systemic allergic response, including of the upper and lower airways. Epicutaneous sensitization to allergen is also suggested by the observation by Lack et al⁴⁹ that atopic children exposed to topical emollients with detectable peanut protein had an increased risk of developing peanut sensitization (91% of children exposed to peanut-containing emollients vs 53% of atopic subjects without peanut allergy and 59% of normal control subjects without peanut allergy). There was no significant difference in exposure to the 3 patient groups to other lotions.

Beryllium sensitization in chronic beryllium lung disease might also be percutaneous, because efforts to decrease inhalation exposure had no effect on disease prevalence.⁵⁰ Topical application of beryllium to C3H mice is able to generate beryllium-specific sensitization, documented by peripheral blood and lymph node beryl-

lium lymphocyte proliferation tests. In addition, beryllium particles (0.5 and 1.0 μ m) are able to penetrate the stratum corneum of flexed human skin explants, but not unperturbed explants, into the epidermis and, to a lesser extent, the dermis, suggesting that the scratching or rubbing of inflamed atopic skin further encourages epicutaneous penetration.

The most definitive evidence that epicutaneous sensitization can lead to systemic allergic responses and airway sensitization comes from experimental studies in mouse models of allergy. Spergel et al⁵¹ initially used the technique of epicutaneous application of ovalbumin applied by occlusive patch to tape-stripped skin to induce dermatitis in mice and amplify total and specific IgE production. This was compared with application of saline or intraperitoneal immunization with ovalbumin. Skin biopsy of the patch test site showed epidermal thickening and spongiotic changes with epidermal infiltration of CD3⁺ T cells and eosinophils. Increases in the expression of both T_H2 and T_H1 cytokines (IL-4, IL-5, and IFN- γ) were noted, consistent with the increase in these cytokines in acute and chronic AD. Epicutaneously sensitized mice were subsequently challenged with a single exposure to inhaled ovalbumin, and bronchoalveolar lavage (BAL) fluid was analyzed 24 hours later. The ovalbumin-treated mice showed a significant increase in the number of eosinophils in the BAL fluid compared with saline-sensitized mice. To determine whether epicutaneous sensitization can prime mice to develop airway hyperresponsiveness, Spergel et al⁵¹ also examined whether inhalation of a single dose of ovalbumin elicited hyperresponsiveness to methacholine. Airway dynamic compliance to graded doses of methacholine was measured by plethysmography 24 hours after inhalation of a single dose of ovalbumin. Ovalbumin-sensitized mice had a 10-fold greater sensitivity to methacholine than saline-sensitized control mice. These studies showed that a single inhalation of antigen elicits a systemic allergic response and an increased airway response (ie, hyperresponsiveness) to methacholine, the cardinal feature of asthma, in epicutaneously sensitized mice.

PROPOSED MOLECULAR MECHANISM FOR THE EPICUTANEOUS SENSITIZATION THAT PROMOTES THE ATOPIC MARCH

Several studies have provided evidence that T cells are essential for inflammation and airway sensitivity.⁵²⁻⁵⁴ Tape stripping with application of an allergen in mice induces a local T_H2 response,⁵⁵ and epicutaneous sensitization through barrier-disrupted skin enhances the T_H2 cytokine expression. When intact skin is exposed to a single topical application of house dust mite antigen, lymph node expression of T_H1 cytokines IL-2 and IFN- γ and of the T_H2 cytokine IL-4 is increased. In contrast, after barrier disruption of the skin, sensitization with dust mite antigen downregulates the expression of the T_H1 cytokine IFN- γ but upregulates IL-4, IgE, and IgG1 expression. Similarly, dermal infiltration of eosinophils

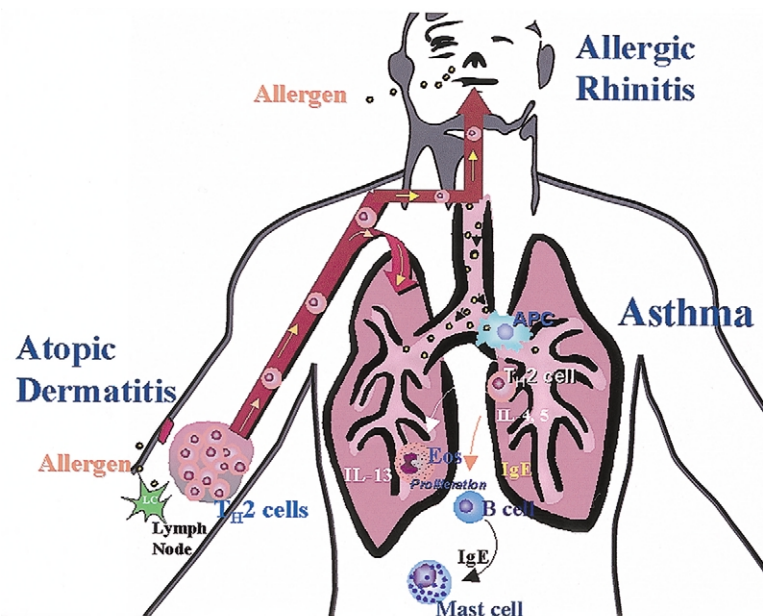


FIG 6. Skin sensitization after allergen exposure leads to systemic immune response. Allergen binding to FcεRI receptors on Langerhans cells (LC) migrate to the lymph nodes, inducing T_H2 cells. Subsequently, T_H2 cells migrate through the circulatory system to various sites including nasal and lung mucosa. Systemic elevated levels of IL-4, IL-5, and IL-13 promote a systemic T_H2 environment. Inhalation of allergens results in presentation of local dendritic cells (APC) to interact with these T_H2 cells. These interactions activate eosinophils (Eos), induce IgE production, mast cell proliferation, epithelial cell activation, and smooth muscle proliferation.

is more prominent after elicitation with dust mite allergen in mice sensitized through barrier disruption than with the hapten PiCl in mice sensitized through intact skin. These findings suggest that the epicutaneous entry of environmental allergens through barrier-disrupted skin is strongly associated with the induction of T_H2-dominant immunologic responses, as is seen in AD,⁵⁵ and are likely to be relevant to both the barrier disruption of the inflamed skin of AD and further disruption by scratching or rubbing. Therefore, the first step in the atopic march seems to be epicutaneous sensitization, which induces a T_H2 milieu in the skin (Fig 6).

How does the local cutaneous sensitization and T_H2 hyperreactivity lead to systemic effects? Cutaneous antigen-presenting cells play a key role in stimulating the T_H2 response and promoting the atopic march. The epidermis of patients with AD contains an increased number of IgE-bearing Langerhans cells and inflammatory dendritic epidermal cells expressing the high-affinity receptor for IgE.^{56,57} These high-affinity receptors (FcεRI) for IgE contribute to the capture and internalization of allergens before their processing and antigen presentation to T cells in atopic skin. The importance of these receptors is noted by the observation that the presence of FcεRI-expressing Langerhans cells that bear IgE molecules is required to provoke eczematous skin lesions after the application of aeroallergens to the skin of atopic patients. In addition,

expression of these FcεRI-expressing Langerhans cells correlates with the severity of AD, asthma, and allergic rhinitis.⁵⁸ Langerhans cells positive for these receptors migrate to the lymph nodes and stimulate naive T cells, thus contributing to expansion of the pool of T_H2 cells with other factors in the skin including histamine.

AD patients have elevated T_H2 and decreased T_H1 expressing cells in the peripheral blood, with elevated IL-13 expression indicating a systemic T_H2 environment.⁵⁹ Subsequently, memory T_H2 cells migrate through the circulatory system to various sites including nasal and lung mucosa and bone marrow. Inhalation of allergens results in presentation by local dendritic cells to T cells in environment rich in T_H2 cytokines, promoting an allergic response in the airways.⁶⁰ These interactions lead to activation of eosinophils, induction of IgE production, mast cell proliferation, epithelial cell activation, mucus hypersecretion, and smooth muscle proliferation observed in asthma.⁵⁴

PREVENTION STUDIES

Current best practice calls for intensive management of asthma early in childhood. The observations of a close relationship between asthma and AD suggest that infants and young children with AD should be a target population for the prevention of asthma. Several preliminary studies have examined the treatment of children with AD pro-

phylactically with antihistamine agents to decrease the severity and risk of developing allergic rhinitis or asthma. Yet, no studies have examined the effect of better control through topical application of an effective anti-inflammatory agent for control of AD in a prospective trial.

In a randomized trial, Iikura et al⁶¹ gave 121 children with AD from 1 to 36 months of age either ketotifen (H₁ antihistamine) or placebo before the onset of asthma. After 1 year of study, significantly fewer patients with high IgE in the ketotifen treatment group had developed asthma than in the placebo treatment group; no difference was detected in children with normal IgE levels (less than 50 IU/mL). A second study examined 100 children up to 2 years of age treated with ketotifen or placebo for 3 years.⁶² All patients had elevated IgE or a family history of asthma or allergic rhinitis. Overall, Bustos et al⁶² found that 25% fewer patients treated with ketotifen had developed asthma by the end of the study (35 in placebo group and 9 in the ketotifen group). No differences were found between treatment groups in IgE levels before, during, and at the end of the trial.

The ETAC (Early Treatment of the Atopic Child) study examined the role of cetirizine in delaying the atopic march. ETAC was a prospective, randomized, double-blinded, parallel group and placebo-controlled trial of 817 infants from 1 to 2 years of age.⁶³ Patients had AD and family history of atopy. The trial duration was 2 years, and total IgE and specific IgEs were measured at baseline and at regular intervals. The infants were treated with high dose cetirizine (0.25 mg/kg twice a day) or placebo. At the end of the study, 40% of the children developed asthma as defined by 3 independent episodes of nocturnal cough with sleep disturbance or wheezing. Similar to previous studies, patients with early sensitization to specific IgE (egg, milk, dust, cat, or grass) had an increased relative risk for asthma. The study found no significant difference between the placebo and cetirizine-treated groups in development of asthma (38% vs 37.7%, respectively). However, the percentage of patients with dust mite sensitization who developed asthma dropped from 51.5% (35 of 68) in the placebo group to 28.6% (16 of 56) in the cetirizine group; similarly, the percentage of children with grass sensitivity who developed asthma was 58.8% (20 of 34) administered placebo versus 27.8% of those taking cetirizine (10 of 36). During the 18-month post-treatment follow-up, the patients with grass sensitivity treated with cetirizine still had a lower rate of asthma symptoms compared with the placebo patients,⁶⁴ whereas the difference between the patients with dust mite sensitivity with and without asthma narrowed between the 2 treatment arms.

CONCLUSIONS

Children with poorly controlled AD have a poorer quality of life, and their families carry a tremendous financial, time, and psychologic burden. Patients with AD are at increased risk for developing other atopic disorders including asthma. Earlier sensitization and a greater severity of

the AD correlate with the highest risk for developing asthma, suggesting a role for percutaneous sensitization through the impaired atopic barrier. Therapies that modify the severity of AD in infants and young children might decrease the risk for the eventual development of asthma.

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