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Atopic Dermatitis in Children, Part 1: Epidemiology, Clinical Features, and Complications

David A. Kiken, MD; Nanette B. Silverberg, MD

Atopic dermatitis (AD), also known as eczema, is a chronic skin condition, characterized by itch (pruritus) and dryness (xerosis). AD lesions appear as pruritic red plaques that ooze when scratched. Children with AD are excessively sensitive to irritants such as scented products and dust due to their impaired skin barrier and skin immune responses. AD is among the most common disorders of childhood and its incidence is increasing. AD is an all-encompassing disease that causes sleep disturbances in the affected child, disrupting the entire household. Patients with AD also are prone to bacterial overgrowth, impetigo, and extensive viral infections. Consequently, familiarity with the most recent literature is of utmost importance so that dermatologists and pediatricians can appropriately manage their patients.

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Incidence and Prevalence

Recent population-based studies from Washington state have estimated that 17.2% of the US population is affected by atopic dermatitis (AD) in their lifetime.[1] An estimated 15 million Americans have AD, and the incidence of AD in the United States has more than doubled in the past 3 decades, mirroring rises in other atopic conditions such as asthma. Some studies report a slight predominance in females.[2] The incidence is not believed to vary by ethnicity. Children in smaller families of a higher socioeconomic class in urban locations are more likely to be affected than children of other backgrounds.

Certain types of AD are more clinically prevalent among certain ethnic groups.[3] Facial and eyelid dermatitis are more common in Asian infants and teenaged girls. Follicular eczema, a variant characterized by extreme follicular prominence, is most common in black individuals. One subtype of AD, a nummular variety, named for the coinlike appearance of lesions, often is associated with contact allergens (ie, allergy to substances that come in contact with the skin), including thimerosal, a preservative used in pediatric vaccines.[3]

Clinical Course

Significant flares of AD usually stop when children are school aged. Complete clearing of AD occurs at puberty or shortly thereafter in 40% to 60% of patients.[4,5] The more severe AD is in infancy and childhood, the less likely a child is to experience clearance or remission of the disorder. Although AD in adults often is limited to the hands, persistent sensitivity to chemicals and fragrances in adult patients remains a leading cause of occupational dermatitis.

Mechanisms of Disease

AD is the cutaneous form of atopy, a multifactorial genetic disorder.[6] The other atopic diatheses include asthma, food and environmental allergies, hay fever, allergic rhinitis, and allergic conjunctivitis. Seventy percent of patients with AD have a family history of the condition, and monozygotic twin concordance rates are high.[6]

Although AD is a form of atopy, true allergy is not the only reason for disease exacerbations. Atopic disease results from the interplay of skin

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From St. Luke's-Roosevelt Hospital Center, New York, New York. Dr. Silverberg also is from Beth Israel Medical Center, New York; Columbia University College of Physicians and Surgeons, New York; and Maimonides Medical Center, Brooklyn, New York.
The authors report no conflict of interest.
Reprints: Nanette B. Silverberg, MD, Director, Pediatric Dermatology, St. Luke's-Roosevelt Hospital Center, 1090 Amsterdam Ave, Suite 11D, New York, NY 10025 (e-mail: nsilverberg@juno.com).

barrier defects, susceptibility genes, susceptibility to infection, and immunologic factors. It has been demonstrated that the keratinocytes in the skin of patients with AD produce decreased amounts of ceramides, thus allowing entry of infectious agents, greater exposure to irritants, and transepidermal water loss.[7-11] Several researchers have suggested a genetic predisposition to AD, and genetic linkage analyses have identified several chromosomal regions with linkage to AD.[8-11]

Third world nations have a lower incidence of AD. It is believed that the higher incidence of parasitic infections in the third world confer protection against AD. Some authors suggest that excessive cleanliness can prevent a child from coming in contact with pathogens (eg, parasites) in dirt. Consequently, inadequate stimulation by pathogens can cause the immune system to act abnormally against nonpathogens.[12-14]

Hygiene Hypothesis—The concept that a lack of exposure to infectious agents early in life predisposes one to the development of atopic disease is called the *hygiene hypothesis*.[14] The theory has become popular because of the rapidly rising prevalence of atopic diseases in recent decades and the lower prevalence of atopy with rising birth order.[15-18] Small family size, high income and education, residence in an urban environment, and increased use of antibiotics all have been implicated as risk factors.[19,20] However, epidemiologic data have been inconsistent.[21] Research has shown that although allergic reactions such as AD are mediated by a T helper 2 (Th2)–type response, infections are mediated by a Th1 immune response, which is known to antagonize Th2 responses.[12-23] Thus, an individual who is exposed to fewer infections (Th1-type response) is prone to developing greater Th2 allergic responses as evidenced by the increased incidence of AD. Realistically, chronic AD lesions can have Th1 cells and cytokines, whereas parasitic infections often initiate Th2 reactions with associated eosinophilia. Therefore, the hygiene hypothesis is flawed.[12-23]

Like other atopic conditions, AD is an immunoglobulin E (IgE)–mediated disorder.[22] In type 1 IgE-mediated allergies, binding of allergen to IgE on mast cells causes mast cell degranulation. In AD, IgE that precipitates disease flares is on the surface of Langerhans' cells, not mast cells. Langerhans' cells have IgE on their surface bound to FcεRI receptors. When an allergen binds to IgE on the surface of the Langerhans' cell, the cutaneous antigen-presenting cells cause T-cell hyperstimulation and a Th2 response that results in the release of a combination of cytokines related to allergic type 1 reactions.[22] Other immunologic events include mast cell degranulation, excessive circulating levels of IgE, and eosinophil hyperreactivity. Medical therapy can address several of these pathogenetic mechanisms.[23]

Triggers—For most patients, disease flares actually are triggered by irritants such as fragrances or chronic allergens such as dust mites. The dust mite is the leading IgE-binding allergen in AD; however, other environmental allergens can play a role.[24] Food allergens such as peanuts, wheat, eggs, milk, and soy have been shown to be triggers for up to 40% of children with AD.[25] Immunologic evidence implicates food allergens as a contributor to but not the cause of AD. T cells specific to food allergens have been cloned from the skin lesions of patients with AD.[26] Furthermore, tests for food allergens have found food allergen–specific T cells in the peripheral blood after food-allergen challenge.[27] Emotional stressors also correlate with AD exacerbations mediated by rising eosinophil and natural killer cell numbers.[28,29]

Seasonal flares of AD at the peak of winter and summer also are common. In the winter, reduced air humidity in the household because of heaters is believed to be the main precipitating factor. In fact, winter babies have been shown to have a higher prevalence of eczema.[30] Summer sweating can exacerbate disease in other patients.

Clinical Features

The classic presentation of AD includes eczematous plaques (ie, erythematous excoriated plaques with serous discharge). The typical distribution is age dependent; however, 90% of patients with AD will experience symptoms by 5 years of age.[31] Although disease usually flares in the winter, some children fare

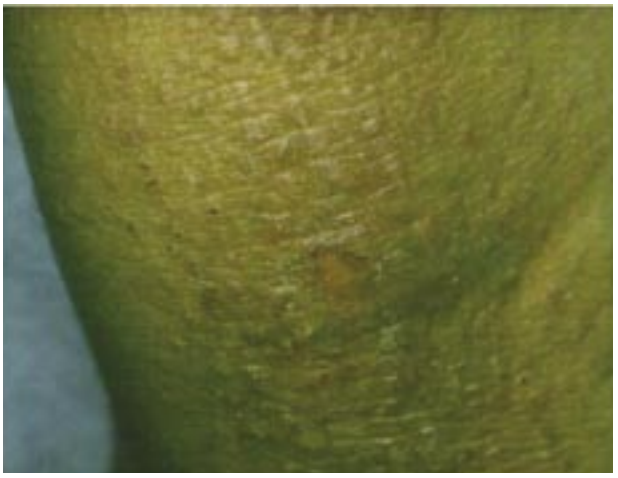

Figure 1. Atopic dermatitis presenting in the antecubital area in a 3-year-old black girl, with excoriated plaques, erosions, and crusting.

poorly with excessive heat. Patients with AD experience flares and remissions.[32]

Infants often present after the first few months of life with widespread plaques on extensor surfaces, particularly over the elbows and knees. Facial involvement presents with bilateral erythematous plaques on the cheeks and characteristic sparing of the nasal region, the "headlight sign," as the nose becomes prominent, similar to a headlight. Facial eczema can be a recalcitrant problem through toddler years and is exacerbated by moisture sources such as drool and baby foods.[5,33]

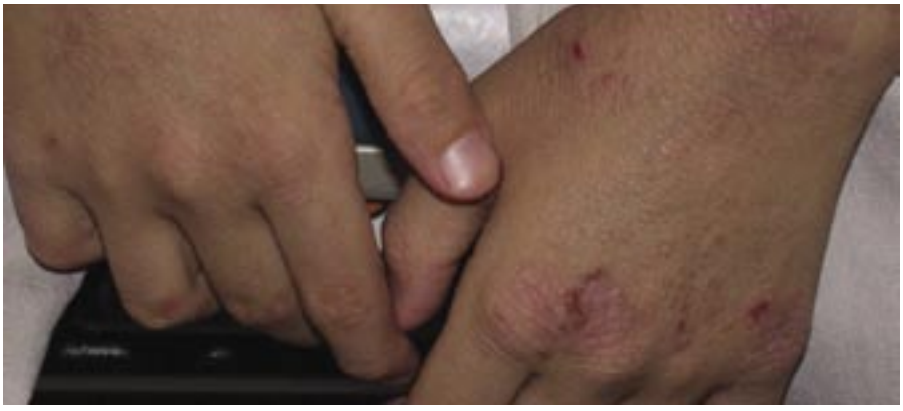

Figure 2. Atopic dermatitis presenting on the dorsal hand in a 5-year-old child, with erythematous plaques, excoriations, and crusting.

The common childhood form of AD usually begins around the first year of life, with eczematous plaques on flexural surfaces, including the postauricular, nuchal, antecubital (Figure 1), wrist (Figure 2), gluteal, popliteal, and ankle regions.

Adult eczema often involves the palmar surface of the hand and is called *dyshydrotic eczema*. Many adults believed to have experienced resolution may develop eczema of the hand and sensitivities to soaps, detergents, and excessive water exposure.[5]

Other Cutaneous Stigmata of AD—Other stigmata associated with AD include palmar hyperlinearity, which also occurs in other disorders such as palmoplantar keratoderma and Down syndrome. Dennie-Morgan folds are common in patients with AD. They are linear infraorbital creases that begin lateral to the medial canthus and extend beneath the eye. These folds also may be seen in children without AD and are not pathognomonic. Children of color are far more likely to have Dennie-Morgan folds irrespective of the presence of AD.[34] Perioral pallor also is a common feature of AD.

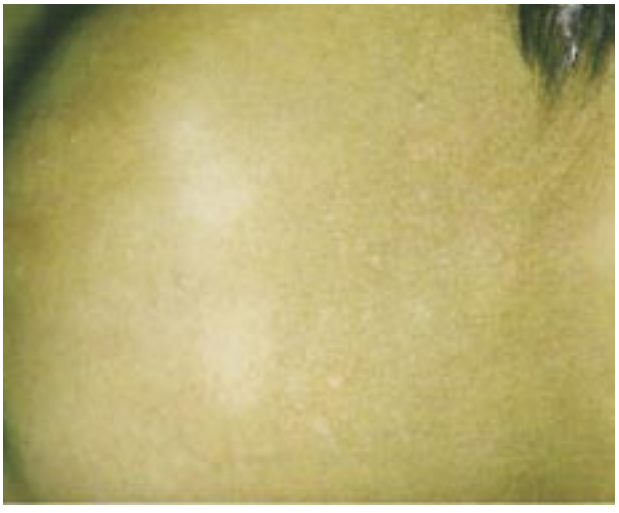

Figure 3. Pityriasis alba in an 8-year-old Hispanic boy, with annular hypopigmentation recurring each spring.

Dermatologic Conditions Associated With AD

Patients with AD may experience a variety of ocular conditions, beginning at birth with keratoconus.[35] As children approach school-age, the onset of atopic conditions such as allergic rhinoconjunctivitis may be heralded by allergic shiners, a darkening and mild swelling of the infraorbital skin, and a transverse nasal crease. The latter also is known as the allergic salute because it is caused by the upward hand rubbing or stroking of the nose precipitated by nasal symptoms such as itch. Other symptoms of allergic diathesis include allergic conjunctivitis resulting from injection of the sclera and conjunctival mucosa.[35]

Other dermatologic conditions associated with AD include pityriasis alba (Figure 3), an annular form of hypopigmentation occurring most commonly on the face and seen most often in the spring and summer months.[35] It is believed to be a form of subclinical eczematous dermatitis, in which erythema does not accompany inflammation. Ichthyosis vulgaris (Figure 4) is an autosomal-dominant genodermatosis presenting with fishlike scales of the forehead and anterior shin. The excessive xerosis accompanying ichthyosis vulgaris can exacerbate AD.[35]

Complications

Patients with AD are more prone to bacterial overgrowth, impetigo, and extensive viral infections.

Bacterial Infections—More than 90% of AD lesions will be colonized with *Staphylococcus aureus* and up to 76% of patients with AD will be colonized

with *S aureus* on nonlesional skin. Patients also may carry *S aureus* in the nares, allowing for repeated reinfection, despite systemic antibiotic administration.[36,37]

In addition, parents and caretakers may harbor *S aureus* in the nares, causing repeated reinfection of their child.[38] With excessive oozing and excoriations, it is not uncommon to find bacterial overgrowth, leading to frank impetigo. Infection with *S aureus* worsens inflammation by secreting superantigens and α toxin, resulting in stimulation of T cells, macrophages, and eosinophils.[39]

Methicillin-resistant *S aureus* (MRSA) has been reported in patients with AD.[40,41] The isolation rate of MRSA is increasing.[42] Akiyama et al[43] reported that 31.1% of patients with AD are infected with MRSA. Consequently, antimicrobial treatment for patients with AD must be carefully tailored to prevent the growth of MRSA infection.

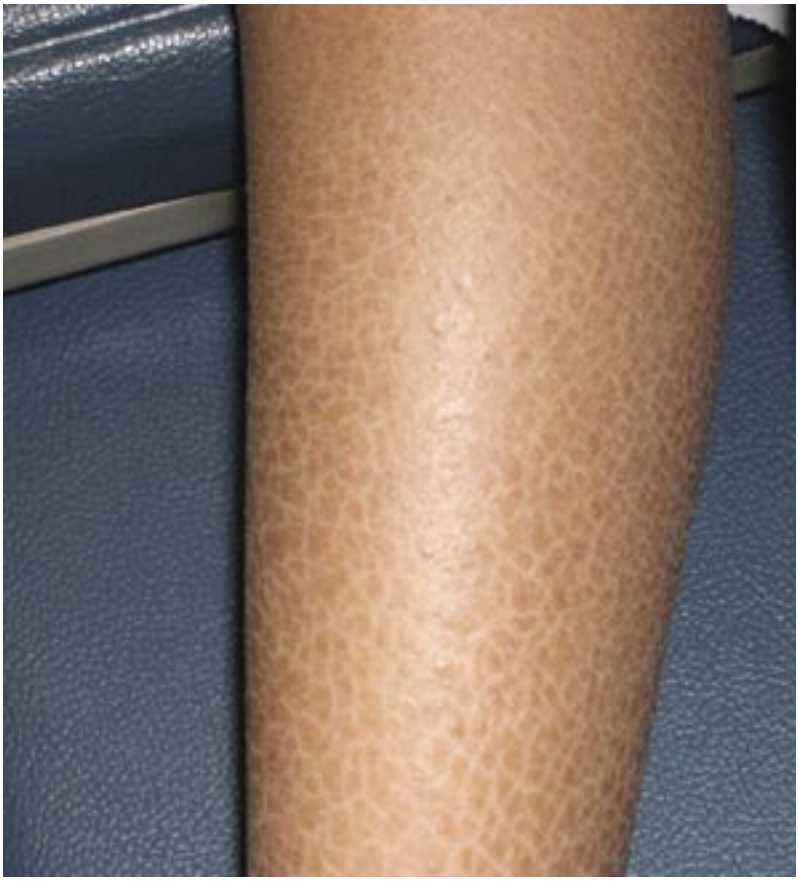

Figure 4. Fishlike scales on the anterior shin, a common presentation of ichthyosis vulgaris.

Viral Infections—In children with AD, cutaneous viral infections are difficult to contain and often lead to extensive viral eruptions.[28,29] Abnormal cutaneous viral processing was reported with smallpox vaccinations in children with AD more than 4 decades ago.[44] Extension and generalization of painful scarring pox lesions was seen in a minority of patients with AD and was termed *eczema vaccinatum (EV)* or *Kaposi varicelliform eruption*. Most of the patients who developed EV in the clinical trials of the 1960s had inactive or quiescent AD, confirming the presence of an abnormal response to viral infections, even in the absence of active AD.[44] In larger vaccinia vaccination trials, one third of patients with EV died because of extensive skin disease.[30] The Centers for Disease Control guidelines recommend that individuals who have ever been diagnosed with eczema or AD (conditions involving repeated episodes of red, itchy, or inflamed skin), even if the condition is mild, not presently active, or was present only in childhood, should not receive the vaccinia vaccine.[45]

When children with AD are exposed to herpes simplex virus (initial infection or recurrence), they might develop eczema herpeticum, herpetic lesions extending beyond the original site to an extended cutaneous surface area. These children may have rapid extension of their cutaneous illness and often are extremely irritable and sick. Eczema herpeticum is painful and is associated with a risk of dehydration and bacterial superinfection. However, use of acyclovir and hydration does speed healing and reduces the extent of infection.[35,46]

It has long been thought that children with AD are more prone to human papillomavirus infections and molluscum contagiosum. Although a greater incidence of viral warts has not been consistently demonstrated in children with AD, immune processing of the human papillomavirus has been shown to be abnormal for dermatitis patients and can result in a prolonged course of disease.[47] Most children with AD will experience a significant flare of AD if they become infected with the molluscum contagiosum virus, often called *molluscum dermatitis*. Molluscum contagiosum infections are more likely to demonstrate extensive lesions and cause severe pruritus in children with AD. Concurrent treatment of the underlying AD and molluscum contagiosum infections is required because the 2 diseases exacerbate each other.[48]

Sleep Disruption and Growth Abnormalities—Sleep disturbances are common in patients with AD.[49] Pruritus often is worst in the evening in children with AD because of the lack of humidity and removal of clothing.[50] As nocturnal sleep is required for release of growth hormone, it is essential for overall growth to ameliorate sleeplessness. Furthermore, the entire household suffers when the child does not sleep; parents often join their child in lack of sleep and frustration. Parental frustration increases when a child with AD spends the night scratching.[51] Children with AD often learn to manipulate their parents with disease complaints and can become small household dictators, particularly when evening disease exacerbations are rewarded by an invitation to join their parents in bed.

Recently, a group of pediatric dermatologists assessed the effect of AD on their patients' quality of life. They found that AD leads to sleep dysfunction in affected children, and sleep deprivation and exhaustion in parents, compromising physical and emotional health of both the child and parents.[52,53]

Food Allergy and AD—In the first 3 months of life, infants with AD are predisposed to developing food allergies and asthma. Food allergy occurs in at least one third of patients with AD; however, whether these food allergies are merely associated atopic conditions or disease triggers is a subject of much debate. Many parents report that their child scratches shortly after introduction or ingestion of specific foods (an atopic food-related exacerbation). However, in a child with extensive disease or intractable pruritus, a diagnosis based on observation is unreliable; allergy testing is necessary to provide guidance in feeding. Although false negatives and positives often occur in infants, radioallergosorbent testing can provide basic guidelines for food introduction. As the child grows older, repeat allergy testing through scratch testing can better identify the food allergies. When the disease state is severe with extensive (>30% body surface area) disease, persistent pruritus, and poor response to topical therapy, particularly in small infants, avoidance of the most common allergens, including milk, peanuts, fish, soy, eggs, and chocolate, is recommended. Breast-fed infants also can benefit from maternal withdrawal of these allergens.[54] Though beneficial to children with AD, restrictive diets can be difficult for parents.

Atopic Triad/Atopic March—In an atopic march, the symptoms of AD precede the appearance of allergic rhinitis and asthma.[55,56] Evidence also has shown that the more severe the AD, the greater the risk of developing allergic rhinitis. Furthermore, the severity of AD correlates with IgE levels, which can predispose patients to developing asthma.[57-60]

The link between AD and asthma is thought to result from genetic and pathogenetic similarities. In addition to being linked by chromosomal regions, AD and asthma also share a common pathogenesis, including eosinophilia, Th2 cytokines, and elevated IgE levels.[61-63] The atopic march is thought to begin with epicutaneous sensitization that stimulates a Th2 response.[64] This localized immune response leads to a systemic response marked by IgE production, eosinophil activation, and increased bronchial mucous secretion, bronchial hyperreactivity, and smooth muscle proliferation, leading to asthmatic symptoms.[65,66]

Comment

AD is a common childhood disease that deserves the attention of dermatologists and pediatricians. Recognition of and attention to its characteristic pruritic and xerotic erythematous rash will greatly relieve patients with AD. Furthermore, this common allergic disorder has been shown to be associated with other allergic conditions such as asthma and hay fever.

This article is the first of a 2-part series. The second part, focusing on treatment options for AD, will appear in an upcoming issue of Cutis®.

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