REPORT

Overview of Atopic Dermatitis

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ABSTRACT

Atopic dermatitis (AD), also known as atopic eczema, is a chronic relapsing inflammatory skin condition. Incidence of AD has increased 2- to 3-fold in industrialized nations, impacting approximately 15% to 20% of children and 1% to 3% of adults worldwide. AD has a wide-ranging impact on a patient's quality of life and the burden from direct and indirect costs (approximately $37.7 billion in out-of-pocket costs) is shared by the families and caregivers of patients with AD. This article reviews the epidemiology, burden of disease, pathophysiology, and diagnostic criteria important for early diagnosis and treatment. New insights related to the genetic, immunologic, and environmental impacts of AD have created new treatment opportunities. Nonpharmacologic and pharmacologic interventions are discussed, with an emphasis on emerging treatments for AD. Healthcare providers play an important role in the management of AD to improve economic and clinical outcomes. Treatment strategies need to be individualized with a strong emphasis on patient education and self-management strategies to optimize outcomes and reduce unnecessary costs associated with the management of AD.

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Atopic dermatitis (AD) is a multifaceted, chronic relapsing inflammatory skin disease that is commonly associated with other atopic manifestations such as food allergy, allergic rhinitis, and asthma.[1-3] It is the most common skin disease in children, affecting approximately 15% to 20% of children and 1% to 3% of adults.[4,5] Onset of disease is most common by 5 years of age, and early diagnosis and treatment are essential to avoid complications of AD and improve quality of life.[5] Individuals with AD were formerly referred to as individuals having eczema. However, the word "eczema" is a broad term that refers to various conditions causing inflammation of the skin. The purpose of this lesson is to review the epidemiology, burden of disease, pathophysiology, diagnostic criteria, and clinical presentation of AD to ensure that patients are correctly diagnosed and receive care in an appropriate and timely manner.

Epidemiology

Incidence of AD, also referred to as atopic eczema, has increased 2- to 3-fold in industrialized nations since the 1970s, with approximately 15% to 20% of children and 1% to 3% of adults affected worldwide.[4,5] Population-based studies in the United States suggest that prevalence is about 10.7% for children and 7.2% for adults.[6,7] Onset of disease commonly presents by 5 years of age, with the highest incidence occurring between the ages of 3 and 6 months, but it can occur at any age.[5,8] Approximately 60% of patients develop disease in the first year of life and 90% within the first 5 years of life.[5] Twenty percent of children who develop AD before 2 years of age will have persisting symptoms of disease; 17% will have intermittent symptoms by 7 years of age. Only 16.8% of adults with AD experience onset after adolescence.[9-11] AD commonly resolves by the time a child reaches adulthood; however, approximately 10% to 30% of patients will continue to have symptoms of disease.[12] A 2014 prospective cohort study of children with mild-to-moderate AD reported that, at any age, including up to 26 years of age, 80% of participants with ≥5 years of follow-up continued to have symptoms or had continued using medications for their AD.[13] Interestingly, investigators from the same cohort study identified that regardless of disease

severity, participants sought out their healthcare provider less frequently as they aged, suggesting that this may account for the common perception that AD resolves over time.[13] In contrast, a 2016 meta-analysis showed that only 20% of childhood AD persisted 8 years after onset and there was a median duration of 3 years for AD persistence.[14] Furthermore, AD was shown to be more persistent in males, in patients with late-onset disease, and in those with severe cases of the disease. Even with the inconsistencies among the above-mentioned studies, it is clear that AD is a chronic disease that is burdensome for many patients. A 2007 study further supports this claim, as an estimated 17.8 million persons, mostly undiagnosed, are living with AD in the United States.[8]

Burden of Atopic Dermatitis

Areas of disease burden most commonly impacted by AD include overall quality of life and the social, academic, and occupational realms.[3] The burden of AD is not limited to just the patient, because AD is a chronic relapsing skin disease that can persist into adulthood and burden of disease is frequently experienced by the patient's family. Several validated tools have been used to measure the adverse impact on quality of life during patient and family interviews, supporting a family-wide burden experience related to AD.[15-18] Similarly, patients, their families, and society bear a significant weight related to the direct and indirect medical costs associated with AD.[3,4,19,20] Direct costs include, but are not limited to, prescription and nonprescription costs, healthcare provider visits, hospital and emergency department visits, and hospitalizations. Indirect costs associated with AD include absenteeism from work, school, and physical activities; decreased productivity (presenteeism); and decreased quality of life (primarily due to sleep disturbance from itching, absenteeism, and time related to care).[21-24]

Quality of Life

Itching is the major symptom associated with impact on quality of life. For example, a US-based survey found 91% (n = 304) of patients with eczema experienced itching on a daily basis,[25] and 36% of patients identified decreasing the amount of itch to be their primary treatment goal.[26] Furthermore, itch has been associated with mental distress and increased risk for suicidal ideation in those with AD.[27] Of note, emotional stress has also been shown to increase itching, implying a bidirectional relationship.[28] Sleep disturbance is a frequent consequence of itching and is experienced by approximately two-thirds of patients with AD.[8,29] Patients with sleep disturbance report difficulty initiating and maintaining sleep, which leads to daytime fatigue.[30] Children with AD who experience sleep disturbances are associated with higher rates of developing attention-deficit/hyperactivity disorder, headaches, and short stature.[30-32] Sleep disturbances experienced by adults with AD are associated with poor overall health perception.[7] In addition to the physical symptoms, AD can lead to embarrassment from appearance, decreased self-esteem, and a negative impact on social life.[33,34] While a patient's quality of life is impacted tremendously, so, too, are the patient's parents and caregivers. An international study conducted in 2006 found that 30% of patients and caregivers believed other individuals in the household were impacted by AD.[34]

Economic Impact

A true economic impact of AD is difficult to measure due to the broad severity of AD disease and multiple cost contributors related to indirect and direct medical costs. A 2010 National Health Interview Study conducted in the United States estimated that 75% of people with eczema had visited a doctor at least once in the last year.[7] Furthermore, among those participating in this study, in the prior year, about 12% missed 1 to 2 days of work due to their eczema, and about 2% missed 3 or more days.[7] The current literature related to economic burden is very sparse, but a comprehensive investigation was conducted in the United States in 2006 by Bickers et al.[35] This study reviewed the financial impact of skin disease overall in the United States using various data sources (eg, surveys, databases, published literature) to estimate the costs of individual diseases.[35] The total burden of AD in Bickers et al was estimated at $4.228 billion (2004 USD) compared with psoriasis at $3.658 billion.[3,35] When converted to 2016 USD using the Consumer Price Index provided by the US Bureau of Labor Statistics, this equates to $5.37 billion (calculation: September 2004 consumer price index [CPI] = 189.9; September 2016 CPI = 241.428; costs in 2016 = $4.228 billion × [241.28/189.9] = $5.37 billion).[3,36] Direct costs were $1.009 billion, decreased productivity costs were $619 million, and costs due to decreased quality of life were $2.6 billion.[35] The costs reported in this study are very likely underestimated in the United States today, because while the prevalence estimate in the 2004 study was about 5%, today's prevalence is estimated at about 10.7%[6] (2011) in children and 7.2%[7] (2014) in adults. It is important to keep in mind that this study did not include nonprescription medication costs and decreased productivity beyond medical visits.[35] Finally, since this study was conducted almost 13 years ago, new research is required to adjust for new prevalence data, changing prescribing patterns, and additional contributing factors (eg, presenteeism) not accounted for previously.[3] A more recent study identified the average personal cost of AD in the month before an office visit (including direct and indirect costs) to be $274 per patient ($75 direct costs; $199 indirect costs).[37] This study also calculated a mean percentage of monthly available money spent on AD to be 34.8%, further supporting the high burden of disease experienced by patients with AD.[37]

Pathophysiology

Two major theories have been proposed to explain the cause of AD, the inside-out and outside-in hypotheses.[38] The inside-out hypothesis

proposes that allergic triggering leads to a weakened skin barrier that furthers allergen introduction and presentation.[38] This would suggest that inflammation is the culprit for an impaired skin barrier, leading to increased penetration of allergens and microbes causing a reaction. The outside-in hypothesis proposes that the impaired skin barrier precedes AD and is required for immune dysregulation to occur.[38] For example, the down-regulation of filaggrin (FLG), required for proper skin barrier function, could make the skin more susceptible to immune dysregulation and lead to AD. It is unlikely that the 2 theories are exclusive and both most likely play a role in the pathogenesis of AD, discussed further below.[38,39]

Risk Factors

There are 2 major risk factors for the development of AD: 1) genetic defect in the *FLG* gene[40] and 2) family history of atopic disease.[5] A family history of atopic disease is strongly correlated with AD, as approximately 70% of patients with AD are positive for this risk factor.[5,41] Risk of AD increases with the number of parents positive for atopic disease by 2- to 3-fold and 3- to 5-fold (1 and 2 parents, respectively).[5,42,43] In addition, a maternal history may be more predictive for AD.[44]

Concordance rate studies for atopic dermatitis are higher among monozygotic twins compared with dizygotic twins (approximately 80% and approximately 20%, respectively).[1,45,46] Thus, there is a genetic predisposition for developing AD. Genome scans have pointed to multiple chromosomes being implicated, with the region of highest linkage found on chromosome 1q21.[1,47] Other reported risk factors include an urban environment, higher socioeconomic status, higher level of family education, female gender (after age 6 years), and a smaller family size.[48]

The *FLG* gene is responsible for the development of the profilaggrin protein, found in the granular layer of the epidermis, and brings structural proteins together to create a strong barrier matrix.[49,50] *FLG* mutations are common particularly among Caucasians. Approximately 10% of individuals of European descent are heterozygous carriers of a loss-of-function mutation in *FLG*, resulting in a 50% reduction in the expression of the protein.[51] When *FLG* mutations are present, disease is more severe and persistent, occurs mainly in early-onset AD, and indicates a propensity toward asthma.[1,52] *FLG* gene defects have also been associated with peanut allergy, contact dermatitis, and infections such as the herpes virus.[39,53] Because *FLG* mutations are identified in only about 30% of European patients with atopic disease, other epithelial genetic variants must also be considered.[1,54,55]

Skin Barrier Dysfunction

The epidermis of the skin consists of several layers that act as barriers to prevent water loss and to protect the body from such foreign substances as microbes and allergens. The *FLG* gene, on chromosome 1q21.3, encodes a key protein in epidermal differentiation.[1] This gene was originally identified as the gene involved in ichthyosis vulgaris, which will be discussed again later,[1,56] and several loss-of-function mutations were identified in European and Japanese patients with AD.[1,57-60] Since then, multiple studies have demonstrated that the *FLG* gene plays a pivotal role in skin barrier function and mutations of the *FLG* gene are a major risk factor for AD.[40,45,61,62] Other skin barrier factors may include a deficiency of skin barrier proteins, increased peptidase activity, lack of certain protease inhibitors, and lipid abnormalities.[40] High-molecular-weight allergens in pollens, house dust-mite particles, microbes, and foods can only penetrate the skin barrier when there is epidermal barrier dysfunction.[63] The strong barrier matrix created by the *FLG* gene, with attached proteins and lipids, forms the stratum corneum, or the outermost layer of the epidermis, which normally provides a barrier to microbes and allergens and minimizes transepidermal water loss.[49] *FLG* mutations or deficiencies result in an abnormality in permeability of barrier function.[62]

Immune Dysfunction

Other immune system–related genes found to be associated with AD include those encoded on chromosome 5q31 to 5q33. These genes code for cytokines that regulate immunoglobulin E (IgE) synthesis: interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-12 (IL-12), interleukin-13 (IL-13), and granulocyte-macrophage colony-stimulating factor.[1] Cytokines are mainly produced by type 1 and type 2 T helper lymphocytes (TH_1 and TH_2, respectively). TH_1 cytokines (IL-12 and interferon-γ suppress IgE production, and TH_2 cytokines (IL-5 and IL-13) increase IgE production.[1,64] Patients with AD have a genetically determined dominance of TH_2 cells that may decrease expression of *FLG* and other molecules found in the skin barrier.[1] Genetically modified mice engineered to overexpress TH_2 cytokines developed skin barrier defects and AD spontaneously.[39] Naturally, many of these cytokines are targets for novel therapies for the treatment of AD.

Atopic March (Triad)

The "atopic march" describes the tendency for AD to precede the development of other atopic diseases such as food allergies, asthma, and allergic rhinitis in a temporal sequence.[65] A 2008 study showed that the march does not necessarily always happen in order, as some patients with asthma develop AD.[66] It has also been reported that while common in childhood, the atopic march can occur at any age.[67] Still, multiple longitudinal studies have provided evidence supporting the atopic march between AD and subsequent allergies, and the interrelationships among subsequent allergic manifestations.[68-76] Patients with atopic dermatitis, allergic rhinitis, and allergic asthma are considered to have the atopic triad. Approximately one-third of patients with AD develop asthma, and two-thirds develop allergic rhinitis.[77,78] Although no recent data exist on the proportion of patients with AD who develop food allergies, it is well known that the 2 conditions co-associate.[79] The common

TABLE 1. Revised Hanifin and Rajka Criteria for Atopic Dermatitis Diagnosis[99]

Essential Features (required)

- Pruritus
- Eczema (acute or chronic)
  - » Typical presentation and age-related patterns
    - › Infants and children: face, neck, extensor involvement
    - › Any age group: history of flexural involvement
    - › Not present in groin and axillae regions

Important Features (present in most cases)

- Early age of onset
- Personal or family history of atopic disease or elevated immunoglobulin E
- Xerosis

Associated Features (nonspecific but may aid in diagnosis)

- Dermatographism
- Keratosis pilaris, pityriasis alba, hyperlinear palms, ichthyosis
- Ocular/periorbital changes
- Periauricular changes (including fissure at ear lobe creases)
- Perioral changes
- Perifollicular accentuation, lichenification, prurigo lesions (often from scratching)

Exclusionary Conditions (required to properly diagnose AD)

- Scabies
- Seborrheic dermatitis
- Contact dermatitis (irritant or allergic)
- Ichthyoses
- Cutaneous T-cell lymphoma
- Psoriasis
- Photosensitivity dermatoses
- Immune deficiency diseases
- Erythroderma of other causes

link among these allergic disorders is atopy, or the predisposition for IgE-mediated responses to stimuli.[80]

Triggers of Atopic Dermatitis

Triggers are the leading cause of an AD exacerbation, and avoidance of triggers is an important mechanism patients can use to control disease activity.[81] Atopic dermatitis may be triggered by viral infections, food allergens, cosmetics, fragrance, weather, and other causes. Extremes of hot and cold weather are poorly tolerated by patients with AD and can lead to sweating and dry skin, respectively, initiating pruritus. In childhood, wool has been found to be a known trigger of AD.[82] Exposure to environmental allergens such as dust mites, pollens, molds, cigarette smoke, and dander from animals may exacerbate symptoms of AD.[81,83] The role of food as antigens in the pathogenesis of AD is controversial. Food allergens contribute to approximately 40% of AD cases in infancy but are not the cause of AD.[84] An allergist should be consulted to assess the level of allergic severity with respect to food allergens via a risk-benefit ratio to determine if food avoidance or introduction is recommended.[85] The most commonly allergenic foods are eggs, milk, peanuts, wheat, soy, tree nuts, shellfish, and fish.[83]

Diagnostic Criteria

Classification

An AD diagnosis is made clinically through an extensive history and physical examination that relies strongly on clinical presentation. Multiple groups have developed classification criteria over the years to aid in diagnosis.[5,86,87] The Hanifin and Rajka criteria are the most recognized set of diagnostic criteria and are widely considered to be the gold standard for AD diagnosis.[5,87] The diagnostic criteria are very thorough, requiring 3 of 4 major criteria and 3 of 23 minor criteria be met for diagnosis. The original version created in 1980 is very comprehensive and applicable to clinical trials, but the large quantity of criteria made its application elsewhere impractical. The United Kingdom (UK) Working Party specifically took on the task of scaling down the criteria to a core set that was amiable to use in clinical practice, consisting of 1 mandatory and 5 major criteria and no requirement for laboratory testing.[88,89] However, skin biopsy or other tests may be necessary to exclude other medical conditions. Both the Hanifin and Rajka and the UK Working Party AD diagnostic criteria have been tested and validated in multiple studies and populations.[5,89-98] An important limitation of the UK Working Party AD criteria is the inability to apply them to very young children, but, notably, revisions have been proposed to address this concern. Therefore, the Hanifin and Rajka criteria were further revised by an American Academy of Dermatology consensus conference.[99] The goal of the revisions was to make the criteria more streamlined and applicable to the broad range of ages of individuals affected with AD (**Table 1**[99]).[99] These 2003 criteria have not been validated, but the work group deemed them appropriate for use in clinical practice for diagnosing infants, children, and adults.

Exclusion of Diseases in Diagnosis of AD

The diagnosis of AD should include exclusion of other similar skin conditions (Table 1[99]).[99] There are multiple skin conditions that can be confused with, coexist with, and/or complicate AD.[100] Seborrheic

dermatitis (SD) is a common inflammatory skin condition that is difficult to distinguish from AD, especially in infancy where they can occur concomitantly or separately.[100] SD is distinguished by a lack of excoriations and sleep impairment and, unlike AD, usually resolves before the age of 2 years.[100] Additionally, SD lesions are typically thick, greasy, white, off-white, or yellow in appearance. In patients with darker skin types, lesions often have hypopigmentation.[100] Psoriasis is another inflammatory skin condition that should be ruled out in patients suspected of having AD. Since scaling in psoriasis is typically more prominent and distribution of lesions includes the face, it is possible for misdiagnosis with AD.[100] Psoriasis is frequently found in the diaper area (unlike AD) and includes nail involvement, which can help distinguish between the 2 skin conditions. Contact dermatitis is the most common form of dermatitis and is characterized by erythema and edema. It can occur simultaneously with other inflammatory skin conditions and complicate AD.[100] Infestations such as scabies should also be excluded when diagnosing AD. Scabies is an allergic response to the mite, eggs, and feces of *Sarcoptes scabiei*. The reaction is characterized by small, red papulovesicles or eczematous lesions.[100] Gradual onset, lack of dry skin, and other family members experiencing itch during the same time frame help to confirm diagnosis. It can also be differentiated from AD by visual inspection of the mite's linear burrows.[100] Other skin conditions that are commonly associated and/or confused with AD are pityriasis alba, keratosis pilaris, ichthyosis vulgaris, and dermatographism, which will be discussed in detail later in this article.[52]

Biomarkers

There are no current reliable biomarkers that can be used to routinely diagnose and differentiate AD from other similar skin conditions. The most common associated laboratory value in current practice is IgE, with approximately 80% of patients with AD experiencing an elevated level.[5] However, it is important to note that there are several limitations with this potential biomarker. Namely, 20% of the AD population does not present with elevated IgE; some individuals develop elevated IgE later; and elevated allergen-specific IgE levels are nonspecific, having been found in approximately 55% of the US general population.[5,101,102] Furthermore, IgE is not a reliable indicator, as some patients with severe disease present with normal IgE levels, and IgE can be elevated in multiple nonatopic conditions (eg, parasitic infection, certain cancers, and autoimmune diseases).[5,101,103,104]

Discovery of new T-lymphocyte subsets and novel cytokines and chemokines have created numerous opportunities for the development of new biomarkers.[5] Potential options include serum levels of CD30, macrophage-derived chemoattractant (MDC), interleukins (IL-12, IL-16, IL-18, IL-31), and thymus and activation-regulated chemokine (TARC). Some of these new biomarkers have correlated with AD severity, but none have shown reliable sensitivity or specificity for AD to support regular clinical use for diagnosis and monitoring.[5]

TABLE 2. Skin Features Associated With Atopic Dermatitis in Children and Adults[83]

Skin Feature	Skin Feature Description
Atopic pleat (Dennie-Morgan fold)	Extra fold of skin that develops under the eye
Cheilitis	Inflammation of the skin on and around the lips
Hyperlinear palms	Increased number of skin creases on the palms
Hyperpigmented eyelids	Eyelids that have become darker in color from inflammation or hay fever
Ichthyosis	Dry, rectangular scales on the skin
Keratosis pilaris	Small, rough bumps, generally on the face, upper arms, and thighs
Lichenification	Thick, leathery skin resulting from constant scratching and rubbing
Papules	Small raised bumps that may open when scratched and become crusty and infected
Urticaria	Hives (red, raised bumps) that may occur after exposure to an allergen, at the beginning of flares, or after exercise or a hot bath

Source: National Institute of Arthritis and Musculoskeletal Skin Diseases.

Clinical Presentation

Atopic dermatitis is considered to be a chronic relapsing inflammatory skin condition. As a result, it generally presents in 3 different clinical phases: 1) acute AD (a vesicular, weeping, crusting eruption); 2) subacute AD (dry, scaly, erythematous papules and plaques); and 3) chronic AD (lichenification, thickening, from repeated scratching).[2] AD is commonly localized to the flexural surfaces of the body, anterior and lateral neck, eyelids, forehead, face, wrists, dorsa of the feet, and hands.[2] As a result of the broad range of severity and presentation, differential diagnosis is essential to the proper diagnosis of AD (see **Table 2**[83]).[52,99] In addition to the clinical phases, the disease course of AD is not static but rather defined by a pattern. A study conducted in 2004 looked at disease course, with AD falling into 1 of 3 disease patterns: 1) persistent (19%; AD at every follow-up until age 7 years); 2) intermittent (38%; early AD not fitting persistent or remission criteria); or 3) remission (43%; no AD after the age of 2 years).[9] Thus, it is important for healthcare providers to be able to recognize and classify AD so that appropriate treatment can proceed.

Age and Disease Presentation

The clinical disease presentation (Table 2[83])[52,99] varies based on the age of the individual affected. In infancy, AD is generally recognized soon after birth, as xerosis occurs early and can involve the entire body, usually excluding the diaper area. The first presentation

in infancy is an erythematous papular skin rash that can affect the creases, particularly on the front of the elbow and behind the knee (antecubital and popliteal fossa).[83,105] This patchy skin rash can progress to redness, scaling, and exudation with a centrifugal distribution affecting the cheeks, forehead, scalp, chin, and behind the ears while sparing the nose.[83,105] Over time, the lesions can spread to the lower legs with potential involvement anywhere on the body but usually still sparing the diaper area and the nose.[83] Uncontrollable itching is characteristic of developed lesions leading to rubbing of the face by the infant to help control the itch. Scratching can develop very early in infants and those impacted by AD can scratch continuously.[83] Excessive rubbing or scratching can result in crusted erosions, excoriation, and subsequent development of secondary infections.[83]

In childhood, xerosis is often generalized, causing rough, flaky, or cracked skin. Lichenification, thickening of the skin, is characteristic in older children and adults.[105,106] Lichenification is representative of repeated rubbing of the skin and seen mostly over the folds, bony protuberances, and forehead.[105] Pallor of the face is common; erythema and scaling occur around the eyes with Dennie-Morgan folds often seen as well.[105] Dennie-Morgan folds are commonly seen under the eyes of children with allergies. Flexural creases, especially the antecubital and popliteal fossae, and buttock-thigh creases are often affected.[105] Excoriations and crusting are also common and can lead to secondary infections; however, it is important to distinguish, as both AD and infections can produce oozing and crusting.[105]

In adulthood, xerosis is prominent and lesions are more diffuse with underlying erythema. The face is commonly involved, presenting as dry and scaly.[105] Like AD in childhood, lichenification may also be present. In addition, a brown macular ring around the neck, representing a localized deposit of amyloid, may also be present.[105]

Hallmark Essential Feature of AD

Pruritus, or itching, is the first essential feature required for diagnosis of AD and the leading symptom that characterizes AD.[5,52] Unfortunately, with this type of atopic skin condition, scratching and rubbing only further irritate the skin and worsen the itchiness experienced by the patient. Itching can also occur during the night and can further exacerbate AD, as there is no conscious control of scratching while sleeping.[83,107] Itching can be triggered by multiple factors, such as heat and perspiration (96%), wool (91%), emotional stress (81%), certain foods (44%), upper respiratory infections (36%), and house dust mites (>35%).[108] Furthermore, once initiation of itching occurs, the surrounding skin (regardless of inflammation) can be very sensitive and involuntarily react (alloknesis) to other stimuli such as light and can begin to itch.[108] Thus, patients with AD with alloknesis can begin itching simply from their skin being touched by mechanical factors such as clothing.[108]

Other Skin Features Commonly Associated With AD

There are 4 features that are commonly associated and/or confused with AD that are important to distinguish from AD: 1) Pityriasis alba is characterized by red, scaly patches that eventually resolve, leaving areas of hypopigmentation. They occur most commonly on the face, upper extremities, and trunk, and may be more pronounced with sun exposure, as surrounding skin tans.[52] 2) Keratosis pilaris is a harmless skin condition that results in tiny bumps on the skin due to plugs of dead skin cells. Patients complain of skin that is rough and "plucked chicken skin" in appearance on the upper arms, thighs, cheeks, and buttocks. 3) Ichthyosis vulgaris results in a "fish-scale" appearance most commonly seen on the lower legs, but it can affect other locations. Approximately half of patients with ichthyosis vulgaris develop AD and it is associated with earlier onset of disease and increased severity of AD.[100] 4) Dermatographism (aka "skin writing") occurs as a result of scratching the skin, producing a reddened raised wheal that appears within 5 minutes of stimulation and can last for up to 30 minutes.

AD-Associated Complications

Bacterial Infections: AD is associated with decreased production of antimicrobial peptides in the skin and an unusual cutaneous microbiome, with decreased diversity and increased *Staphylococcus aureus* colonization.[109,110] Approximately 80% to 90% of patients with AD are carriers for *S. aureus*.[111] Patients with AD who are colonized by *S. aureus* are not necessarily infected; however, they are at risk for superinfection of their cutaneous lesions (impetiginization).[110] Patients with AD are, however, at increased risk for colonization with methicillin-resistant *S. aureus* (MRSA), compared with the general population.[112] Those colonized with MRSA are also at an increased risk for skin infection compared with those colonized with methicillin-sensitive *S. aureus*.[113,114]

Viral Infections: Patients with AD are at a higher risk for eczema herpeticum (EH), an acute, potentially life-threatening viral infection caused by the herpes simplex virus.[100] Approximately 20% of patients with AD develop EH.[115] EH is more common among patients with AD with severe disease or IgE-mediated disease. Molluscum contagiosum (MC) is a benign viral skin infection that presents as flesh-colored, pink, or pearly white papules. The virus can last an average of 1 to 2 years and can leave pitted scarring.[52] The MC virus in patients with AD can be more involved, leading to molluscum eczema, in which dermatitis develops surrounding the molluscum lesions.[100]

Fungal Infections: These may also invade compromised skin, leading to colonization with tinea or yeast. Appropriate cultures may be needed in those patients who have risk factors for tinea or yeast colonization or who remain unresponsive to treatment. Evidence is lacking for increased risk due to AD; however, the broken skin, erosions, and excoriations that are common in patients with AD can become colonized.[100]

AD-Associated Comorbidities

Recent studies have linked AD with nonatopic comorbidities such as attention-deficit/hyperactivity disorder and speech disorders.[116,117] Anxiety and depression have also been associated but are more common among adults with AD.[118,119] It is unclear why these associations exist in patients with AD; however, psychosocial impacts, such as embarrassment and sleep disruption, may contribute.[110] Other comorbidities in children with AD include headaches,[31] anemia,[120] and epilepsy.[121] Both adults and children have been associated with injuries such as fractures, and with low bone mineral density (BMD), possibly related to the use of oral corticosteroids for AD.[122-124] The lower BMD and fracture risk may also be associated with the cutaneous inflammation in AD that leads directly to bone loss.[125] Recent attention has focused on whether there is an association between AD and increased cardiovascular (CV) risk. AD has been consistently associated with obesity in both children and adults, and with other CV risk factors such as hypertension, hypercholesterolemia, and diabetes.[126-128] There is controversy with respect to risk of CV outcomes such as myocardial infarction and stroke in patients with AD. Some studies report an increased CV morbidity[129,130] and other studies showed no independent association[131,132] in patients with AD. A 2016 study from the Nurses' Health Study 2 found no significant association between AD and myocardial infarction or stroke.[132] This study controlled for other AD comorbidities, including asthma, suggesting that comorbid asthma may be driving the CV risk.

Conclusion

In summary, AD is the most common skin disease affecting children. The burden of disease from AD is significant for not only the patients but also their families. The disease can persist throughout a patient's lifetime, notably affecting quality of life, and the costs associated with AD are difficult for patients and their family members to manage. In the last 3 decades, there has been substantial progress with respect to understanding the pathogenesis of AD. These new insights related to the genetic, immunologic, and environmental impacts have paved the way for future novel treatments. Early diagnosis and treatment may help decrease the morbidity of the disease and prevent progression to other associated atopic diseases.

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