Atopic Dermatitis in Adults

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KEYWORDS

• Atopic dermatitis • Eczema • Epidemiology • Treatment • Comorbidities • Burden

KEY POINTS

- Atopic dermatitis is common in adults in the United States and worldwide.
- Atopic dermatitis is associated with different genetic, immunologic, and epidemiologic risk factors in adults than in children.
- One in 4 adults with atopic dermatitis report adult onset of their disease.
- Atopic dermatitis is associated with major patient and societal burden.
- Atopic dermatitis is associated with multiple atopic and mental health comorbidities.

INTRODUCTION

Atopic dermatitis (AD) was once thought to be primarily a pediatric disease that remitted with increasing age. However, recent epidemiologic studies showed that AD is a common and burdensome disorder in adults. Moreover, emerging studies have shown that there are different genetic, immunologic, and epidemiologic risk factors for AD in adults than in children. This article examines the pathophysiology, epidemiology, heterogeneous clinical presentation, burden, diagnosis, and treatment of adult AD.

PATHOPHYSIOLOGY

Genetics

AD is thought to occur via a combination of genetic, environmental, immunologic, and behavioral factors.[1–3] Genetic inheritance plays an essential role in the predisposition for childhood AD. Monozygotic twins have a higher rate of AD concordance than dizygotic twins (~80% vs ~20%).[4,5] Filaggrin (FLG) gene null mutations are the most well-

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studied genetic determinant of AD. FLG codes for the protein filaggrin, which is broken down into a natural moisturizing factor in the stratum corneum and plays an integral role in skin-barrier function.[6] FLG null mutations lead to a deficiency of natural moisturizing factor,[7] xerosis in AD,[8] and disrupted epidermal barrier function allowing increased penetration of allergens and development of a T-helper cell type 2 (Th-2)–predominant phenotype.[9] FLG loss-of-function mutations lead to AD with early childhood onset, greater severity,[10] and persistence into adulthood.[11,12]

However, FLG null mutations are not detected in most children with AD. FLG mutations were only identified in a large minority of European[13] and Asian[14] populations,[15] and not South African and Ethiopian[16,17] or African American populations.[15] Moreover, FLG mutations may not be responsible for adolescent-onset and adult-onset AD. A study of 241 patients with AD found that the 4 most common filaggrin loss-of-function mutations were only associated with early childhood-onset AD ($\leq$8 years), but not late childhood–onset (8–17 years) or adult-onset disease ($\geq$18 years).[10] In contrast, the −1903/A polymorphism of the mast-cell chymase (MCC) gene may play a role in adult-onset AD because it is associated with AD in adults, but not allergic rhinitis or asthma,[18,19] and is inversely associated with serum immunoglobulin (Ig) E levels in adult patients with AD.[19,20] Other important genetic factors linked to adult AD include polymorphisms of the interleukin (IL)-4 receptor[21] and the vitamin D receptor.[22] Future research is needed to understand the genetics of adult AD, particularly adult-onset AD.

Immunologic Factors

Th-2 and other T-cell subsets contribute to AD pathogenesis. In the acute and chronic phases of AD, a skewed Th-2 response is seen, leading to increased activity of IL-4, IL-5, IL-13, IL-31, and so forth. However, Th-1 responses are upregulated in the chronic phase of AD. A study of 28 adults with AD and 6 healthy controls found that IL-13 messenger RNA (mRNA) was expressed in 27 of 28 AD skin lesions examined, but only 3 of 6 controls; the level of expression of IL-13 mRNA was significantly higher in lesional skin compared with healthy controls.[23] However, IL-4 mRNA was expressed in only 3 of 28 AD lesions and 0 of 6 controls.[23] A study of 16 patients with AD and 12 healthy controls found significantly higher expression of IL-1b, IL-1RA, IL-5, IL-6, IL-8, IL-13, IL-18, thymus and activation regulated chemokine (TARC), tumor necrosis factor alpha, Monokine induced by gamma interferon (MIG), and interferon γ-induced protein 10 kDa (IP-10) in AD skin lesions compared with nonlesional AD skin and/or healthy skin.[24] Furthermore, interstitial fluid levels of IL-13 and IP-10 but not IL-4 in AD skin lesions strongly correlated with AD severity as judged by the SCORAD Scoring Atopic Dermatitis) total and objective scores.[24]

Few studies have compared the immune differences of AD in children versus adults. A recent study of 19 children aged less than 5 years with new-onset AD compared the immune phenotype in skin with 15 adults with AD.[25] Children compared with adults with AD showed comparable or greater epidermal hyperplasia and immune infiltration, and decreased filaggrin expression on histology and immunohistochemistry as well as activation of Th-2, Th-22, and Th-1 axes on quantitative real-time polymerase chain reaction. However, children showed higher induction of Th-17–related cytokines, antimicrobials, Th-9, IL-33, and innate markers than adults. These results suggest that the immune mechanisms of AD may differ between children and adults.

EPIDEMIOLOGY OF ADULT ATOPIC DERMATITIS

A study of 27,157 adults (aged 18–85 years) from a US population-based study (2010 National Health Interview Survey) found the prevalence of "dermatitis, eczema, or any

other red, inflamed skin rash" in the past year with or without a personal history of asthma and/or hay fever was 3.2% and 10.2%, respectively.[26] The former definition likely underestimates the true prevalence by excluding patients without atopic disease. The latter likely overestimates the true prevalence by including other dermatoses. The true prevalence of AD is likely between 3% and 10%. A study of 34,613 adults (2012 National Health Interview Survey) found the prevalence of "eczema or skin allergy" in the past year to be 7.2%.[27] The question used was similar to one previously validated for self-report of AD, but did not include health care diagnosis.[28] A study of 4972 adults (2005–2006 National Health and Nutrition Examination Survey) found that the lifetime prevalence of health care–diagnosed eczema in adults was 7.4%.[29] A study of 2893 adults from a US population-based study (AD in America) found the prevalence of AD to be 7.3% using adapted United Kingdom Working Party criteria. Together, these studies suggest that the prevalence of AD in US adults is ~7%.

The prevalence of adult AD ranged from 2% to 17% in previous international studies.[30] A recent international, Web-based survey found the prevalence of previously diagnosed and active AD ranged from 2.1% to 4.9%.[31] Similar to the results of the National Health Interview Survey in the United States, AD prevalence was found to decrease from childhood to adolescence but remained stable into adulthood.[30,32] Together, it seems that the prevalence of AD in adults is similar to that in adolescents and is stable throughout adulthood. Globally, AD prevalence is often highest in high-income countries.[32,33]

It has been widely observed that AD shows a female preponderance, particularly in adolescence and adulthood.[32,34,35] This increased prevalence in female patients from puberty onward is also observed in other atopic disorders.[36]

HETEROGENEITY OF ATOPIC DERMATITIS

Morphology

AD is a heterogeneous disease with a broad spectrum of clinical manifestations. AD is highly polymorphic with a wide spectrum of lesions including acute oozing and crusting, subacute lesions with dryness and scaling, and chronic lesions with lichenification and/or prurigo nodules; erythema, excoriations, and dryness can occur at all stages of disease. In addition, there are myriad lesional morphologies that are present in AD, including nummular, psoriasiform, papular lichenoid lesions, and follicular eczema.

There are also several distinguishing clinical features that occur more commonly in some racial and ethnic groups than others. Erythema in skin of color often appears hyperpigmented or violaceous. A previous study of Nigerian patients with AD found that 54.1% had lichenoid lesions and 70.3% had a perifollicular, micropapular rash on the extensor aspects of the joints.[37]

A recent systematic review and meta-analysis of 101 studies identified 78 different clinical signs and characteristics of AD, with considerable variability by global region and patient age.[38] The review included 38 pediatric and 36 adult studies that reported a proportion of at least 1 AD feature with sufficient data for meta-analysis. Adults studies reported 2-fold or higher rates of erythroderma, Hertoghe sign (thinning or loss of outer third of eyebrows), hand eczema, papular lichenoid lesions, course influenced by emotions and/or environment, prurigo nodules, lichenification, nail involvement, nipple eczema, and nummular lesions. Thus, it seems that AD manifests differently in adults than in children, and in different races/ethnicities and regions.

Distribution

The distribution of lesions is also heterogeneous. In early childhood, lesions have a predilection for the face and extensor areas, whereas older children and adults tend to have flexural eczema. Adults, particularly those with adult onset or recurrence, seem to have a lesional predilection on the head/neck and hands.[39,40]

A recent US population-based study of 602 adults with AD found that the most common sites of skin lesions were reported to be the popliteal fossae, lower legs, dorsal feet, and antecubital fossae.[41] Other commonly reported sites include the face, scalp, hands, and genitals. Most persons with AD reported symmetry of lesions on the extremities. Most persons with active lesions in the antecubital or popliteal areas reported lesions elsewhere. There were no significant differences of lesional distribution by sex. Lesions on the trunk were significantly more common in black and Hispanic people. Age greater than or equal to 60 years was associated with a significantly higher proportion of lesions on the buttocks or genitals.

A statistical approach called latent class analysis was used to identify the dominant patterns of AD lesion distribution and revealed 5 different subsets. The most common subset (35.3% of adults with AD) consisted of lower probabilities of lesions affecting any sites, consistent with milder and less extensive disease. The second most common subset (26.9%) consisted of higher probabilities of lesions involving the anterior and posterior neck and trunk. The third most common subset (19.0%) consisted of higher probabilities of lesions involving the antecubital fossae and upper extremities. The fourth most common subset (9.7%) consisted of lesions involving the arms, posterior hands, genitals, and buttocks, and to a lesser extent face, palms, and legs. The least common subset (9.1%) consisted of higher probabilities of lesions affecting all sites, consistent with severe and more extensive disease.

Atopic Dermatitis Symptoms

There is a complex constellation of symptoms in AD, including pruritus, xerosis, pain, and sleep disturbance, which leads to a large impairment in quality of life.[27,42,43] A US population-based survey (AD in America study) found that pruritus was reported to be the most burdensome symptom by more than half of adults with AD (54.4%), followed by excessive dryness or scaling (19.6%) and red or inflamed skin (7.2%).[42] However, adults with moderate to severe AD in particular were less likely to report itch or excessive dryness and scaling as their most burdensome symptoms. Adults with moderate to severe AD were more likely to report that other symptoms were most burdensome, such as blisters or bumps, red or inflamed skin, sleep disturbance, pain, open sores, or oozing.

Pain

Skin pain has recently been recognized as an important symptom in AD. A prospective dermatology practice–based study of 305 adolescents and adults found that 42.7% of patients reported skin pain in the past week, with 13.8% reporting severe or very severe pain.[44] Skin pain was heterogeneous, with patients regarding pain as part of their itch (16.8%), secondary to scratching (11.2%), or both (72.0%). Patients with skin pain were more likely to describe their itch using descriptors similar to those used in neuropathic pain; for example, sharp, tingling, and pinpricklike. Patients with both severe itch and skin pain had even poorer quality of life and mental health symptoms than patients with either or neither being severe.

Pain from AD was reported in 61% of adults with AD from the AD in America study, of whom 33% experienced pain at least weekly and 22% reported severe pain (intensity $\geq$7).[45] AD pain was heterogeneous, with 27% reporting pain from open areas

caused by scratching, 27% from fissures, 25% from inflamed red skin, and only 10% from burning secondary to creams or ointments. AD severity and pain were correlated overall. However, pain from scratching was more likely in mild AD; constant pain and pain from inflamed skin were more likely in severe AD. Overall, 3.8% and 8.2% of adults with AD from the AD in America study reported that pain was the most or second most burdensome symptom of their AD; the proportion increased in those with moderate-severe AD.[42] Optimal treatment approaches for pain in AD have not yet been examined.

Sleep disturbance

Patients with AD have sleep disturbances secondary to severe itch and secondary itch-scratch cycle,[46] poor sleep hygiene, circadian rhythm–induced modification of itch,[47] and potentially secondary effects of inflammatory cytokines on sleep regulation.[48] Adults with AD were found to have poor sleep quality with less sleep, more frequent and prolonged awakening, overall lower sleep efficiency, and increased daytime dysfunction.[49–53] A US population-based study of 34,613 adults (2012 National Health Interview Survey) found that adults with self-reported AD were more likely to report fatigue, regular daytime sleepiness and regular insomnia (25%–33%), and either short or long sleep duration.[27] Adults with AD and sleep disturbances reported poorer overall health status, and a higher number of sick days and doctor visits.[27] Another US population-based study of 5563 adults (2005–2006 National Health and Nutrition Examination Survey) found that adults with AD were more likely to report short sleep duration, trouble falling asleep, nighttime awakenings, early morning awakenings, leg jerks, and leg cramps during sleep. They were more likely to feel unrested, being overly sleepy during the day and feeling as if they did not get enough sleep.[43] Sleep disturbances are well recognized to have detrimental effects throughout all fields of medicine, including poor school and work performance; impaired health-related quality of life[49,54–57]; increased direct and indirect costs for patients, payers, and society[49,54,56–58]; psychological distress[59,60]; motor vehicle accidents; and workplace injury.[61–63] Together, sleep disturbances seem to be both common and burdensome in children and adults with AD. In addition, sleep disturbances may be an important mediator of poor outcomes and the development of comorbid health conditions in adults with AD.

Profound sleep disturbances despite optimized topical therapy for AD should prompt consideration for stepping up treatment using oral systemic therapy, biologics, or phototherapy. Patients with AD can develop poor sleep hygiene over many years of being unable to fall or stay asleep at night; for example, watching late night movies or infomercials, or consumption of large amounts of caffeine or other stimulants to overcome fatigue. Efforts should also be made to improve the sleep hygiene of patients with AD. Adjunctive treatments should be considered to improve the sleep of adults with AD. Sedating antihistamines may improve patients' sleep, even though there is insufficient evidence to support their efficacy as a treatment of itch or inflammation in AD.[64] A recent randomized controlled trial of 48 Taiwanese children with AD found high-dose melatonin (3 g/d) was well tolerated and resulted in modest improvements of AD severity and decreased sleep-onset latency.[65] In addition, referral to a sleep medicine specialist may be warranted when sleep disturbances do not improve with optimal control of AD and/or adjunctive treatments for sleep.

Age of Onset

AD is typically reported to begin in the first year of life in 50% of cases and by age 5 years in 85%.[66–68] However, the cited studies included cohorts of children, but

did not assess adolescents or adults. As such, it is impossible to extrapolate about how commonly AD starts in adolescents or adults. Recent studies suggest there is considerable heterogeneity with respect to the course of AD in adults, including adult-onset AD.

A few studies examined whether adult-onset AD presents with distinct phenotypes compared with childhood-onset AD. Wang and colleagues[69] found that adult-onset AD (n = 407) versus pediatric-onset AD (n = 275) was associated with higher rates of dermatitis affecting the feet, with lower rates of dermatitis affecting the conjunctiva/eyelids (7.1% vs 21.8%), ears (9.6% vs 18.9%), and face (16.7% vs 51.3%). The study also found that adult-onset AD was more associated with the presence of vesicles and nodules (19.7% vs 9.8%; 13.8% vs 4%, respectively), and less associated with xerosis (55% vs 60.7%). Son and colleagues[70] found that adult-onset AD (n = 48) versus pediatric-onset AD (n = 232) was associated with higher rates of dermatitis affecting the head/neck (22.9% vs 16.4%), and possibly lower rates of dermatitis of the flexor surfaces of the extremities (29.2% vs 51.3%). The study also found that adult-onset AD was more associated with white dermatographism (4.2% vs 2.6%) and sign of Hertoghe (thinning or loss of outer third of eyebrows; 8.3% vs 3.9%), but less associated with xerosis (56.3% vs 63.8%) and pruritus after sweating (37.5% vs 51.3%). A recent study also examined phenotypical differences, and found that adult-onset AD (n = 149) versus pediatric-onset AD (n = 207) was associated with lower rates of dermatitis affecting the conjunctiva (24.2% vs 53.6%) and face (28.2% vs 57%); possibly more likely to present morphologically with nummular eczema (14.1% vs 5.8%); and was less associated with pruritus after sweating (60.4% vs 66.7%) and Dennie-Morgan fold (extra infraorbital crease; 10.7% vs 36.2%).[71] However, a US population-based study found no significant differences of lesional distribution by age of onset.

Patients with adult-onset AD were consistently found to have lower rates of conjunctivitis or any allergic disease in multiple studies, although higher rates of allergic rhinitis in some studies, lower rates of family history of allergic disease, but no differences in asthma.[72]

A systematic review and meta-analysis of 17 studies examining AD onset later than 10 years of age found that 26.1% of adults with AD reported adult onset of their disease overall, with all studies reporting substantial proportions of adult-onset AD.[72] AD onset was found to commonly occur even at middle and mature age. Most of the studies that found high proportions of childhood-onset AD only studied patients into early adulthood. Five studies retrospectively examined medical records and confirmed that patients with adult-onset AD did not have childhood AD.[39,40,73–75] Three studies followed patients prospectively and verified that the AD diagnosis was correct and did not change over time.[76–78] Thus, AD seems to commonly begin at all ages. Pediatric and adolescent studies may have missed this observation because they did not examine cohorts with older adults.

BURDEN OF ATOPIC DERMATITIS

AD is associated with a substantial patient burden and poor health-related quality of life secondary to its heterogeneous and often severe signs and symptoms.[79,80] The high prevalence and patient burden of AD made it one of the most burdensome skin disorders globally in 2013 in both children and adults.[81] A recent cross-sectional study of 2893 adults found significantly decreased short-form 6D health utility scores in adults with mild AD and even lower scores in moderate and severe AD.[82] AD was associated with higher total loss of quality of life–adjusted years than

autoimmune disorders, diabetes, food allergy, and heart disease in both men and women, indicating a major population or societal burden.[82]

In the United States, adults with AD reported significantly limited access to care with inability to afford prescription medications and inability to get a timely medical appointment, both contributing to delay of care or inadequate treatment.[83]

AD may also affect performance at school and/or work. Roughly one-third of patients with AD thought that their disease affected their occupational performance; 14% thought that AD negatively influenced their career trajectory.[51] Previous studies found that adults with AD are more likely to take sick leave,[84,85] retire early,[84] and change occupation.[85,86] In the United States, adults with AD were more likely to have greater than or equal to 6 half-days in bed and greater than or equal to 6 lost workdays from all causes, with approximately 6 million lost workdays from their eczema.[83]

Health care Use for Adult Atopic Dermatitis

A US population-based survey (AD in America study) found that outpatient use for AD was low in adults with mild AD (29.3%–34.7%) and increased in those with moderate (36.2%–49.8%) and severe (50.6%–86.6%) AD. AD severity was the major predictor of outpatient use, followed by timeliness of appointments, expenses, and insurance coverage. One in 10 adults with AD reported having greater than or equal to 1 urgent care, emergency department or hospital visit in the past year. Urgent care or emergency department visits were more common among adults with black and Hispanic race/ethnicity, lower household income, lower education level, and AD prescriptions being denied by their insurance companies. Similarly, US adults with AD (2010 and 2012 National Health Interview Survey) had more visits to doctors, urgent/emergency care, and hospitalizations.[83]

A study of the patterns and predictors of outpatient use (1993–2015 National Ambulatory Medical Care Survey) found that AD visits occurred predominantly at primary care providers (PCPs), followed by dermatologists, and far less commonly allergists.[87] The frequency of AD visits increased from 1996 to 2015 overall and particularly among PCPs. However, the frequency of AD visits to dermatologists decreased over time.[87] Adults with self-pay were more likely to see a dermatologist, whereas adults with comorbid allergic rhinitis or food allergies were more likely to see an allergist.[87] AD visits were more likely to be acute visits among PCPs, and chronic visits among dermatologists.[87]

A study of emergency department use in the United States (2006–2012 National Emergency Department Sample) estimated that the incidence of emergency department visits for AD or eczema significantly increased between 2006 and 2012. Emergency department visits with versus without a primary diagnosis of AD were associated with Medicaid or no insurance and lower household income quartiles, and were more likely to occur during weekends and summer months. These results suggest there are socioeconomic and health care disparities with respect to emergency department use and access to care in general for AD. The total costs of emergency department visits for AD significantly increased, from $127,275,080 in 2006 to $265,541,084 in 2012. In addition, hospitalizations for AD or eczema were estimated to have $8,288,083 and $3,333,868 total annual costs per year for US adults and children (2002–2012 National Inpatient Sample).[88] Further, adults with AD were estimated to have $371 to $489 higher out-of-pocket costs per person-year compared with those without AD (2010 and 2012 National Health Interview Survey).[83] Together, the outpatient, emergency department and inpatient direct costs and indirect costs of AD are estimated to be approximately $5.2 billion annually in the United States.[89]

COMORBIDITIES OF ATOPIC DERMATITIS

Emerging research has shown that AD is associated with numerous medical and mental health comorbidities in adults. However, much of the research into these comorbidities is nascent. There is strong evidence to support the association of AD with atopic disease, as well as depression, anxiety, and suicidality.

Atopic Disease

Several US population-based studies examined the prevalence of atopic comorbidities in adults with AD. The lifetime and 1-year prevalences of self-reported asthma were 25.5% and 18.7%; 1-year prevalence of allergic rhinitis was 28.4%; and 1-year history of food allergy was 13.2% (2012 National Health Interview Survey).[90] The lifetime prevalence of asthma and allergic rhinitis and 1-year prevalence of food allergy were increased in adults with more severe AD.[91] Eosinophilic esophagitis has more recently been recognized as a comorbidity of AD and atopic disease.[92] Patients with AD, particularly those with severe AD, warrant increased screening for the presence and control of comorbid atopic disease. There is an enormous body of literature examining the relationship of AD with atopic comorbidities that is beyond the scope of this review. Of note, AD can present in the context of systemic atopy, and exposure to allergens may exacerbate the AD or make it difficult to control. Aeroallergens (eg, dust mite) can contribute to allergic asthma and rhinoconjunctivitis, and in some patients may contribute to AD. Inhalation of house dust mite has been shown to exacerbate AD in sensitized patients. Patients with allergic rhinoconjunctivitis may rub their eyes and face, thereby worsening their AD on the eyelids and face. Screening for systemic atopy, treatment such as nasal steroids, and aeroallergen avoidance might therefore result in improved skin disease in some individuals, in addition to improving allergic airway disease. However, recent systematic reviews and meta-analyses found no consistent evidence of efficacy for dust mite reduction and avoidance measures alone[93] or specific allergen immunotherapy[94] in treating AD. Moreover, dust mite avoidance was not found to be effective for primary prevention of AD.[95] For patients with a history of worsening or difficult-to-control AD, or those with signs or symptoms on exposure to 1 or more potential allergens, referral to an allergist should be considered. AD can also be exacerbated by food exposures in a small subset of patients with AD, particularly in infants and young children with severe AD.[96] However, a systematic review of 9 studies found no benefit for unselected egg and cow's milk elimination diets in AD.[97] In addition, foods as a cause of AD exacerbation in adults is extremely rare. Thus, patients with AD should not be advised to empirically eliminate different foods from their diet. Rather, appropriate food allergy testing by an allergist should be considered in patients with persistent AD in spite of optimized management and topical therapy and/or a reliable history of an immediate allergic reaction after ingestion of foods, with careful interpretation of test results.[98]

Depression, Anxiety, and Suicidality

Two systematic reviews and meta-analyses examined the relationship of AD with depression, suicidal ideation, and/or anxiety. The first performed a meta-analyses of depression (n = 23 studies), anxiety (n = 13 studies), and suicidality (n = 6 studies), and found significant higher odds ratio of depression and anxiety in adults with AD, depression in children with AD, and suicidality in adults and adolescents with AD.[99] The second performed a meta-analysis of 36 studies and found that 1 in 5 persons with AD had depression[100] and patients with AD had higher rates of clinical depression, antidepressant use, and suicidality in adults.[100] Depression occurred particularly

in patients with moderate-severe AD.[100] AD was also associated with higher rates of depressive symptoms overall,[100] including having little interest in doing things, feeling down, feeling hopeless, feeling tired or having little energy, having a poor appetite, feeling bad about themselves, having difficulty concentrating, moving or speaking slowly or too fast, and having thoughts of being better off dead.[101]

Adults with AD had higher prevalences of abnormal (≥11) Hospital Anxiety and Depression Scale anxiety and depression subscores, particularly in more severe AD (AD in America study).[102] Importantly, 100% of respondents with severe scores for AD and itch had borderline or abnormal anxiety and depression scores. However, 13% to 55% of adults with AD who had borderline and/or abnormal anxiety or depression scores reported not being diagnosed with anxiety or depression. These results suggest that many patients with AD have undiagnosed anxiety and depression, and underscore the important of increased mental health screening in primary care and specialty practice settings.

Symptoms of anxiety and depression may be secondary to AD; that is, Diagnostic and Statistical Manual of Mental Disorders (DSM) IV Axis III disorders (secondary to a medical condition). In many (if not most) instances, these symptoms resolve with improved control of AD signs and symptoms. However, symptoms of anxiety and depression may be indicators of DSM-IV Axis I diagnoses, such as major depressive disorder or generalized anxiety disorder. It is important that clinicians managing patients with AD screen for anxiety and/or depression and treat or refer appropriately.

Other Comorbidities

Patients with AD were also found to have increased body mass index and/or obesity,[103,104] poor cardiovascular outcomes,[105] type II diabetes mellitus,[105] ocular complications such as atopic keratoconjunctivitis and keratoconus,[106–108] osteoporosis and fracture of bone or joint disease,[29,109] dental complications,[110] warts, and extracutaneous infections.[111] Many of these comorbidities are related to AD severity and poor long-term disease control. Future research is needed to determine the mechanisms of association between AD and comorbidities and optimize screening and treatment approaches for comorbidities.

DIAGNOSIS

Diagnostic Criteria

AD is diagnosed clinically based on a combination of history, physical examination, and ruling out other entities in the differential diagnosis. There are no specific diagnostic criteria for AD in adults. The diagnostic criteria of Hanifin and Rajka[112] (H-R) were developed for AD in children and adults in 1980 (**Box 1**) and are the most commonly used criteria in clinical trials of AD in both children and adults.[113] H-R criteria include flexural eczematous lesions as a major criterion. Early age of onset is a minor (but not major) criterion in H-R. Thus, a patient can meet the H-R criteria if they have adult-onset disease with flexural involvement. Further research is warranted to determine the optimal criteria for diagnosing adult-onset or adult-recurrent AD in clinical practice and trials. Formal diagnostic criteria are rarely used in clinical practice. However, they can be helpful in guiding clinicians toward the diagnosis of AD, particularly in adult-onset cases of eczema. However, all criteria for AD are imperfect. Other disorders, such as allergic contact dermatitis or cutaneous T-cell lymphoma, occasionally fulfill the clinical criteria for AD. Therefore, it is imperative that clinicians consider the broader differential diagnosis of AD in adults (**Box 2**). Of note, many disorders in the differential diagnosis of AD can mimic AD (eg, allergic

Box 1
Hanifin and Rajka diagnostic criteria for atopic dermatitis

- At least 3 major criteria:
  - Pruritus
  - Typical morphology and distribution (flexural lichenification/linearity in adults)
  - Chronic or chronically relapsing dermatitis
  - Personal or family history of atopy
- At least 3 of 23 minor criteria:
  - Xerosis
  - Ichthyosis, palmar hyperlinearity, or keratosis pilaris
  - Immediate skin-test reactivity
  - Increased serum IgE level
  - Early age of onset
  - Tendency toward cutaneous infections
  - Tendency toward nonspecific hand or foot dermatitis
  - Nipple eczema
  - Cheilitis
  - Recurrent conjunctivitis
  - Dennie-Morgan infraorbital fold
  - Keratoconus
  - Anterior subcapsular cataracts
  - Orbital darkening
  - Facial pallor or erythema
  - Pityriasis alba
  - Anterior neck folds
  - Itch when sweating
  - Intolerance to wool and lipid solvents
  - Perifollicular accentuation
  - Food intolerance
  - Course influenced by environmental or emotional factors
  - White dermatographism

From Hanifin J, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol (Stockh) 1980;92(Suppl):44-47; with permission.

contact dermatitis or cutaneous T-cell lymphoma) or develop as comorbid diagnoses in patients with long-standing AD (eg, allergic or irritant contact dermatitis).

Biopsy

Diagnostic testing is not required but can support the diagnosis of AD and exclude alternate diagnoses. Biopsy should be considered for lesions that are atypical appearing and/or refractory to conventional therapy. A punch biopsy with standard hematoxylin-eosin staining can be helpful to exclude other disorders that have distinct histologic patterns; for example, cutaneous T-cell lymphoma, psoriasis, and cutaneous lupus. Acute eczematous lesions are characterized by epidermal spongiosis and dermal perivascular mononuclear infiltrates with eosinophils and a predominance of T cells and presence of eosinophils. Chronic eczematous lesions are characterized hyperkeratosis, epidermal hyperplasia, irregular elongation of the rete ridges, and variable amounts of spongiosis and dermal eosinophils. These histologic patterns are found in other eczematous disorders and cannot distinguish AD from other eczematous disorders, such as allergic contact dermatitis, irritant contact dermatitis, or nummular dermatitis. An additional punch biopsy of perilesional skin and examination using direct immunofluorescence may help exclude autoimmune blistering disorders, such as bullous pemphigoid and dermatitis herpetiformis. Biopsies and

Box 2
Differential diagnosis of adult-onset atopic dermatitis

- Allergic contact dermatitis
- Irritant contact dermatitis
- Cutaneous T-cell lymphoma/Sezary syndrome
- Psoriasis
- Nummular dermatitis
- Cutaneous lupus
- Eczematous drug eruption
- Dermatomyositis
- Urticarial bullous pemphigoid
- Dermatitis herpetiformis
- Transient acantholytic dermatosis
- Seborrheic dermatitis
- Asteatotic eczema
- Skin infection (ie, impetigo)
- Molluscum dermatitis
- Langerhans cell histiocytosis
- Scabies
- Zinc deficiency
- Immunodeficiency (Wiskott-Aldrich syndrome, hyper-IgE syndrome)

histopathology have low reliability to distinguish between inflammatory skin diseases.[114] They cannot and should not substitute for a thorough history and physical examination.

Patch Testing

A multidisciplinary consensus guideline recommended that patch testing be performed in all patients with adolescent-onset or adult-onset AD, because allergic contact dermatitis can mimic AD.[115] Patients with AD that has worsened or become more generalized should also be patch tested, because there may be an allergenic trigger of their underlying AD. Patch testing is indicated in patients with a lesional distribution that is changing or atypical for AD, or one that is localized and suggestive of contact dermatitis, such as dermatitis of the head and neck, eyelids, hands, and feet. Nummular eczematous lesions can occur in patients with AD without evidence of allergic contact dermatitis,[71] but may be a sign of allergic contact dermatitis and warrant patch testing.[116,117]

Patients with AD have higher rates of positive patch test reactions to ingredients in their topical medications, including corticosteroids and antibiotics, and personal care products, including emollients, salves, and cleansers.[118–120] An expanded patch-testing screening series is recommended in order to assess these allergens, such as American Contact Dermatitis Society Core Allergen Series or North American Contact Dermatitis Group standard series, with supplemental allergen series as indicated.[120] The Thin-Layer Rapid Use Epicutaneous test lacks many of the allergens

previously found to be relevant in patients with AD and is generally inadequate in patients with AD.[120]

Other Laboratory Tests

Skin scrapings with in-office microscopic evaluation may be warranted to exclude scabies or fungal infections, which are important clinical disorders to exclude in patients presenting for a new-onset pruritic dermatitis.

Skin prick testing, total serum IgE, allergen-specific IgE, and peripheral eosinophil levels are not required to diagnose AD. These tests are not useful in patients with suspected adult-onset AD, which has been shown to be associated with lower rates of atopy and atopic disease than child-onset AD.[72] Moreover, food allergy testing is not routinely recommended for the assessment of AD in children or adults.

A white blood cell count may reveal abnormalities secondary to lymphoma. Severe pruritus in general and even classic-appearing AD can develop in patients as a paraneoplastic disorder in non-Hodgkin lymphoma. Anecdotally, I have observed multiple cases of severe pruritus and/or AD appearing as early as 1 to 2 years before the diagnosis of lymphoma. All patients with elderly onset of AD should have close clinical follow-up and be up to date with all age-appropriate malignancy screenings. This scenario can also occur in younger patients and should be considered in the differential diagnosis of severe generalized pruritus.

Genetic testing may help exclude immunodeficiencies that manifest with AD, such as Job syndrome. Of note, extreme increases of total serum IgE level (>10,000 IU/mL) are commonly found in patients with AD, particularly in those with moderate to severe disease. However, such extreme increases are typically not associated with recurrent infections, skeletal abnormalities, or other stigmata of Job syndrome or other immunodeficiencies. Work-up for immunodeficiencies should be prompted by a relevant clinical history, and not only by very high IgE levels.

Other laboratory tests are rarely needed and the clinical scenario should guide their use. Antineutrophil cytoplasmic antibody may help exclude Churg-Strauss syndrome, which can manifest with a classic presentation of AD and/or asthma.[121] Antinuclear antibody, complement levels, erythrocyte sedimentation rate, and other laboratory testing may help exclude systemic lupus erythematosus or other autoimmune disorders. Indirect immunofluorescence may be helpful to exclude autoimmune blistering disease. Testing for human immunodeficiency virus (HIV) may be indicated to rule out atopiclike dermatitis in HIV in patients with specific risk factors and/or other stigmata of HIV (eg, increased infections).[122] Testing may be indicated for syphilis, which rarely can present with an eczematous pattern.[123]

TREATMENT

There are no treatment guidelines specifically for adult AD. Current AD treatment guidelines for adults and children recommend a step-care approach.[124,125] Patient education should encourage gentle skincare, bathing practices, trigger avoidance, and appropriate use of moisturizers and emollients. Regular tap water baths have been shown to be effective at reducing AD severity. A recent meta-analysis found that bleach baths were no more effective than water baths.[126] Patients should be encouraged to shower or bath daily using gentle nonsoap cleansers, avoid excessively prolonged water-exposure time or use of scalding hot water, and apply moisturizers immediately after drying off.[126] Patients may require additional application of moisturizers throughout the day to offset severe xerosis, particularly during colder weather months. The choice of emollients should be based on patient preference, with

ointments generally being more effective and creams and lotions being more patient friendly. Moisturizers and emollients have shown good efficacy in AD and may have adequate efficacy as a monotherapy in the mildest forms of AD. However, they have inadequate efficacy as a monotherapy in many cases of mild AD and virtually all cases of moderate or severe AD. The next treatment step includes adding antiinflammatory agents, such as topical corticosteroids (TCSs), calcineurin inhibitors (TCIs), and/or phosphodiesterase E4 (PDE4) inhibitors. Midpotency TCSs (eg, triamcinolone and mometasone) can be applied to most body sites with AD lesions. Superpotent TCSs (eg, betamethasone and clobetasol) should be reserved for refractory lesions. Mild-potency TCS (eg, desonide or hydrocortisone) and steroid-sparing agents (eg, TCI and PDE4 inhibitors) can be used in sensitive areas, such as face, axillae, and groin. Once-daily application of TCS, TCI, or PDE4 inhibitors can be effective to treat active lesions, although twice-daily is more effective than once-daily application. TCS should not be applied to the same skin areas daily for more than 3 to 4 consecutive weeks owing to concern about skin atrophy. TCS and TCI can also be applied proactively 1 to 2 times a week to clear skin in areas prone to flaring in order to prevent recurrent flares. When optimal use of topical therapy is inadequate, the next treatment step includes adding oral systemic therapy, biologic therapy, and/or phototherapy. Patients with inadequate response to topical therapy in the primary care setting should be referred to an appropriate AD specialist for advanced treatment. Topical and/or oral antibiotics should only be used for frank skin infections, and are not recommended for the treatment of AD.[127]

SUMMARY

AD is common in adulthood, and is associated with a large patient-based and population-based burden. Adult AD shares many common features with childhood AD, although it has different epidemiology, immune phenotypes, and clinical manifestations in adults than in children. AD has a very negative effect on quality of life in both children and adults so referral to a specialist should be considered in patients whose AD is difficult to control or refractory to therapy. Newer, more targeted therapies, including biologics, are available but further research is necessary to better understand the pathogenesis and optimal treatment approaches in adult AD.

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