



Skin diseases associated with atopic dermatitis

Justine Fenner, BS, Nanette B. Silverberg, MD*

Department of Dermatology, Mt Sinai West, Icahn School of Medicine at Mt Sinai, New York, New York, USA



Abstract Atopic dermatitis (AD) is a common chronic pruritic inflammatory skin disorder, characterized by an abnormal skin barrier, immune dysfunction, and an altered skin microbiome. AD may be seen in conjunction with a variety of other skin disorders due to the complex pathogenesis of AD, involving genetic and environmental factors that are associated with immune dysfunction, barrier defects, and altered skin microbiomes. Skin disorders associated with AD include diseases sharing similar genetic origins like ichthyosis vulgaris, infectious diseases such as impetigo, and eczema herpeticum, in addition to the cutaneous autoimmune diseases, alopecia areata, and vitiligo. AD is also often linked to such benign conditions as pityriasis alba and keratosis pilaris. This review discusses the cutaneous comorbidities of AD and their relationship via their occurrence in conjunction with atopic dermatitis.

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Introduction

Atopic dermatitis (AD) is a common, chronic inflammatory skin condition with an increasing prevalence over the past 30 years.¹ The presentation of AD depends on age and ranges from weeping papulovesicles to lichenified plaques.² The pathogenesis of AD is multifactorial, including genetic and environmental factors. (See [Figure 1](#).)

AD is characterized by skin barrier defects, immunologic dysfunction, and alterations in the skin microbiome. As a result of these deficits, AD is also seen with a variety of comorbidities, including those of genetic, infectious, and autoimmune etiology. Barrier defects resulting from filaggrin mutation and/or acquired deficiency result in overlap with ichthyosis vulgaris and keratosis pilaris. Barrier defects also result in increased allergic, irritant, and bacterial penetration,

leading to contact dermatitis and infection. Inflammation due to allergic, irritant, and bacterial penetration is facilitated by an abnormal immune response found in AD patients. This abnormal immune response also results or contributes to the pathogenesis of comorbid autoimmune diseases such as alopecia areata (AA) and vitiligo. We have reviewed the published literature for skin diseases associated with AD through PubMed searches and augmented by an analysis of selective references from these publications.

Barrier defects

Ichthyosis vulgaris

Ichthyosis vulgaris (IV) is a group of disorders characterized by abnormal skin barrier function, keratinization, and desquamation.^{3, 4} IV is the most common form of ichthyosis with an incidence of up to 1 in 250.³ There is strong evidence showing that certain populations with IV are at increased risk of

* Corresponding author. Tel.: +1 212 523 3888.

E-mail address: nanette.silverberg@mountsinai.org (N.B. Silverberg).

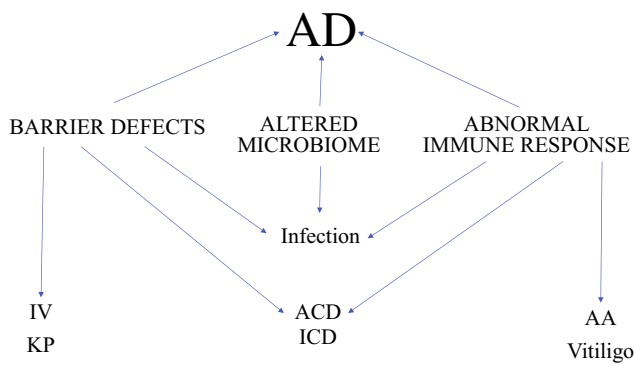


Fig. 1. Atopic dermatitis skin comorbidities.

AD^{5–7} due to shared altered genetics between the diseases. IV is caused by a loss of function mutation in the *filaggrin* (FLG) gene, resulting in xerosis and scaling.⁸ FLG and its byproducts are essential for normal stratum corneum biogenesis and physiology and constitute a large component of the natural moisturizing factor.⁹ FLG mutations result in reduction of skin hydration, elevated skin surface pH, and increased transepidermal water loss.⁸ The degree of FLG deficiency correlates with the risk for AD. An Irish case-control study found that the five most common European mutations showed a strong association with moderate to severe childhood AD.⁷ Patients with two FLG null mutations express no protein and had a massive risk of AD, where virtually all individuals with this mutation developed AD (OR 151.85, 95% CI 20.29–1136.46, $P = 2.1 \times 10^{-20}$).⁷ Patients with heterozygous mutations have about half of the normal amount of FLG in their skin and had a high risk of AD (OR 7.44, 95% CI 4.9–11.3, $P = 9.56 \times 10^{-19}$).⁷

FLG deficiency is believed to contribute to atopy by way of cutaneous antigen priming, which can cause development of a systemic allergic immune response in the skin or lungs.¹⁰ As might be predicted, FLG mutations have been associated with asthma, hay fever, and food allergy as well.¹¹ Mice models have shown that FLG deficiency allows allergens to cross the epidermis easily and trigger a type 2 T help cell allergic response.¹²

The association between IV and AD is significant for a variety of reasons. Patients with both AD and IV are at an increased risk for developing asthma and allergies.³ Additionally, treatment of IV usually involves salicylic acid, lactic acid, or urea lotion, cream, or ointment, which may also be beneficial in the care of AD. Although these products help to moisturize the skin in IV, they can cause irritation in some AD patients.³

Keratosis pilaris

Keratosis pilaris (KP), being a common but benign skin condition, affects nearly 50%–80% of adolescents and 40% of adults.¹³ Although KP is commonly encountered in clinical practice, there is little information about the condition in the

medical literature.¹⁴ KP is an autosomal dominant disorder, characterized by keratinous plugs in the follicular orifices with varying degrees of perifollicular erythema. Although most people with KP are asymptomatic, patients are often disturbed by the cosmetic appearance of the condition. KP is associated with AD as well as IV^{15–17} and is considered a minor criterion in the Hanifin and Rajka Criteria for Atopic Dermatitis and an associated feature of AD by the American Academy of Dermatology Guidelines.¹⁸ The association between AD and KP may result from some shared genetic mutations.

Although the etiopathogenesis of KP remains unknown, like AD, it has been associated with FLG mutations.^{19, 20} A recent study with 20 Caucasian KP patients from California and Austria having a median age of 31 years revealed that 35% of these patients displayed common null mutations in FLG, which is significantly higher than the study's control population of 5% and the averaged carrier frequency of 4%–9% in Europe.¹⁹ It is possible that follicular abnormalities in KP result from FLG deficiency. Additionally, all patients with KP, regardless of FLG status, showed acanthosis and hypergranulosis on biopsy, most likely reflecting hyperplasia due to barrier abnormalities. The abnormal barrier in KP may facilitate the development of AD through increased allergen penetrance through the epidermis. Treatment of KP is challenging, and no controlled clinical trials have been found in the literature. Emollients, topical keratolytics, and retinoid containing agents are often used with some effect, but cure does not exist.¹⁴

Pityriasis alba

Pityriasis alba (PA) is also a common condition found in children and adolescents. Similar to KP, PA is associated with AD and is considered a minor diagnostic criterion in the Hanifin and Rajka Criteria for Atopic Dermatitis and an associated feature of AD by the American Academy of Dermatology Guidelines.^{18, 21} PA is characterized by poorly circumscribed, hypopigmented patches on the face and proximal area of the arms. Lesions often become more prominent during the summer as the unaffected skin tans, making hypopigmentation areas more prominent on sun-exposed skin.

There are three clinical variants of PA: classic, extensive, and pigmented.

1. The classic presentation is the most common form, affecting primarily school-aged children of both sexes.²²
2. Extensive PA is less common and often affects teenagers and young adults, with a female predominance. Lesions are not limited to the face and often involve the neck, shoulders, trunk, and arms.^{23, 24}
3. The least common variety is pigmented PA, which has only been identified in non-Caucasian individuals and presents with tinted blue lesion, from melanin deposition and with a halo of depigmentation.²⁵ This form of PA may be differentiated from trichrome vitiligo through biopsy.

The cause of PA is unknown, whereas the hypopigmentation may be caused by inflammation and aggravated by a lack of tanning in the inflamed skin.^{20, 26} Additionally, no infectious etiology has been identified.^{25, 27} PA resolves spontaneously over the course of months to years, and the principles of treatment are mainly reassurance and trigger avoidance.²⁸ Parents and patients should be reassured about this harmless self-resolving condition. Sun avoidance and use of sunscreen can help prevent accentuation of the hypopigmented lesions. Emollients may be used to minimize scaling but will not aid in repigmentation.²¹ Agents that have been documented as efficacious in the treatment of PA include tacrolimus, pimecrolimus, and calcitriol.^{25, 29, 30} Treatment is often not carried out due to the benign self-resolving nature of the condition, the slow response to therapy, and the concomitant high cost of treatment options.²⁸

Barrier defects and an abnormal immune response

Contact dermatitis

Contact dermatitis may be considered as two types: allergic and irritant contact dermatitis, the former being caused by an immune reaction and the latter the result of sensitivity.

Allergic contact dermatitis

The relationship between AD and allergic contact dermatitis (ACD) is controversial due to difficulties in clinical differentiation and concomitant risk factors.³¹ ACD is a type IV hypersensitivity reaction, resulting from exposure to a cutaneous allergen in a presensitized individual.³² In theory, the impaired skin barrier of AD would permit penetration of allergens. Additionally, children with AD are exposed at an early age to topical agents that have the potential to cause ACD with prolonged usage over an impaired skin barrier.³³

ACD is confirmed by patch testing.³² Patch testing may complement the diagnosis of AD by detecting allergens that could be aggravating and preventing treatment of underlying disease.³³ The number of positive patch test results in children has been increasing in recent years, resulting in several systematic reviews.^{32, 34, 35} A 2017 meta-analysis of 56 studies found no significant correlation between AD and contact sensitization overall. Subgroup analysis of 24 studies also found no association between ACD and AD in pediatric patients. Interestingly, there was a positive correlation in studies that compared AD to patients in the general population (OR 1.50, 95% CI 1.23-1.93), but an inverse association when comparing patients from within a referred population (OR 0.753, 95% CI 0.63-0.90).³² A different 2017 systematic review, including 31 studies, found that the prevalence of contact allergy was significantly higher among children without AD compared with patients with AD.³⁵

Discordance among these major reviews highlights the dynamic and complex nature of this association. This is even further shown by a recent large retrospective case review of North American Pediatric Contact Dermatitis Registry data, which had compared children with and without AD for individual contact sensitizers. In this series of 1142 children analyzed, patients with AD had a different reaction profile compared with patients without AD. Patients with AD were more likely to react to cocamidopropyl betaine, wool alcohol, lanolin, tixocortol pivalate, and parthenolide. These sensitizers are frequently present in skin care products and topical medications. Conversely, patients with AD were less likely to react to methylisothiazolinone, cobalt, and potassium dichromate.³³ Asian and African-American children with AD were more likely to have contact allergies. Currently, the AAD Guidelines suggest excluding a component of CD in individuals with AD through patch testing, when appropriate.^{35, 36}

Irritant contact dermatitis

The relationship between AD and irritant contact dermatitis (ICD) is better defined than the relationship of AD and ACD. Although epidemiologic data suggest that patients with AD are more prone to acute irritation than the normal population, controlled experiments have less consistent findings.³⁷⁻³⁹ ICD occurs by way of activation of the innate immune response by keratinocytes after exposure to irritants, such as soaps, detergents, disinfectants, and water.^{40, 41} Interestingly, irritant exposure in ICD may decrease the threshold for generating ACD reactions. This threshold may be decreased even further in AD patients with defective skin barriers.⁴⁰

The mechanism by which AD affects the development of ICD is unknown but theorized to involve impaired epidermal barrier function and FLG deficiency.⁴¹ FLG is important for the maintenance of the stratum corneum, being the main barrier. Reduction in levels of FLG may allow for increased penetration of irritants through the skin resulting in inflammation.⁴¹

There is an association of FLG loss of function mutations with ICD, even when adjusted for AD (OR 1.61; 95% CI 1.01-2.58), according to a study consisted of 634 patients, 62% of which were women, with a median age of 43. A history of AD increased the risk to develop ICD approximately threefold (OR 2.89; 95% CI 2.08-4.03). Additionally, according to the regression model, the presence of both AD and FLG mutations would result in a 4.7-fold increased risk.⁴¹

The fact that AD had a more profound effect than FLG loss of function mutation on ICD development suggests that other factors, such as a more sensitive inflammatory response, play a role in ICD development. AD patients with FLG mutations have elevated levels of pro-inflammatory cytokines, which may facilitate the immune response after exposure to irritating chemicals.⁴² Additionally, FLG-deficient mice have been shown to have a reduced threshold for inflammation.^{39, 43}

Hand dermatitis

The association between AD and hand dermatitis (HD) is well known.^{38, 44–47} Although AD is the single most important risk factor for HD, exposure to irritants is the most common cause of occupational HD.⁴⁸ The association is strongest in patients with severe AD, persistent AD on parts of the body other than the hands, and patients with atopic HD since childhood.^{38, 49} AD has also been associated with more severe HD.^{38, 50} A thorough history sometimes may help in determining whether the dermatitis is irritant, allergic, or due to protein exposure at work and home.⁴⁸

Cutaneous infections

Many studies have found higher rates of infection, both cutaneous and extracutaneous, in patients with AD.^{51–56}

Bacterial infections

The most frequent of skin infections in AD is caused by *Staphylococcus aureus*, and *Streptococcus pyogenes* infection is also relatively common.⁵⁷ Colonization with *S. aureus* is part of the normal phenotype in AD, and its presence is not enough to indicate infection without the signs of impetiginization, that is, weeping, crusting, presence of small superficial pustules, and periauricular fissuring.⁵⁸ A recent cohort study with more than 3 million subjects with a mean age 13.7 found that patients with AD were 55% more likely to develop impetigo compared with subjects without AD after controlling for age, sex, and time under observation (OR 1.55, 95% CI 1.47–1.64).⁵⁵

The role of infection and *S. aureus* in AD is complex, because patients with AD appear to be at increased risk for infection, but infection can also exacerbate AD and trigger the accompanying viscous cycle of skin disease.⁵⁷ Patients with AD are colonized with *S. aureus* at higher rates than healthy controls contributing to the increased risk of infection.^{59, 60} Additionally, patients with AD, especially those with more severe disease, are more likely colonized with methicillin resistant *S. aureus* (MRSA).^{57, 61} MRSA produces more superantigens, and patients colonized with MRSA are more likely to develop skin and soft tissue infections.^{62, 63}

Viral infections

Although less common, patients with AD are also at risk for viral infections, including eczema herpeticum (EH), eczema vaccinatum, and eczema coxsackium.⁵⁷ EH is one of the most common viral infections in AD with potentially serious complications. In EH, *Herpes simplex* virus infection (HSV) may result in disseminated vesicles, viremia, and fever.⁶⁴ More serious complications include keratoconjunctivitis and meningitis. Although the majority of patients have serologic

evidence of HSV1 exposure during their lifetime, only 3% of AD patients develop disseminated cutaneous HSV infection.⁵¹

This suggests that EH infection is the result of more than just environmental factors. Risk factors for the development of EH include severe and early onset AD, high serum IgE/eosinophils, and the presence of allergic diseases.^{51, 57} Reduced epidermal plasmacytoid dendritic cells and reduced production of interferon have been described as contributory.⁶⁵ Despite the environmental issues, there is significant evidence to show that EH in the setting of AD reflects the atopic patient's inability to produce such intrinsic antiviral molecules as cathelicidin and human beta defensin 2 and 3, allowing for viral disease spread across the cutaneous surface.⁶⁶

Eczema vaccinatum (EV) may occur in AD patients after small pox vaccination. This disease is poorly studied, because small pox vaccine is not routinely given at this time due to the prior WHO declaration of disease eradication in 1980, and smallpox vaccination is contraindicated in patients with AD. It is speculated that whatever mechanism increases the risk of EH in AD patients, likely contributes to EV infection as well.¹⁶ Like EH, EV has an association with reduced human beta defensin 2 and cathelicidin antimicrobial peptide LL-37 production in response to cutaneous viral infection.⁶⁷

Similarly, AD patients exposed to the coxsackie virus can develop eczema coxsackium (EC). Although EC is not deadly, it can present similarly with extensive vesicle eruptions and skin breakdown.⁶⁴ Severe widespread vesiculation, Gianotti Crosti–like appearance, and hand and foot severe dactylitis have been described to be seen in EC.⁶⁸

The association between other cutaneous viral infections and AD is not as well established. Some studies have found increased rates of molluscum contagiosum (MC) in AD, whereas other studies have found no such correlation.^{55, 69–73} MC is caused by the poxvirus and results in one or more smooth umbilicated, flesh colored, dome-shaped lesions.^{69–71} Individuals with AD are thought to be susceptible to more severe and widespread infection.⁶⁴ Studies have also found that patients in whom EH develops are more likely to develop molluscum contagiosum,⁵¹ suggesting that poor cutaneous production of cathelicidin and beta defensin may contribute to disease acquisition and/or spread of MCV in AD patients

Warts are common benign tumors of the skin and mucous membranes caused by human papilloma virus (HPV) infection.⁷⁴ Some studies have found that patients with AD are no more likely to be treated for warts^{53, 75–77}; however, a recent study from the 2007 National Health Interview Survey with more than 9000 children found that whereas patients with AD alone are at no greater risk for warts, patients with AD and other atopic disease are at greater risk for warts.⁵³ In the same study, patients with AD and warts had more infections than those with either disorder alone. Additionally, patients with AD with warts had even higher odds of asthma, hay fever, and food allergies than those with AD and no warts. These are intriguing observations that suggest that warts are a sign of greater immunologic dysfunction or impaired barrier protection in AD patients. A recent retrospective case-control study

with 1160 adult white women found that AD was associated with high-risk cervical HPV infection (OR 3.75, 95% CI 1.3-10.9, $P = 0.02$) after controlling for age and marital status.⁷⁸ Case reports of other HPV infections associated with AD have been published, including a case of multiple Bowenoid diseases and a case of lower leg verrucosis.^{79, 80}

Fungal infections

Fungi, including *Malassezia* species, are a part of the healthy skin flora, comprising up to 22% of the skin microbiome.^{81, 82} Surprisingly, studies comparing AD patients with healthy individuals have found no difference in frequency of skin colonization with *Malassezia* species.⁸¹ Despite a lack of difference in the frequency of *Malassezia* colonization between AD and healthy individuals, there does seem to be a difference in the way the immune system of AD patients interacts with the yeast. *Malassezia*-specific IgG and IgM can be detected in healthy individuals as a result of normal skin flora interactions with skin immune cells. Conversely, *Malassezia*-specific IgE is hardly detected in the skin of healthy individuals.⁸³ In contrast, a high proportion of AD patients exhibit IgE-mediated sensitization to *Malassezia* species, as shown by positive skin prick tests.⁸⁴⁻⁸⁷ The rate of IgE-mediated *Malassezia* sensitization has been shown to correlate with disease severity.⁸⁸⁻⁹⁰ Interestingly, sensitization rates to *Malassezia* species are higher in patients with head and neck AD.⁹¹ This is believed to be due to the fact that the yeast has a predilection for seborrheic areas rich in lipids. It is unclear whether increased IgE sensitization in AD plays a pathogenic role or is simply a response to allergen exposure.

The defective skin barrier found in AD may allow *Malassezia* yeast cells and their allergens to enter the skin more readily and be taken up by Langerhans cells, resulting in inflammation. *Malassezia* causes inflammation by facilitating the maturation of dendritic cells and resulting in proinflammatory cytokine production. *Malassezia* is also known to induce a Th-2 cell response and activate the alternative complement pathway.⁹²

The role of other fungal species in AD is not as well studied. Similar to *Malassezia*, no differences in frequency of *Candida* species colonization have been found between AD patients and healthy individuals.⁹³⁻⁹⁵ The level of IgE antibody to *Candida albicans* has been found to be significantly higher in AD patients than in controls.^{93, 96} IgE levels to *Candida* have also been shown to correlate with disease severity.⁹⁷ AD has additionally been shown to be associated with dermatophyte infection, including *Trichophyton* species,^{55, 97-100} and potentially tinea incognito when topical corticosteroids are applied over tinea.

Trials studying the role of antifungal in AD have had ambiguous results.⁸¹ A placebo controlled trial with miconazole-hydrocortisone cream with ketoconazole shampoo appears to have no benefit over hydrocortisone alone in patients with head and neck-type AD.¹⁰¹ Some studies have shown that treatment with oral antifungals diminishes AD severity,

whereas others have found no benefit.¹⁰¹⁻¹⁰⁴ Antifungals may diminish AD as a result of their antiinflammatory properties. Azoles have been shown to inhibit production of IL-4 and IL-5 by T cells.¹⁰⁵ More large-scale, randomized placebo controlled trials are needed to assess the role of antifungal therapy in AD before recommendations can be made.

The cause of increased susceptibility to infection in AD is poorly understood but believed to result from skin barrier defects, altered immunologic function, and variation in the patient's microbiome.⁵⁷ Barrier defects is a universal feature of AD, but not all patients with AD are at risk for cutaneous infections.⁵⁷ Patients with FLG mutations are seven times more likely to have over four episodes of skin infections requiring antibiotics in a year.¹⁰⁶ Immunologic deficits found in AD include decreased antimicrobial peptides, increased skin pH, and increased Th2 cytokines, including IL-4 and IL-13. Genetic variants in the innate immune response, such as thymic stromal lymphopoietin, type 1 and 2 interferon, and molecular pathways that result in production of abnormal interferons, are also believed to play a role.

Changes in the integrity of the skin barrier may alter the microbiome diversity in AD. AD severity has been shown to correlate inversely with microbiome diversity.¹⁰⁷ AD patients are known to be colonized with *S. aureus*, which may contribute to an increased risk of infection through production of virulence factors. As an example, α -toxin produced by *S. aureus* is known to enhance HSV infections in AD by increasing the number of HSV copies in keratinocytes.¹⁰⁸ Although the precise mechanism of increased susceptibility to infection in AD is unknown, this association may lead to severe and potential fatal complications if left untreated.

Abnormal immune response

Autoimmune skin diseases

AD has been linked to autoimmune skin conditions, including lupus erythematosus, vitiligo, and AA.¹⁰⁹⁻¹¹² Genome-wide association studies have identified 31 genes/loci associated with AD, some of which share associations with other autoimmune diseases. The *UBASH3 A* gene may correlate with multiple autoimmune diseases, including AD susceptibility.¹¹³ A review of 22 studies found that patients suffering from autoimmune diseases of the skin and intestine were more likely to have comorbid AD.¹¹⁴ Conflicting evidence has been published regarding other systemic autoimmune diseases and AD, including rheumatoid arthritis, type 1 diabetes, and inflammatory bowel disease.^{112, 115-121}

Alopecia areata

Alopecia areata (AA) represents an organ-specific autoimmune disease of the hair follicle¹²² and is characterized by round or oval patches of hair loss. If the entire scalp is

involved, the disease is called alopecia total (AT). If the hair of the entire body is lost the disease is called alopecia universal (AU). Several studies have investigated the association between AA and AD.^{109, 111, 123, 124} A recent meta-analysis identified 17 studies observing the link between AD and AA.¹¹¹ While pooled analysis of these studies identified 2-3 times higher odds of AD in patients with AA compared with controls, all but 3 studies were excluded due to the lack of a control group (OR 2.57, 95% CI 2.25-2.94, $P < 0.001$). Included studies consisted of a case-control study and two cross-sectional studies with a combined total of 1296 patients with AA. Studies were from the United States, India, and Taiwan. Additional pooled analysis of four studies found higher odds of AD in patients with more severe alopecia, including AT or AU compared with those with patchy alopecia (OR 1.22, 95% CI 1.01-1.48, $P = 0.04$). These associations should be taken with caution, because 8 out of the 14 studies, which were not included due to lack of a control group, had found an AD prevalence in AA patients within or below the prevalence of the study location. This lack of difference may be due to differences in age, as patients from studies were generally adults, whereas data for location prevalence came from children. Additionally, most of the studies were not considered of high quality, with major deficiencies and poor reporting measures.

More recent studies have also found a correlation between AD and AA.^{112, 123} A cross-sectional Danish study with 8112 patients with AD found a strong association between AD and AA (OR 26.31, 95% CI 14.48-47.80 $P < 0.001$).¹¹² Results were adjusted for age, sex, smoking, socioeconomic status, and number of dermatologist visits. An ongoing prospective cohort study of female U.S. registered nurses with 87,447 patients with AA also found that AD was associated with increased risk of developing AA (OR 1.80, 95% CI 1.18-2.76) over the 2-year study follow-up.¹²³ The mean age for this predominately white population was 54.5.

Vitiligo

Vitiligo, as a common autoimmune disorder, has been linked to AD.¹²⁵ A recent meta-analysis identified 16 studies observing the link between AD and vitiligo. Unfortunately, only two studies contained control groups. Meta-analysis of the two cross-sectional studies found higher odds of AD in patients with vitiligo (OR 7.82, 95% CI 3.06-20.00, $P < 0.001$). These studies were conducted in Turkey and Italy. One reported the median age to be 34.9 (53%-58% women), whereas the other included children 12-17 years old (49% girls). Pooled analysis of three studies found higher odds of AD in patients with early-onset vitiligo (<12 years), compared with those with late-onset vitiligo (OR 3.54, 95% CI 2.24-5.63, $P < 0.001$). A single study found the observed AD prevalence to be higher in patients with extensive vitiligo, defined as more than 75% body surface area. Similar to this group's findings in AA,

12 out of 14 studies, which were not included due to lack of control, found AD prevalence to be lower or within the range of prevalence in the location of the investigation.

More recent studies have also found a correlation between AD and vitiligo.^{112, 123} The prior mentioned study from Denmark found increased odds of AD in patients with vitiligo (OR 20.10, 95% CI 8.76-45.95, $P < 0.001$). Additionally, the ongoing prospective cohort study of female U.S. registered nurses with 87,406 patients with vitiligo found increased odds of AD in patients with vitiligo (OR 17.98, 95% CI 7.70-42.01).

A 2017 review, including studies from 2000 to 2016, further analyzed the association between AD and autoimmune diseases. This review identified three large-scale studies, analyzing the association between AD and AA.¹¹⁴ All three studies shown a statistically significant association between AD and AA with odd ratios (OR) ranging from 1.7 to 2.34. All studies were of case-control design with between 2613 and 1.64 million subjects. Two studies included adult populations, whereas one study included patients between 0 and 18 years of age. The same review identified five studies analyzing the link between AD and vitiligo.¹¹⁴ All but one study found a statistically significant association between AD and vitiligo. One large case-control study analyzed the prevalence of vitiligo in patients with AD and found a significantly higher prevalence of vitiligo in AD patients (prevalence ratio, 3.26; 95% CI, 2.51-4.22) than in controls. The remaining three studies, one case-control and two case series, studied the prevalence of AD in patients with vitiligo. One study reported a relative risk of 2.70 (95% CI, 1.00-2.79). The other two studies reported odds ratio of 1.52 (95% CI, 1.41-1.63) and 1.71 (95% CI, 1.26-2.31). The latter found an association between AD and vitiligo in patients with vitiligo involving at least 76% body surface area.

The mechanism of the link between patients with autoimmune disease and AD is unknown at this time; however, shared genetics are believed to play a role.¹¹¹ A recent multiethnic genome-wide association study of 21,000 cases found new risk loci for AD that include genes with roles in regulation of the innate immune response and T cell function.^{112, 126} Although these findings suggest a possible contribution of autoimmune mechanism to AD pathogenesis, more evidence is needed to establish a relationship. Additional evidence for a genetic role is found in the fact that AD gene mutations are associated with more severe AA in patients with comorbid AD.¹²⁷ Common pathways may be activated in these disorders, including T helper and thymic stromal lymphopoietin.¹¹¹ Links between AD, AA, and vitiligo may have therapeutic implications, as all have been reported to respond to inhibition of the JAK-STAT pathway.¹²³ Patients with AD and AA may both respond to ustekinumab, an anti-p40 IL-12/23 monoclonal antibody. Patients with more than one of these conditions may benefit from treatments that affect a common pathway in these diseases.

Other

Case reports of other diseases associated with AD include lichen amyloidosis, mycosis fungoides, and palmar-plantar keratoderma of Unna.^{128–135}

Conclusions

We have reviewed the major skin diseases associated with AD. Causes for overlap can include joint genetics, overlapping pathogenesis or triggers, environmental triggering, poor production of antimicrobial substances, and chronicity of the weakened skin barrier. The variety of skin conditions associated with AD range from dry skin, dermatitis, irritant-caused disease, to autoimmunity and point to the fact that AD is not one illness but a broad chronic derangement of the skin function largely in the immune and barrier realms. Larger studies are needed to show a true correlation between other forms of cutaneous inflammation and autoimmunity and AD.

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