

## Diagnosis, comorbidity, and psychosocial impact of atopic dermatitis

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### ■ Abstract

Atopic dermatitis (AD) is a chronic inflammatory skin disease, with a remitting relapsing course. The central diagnostic features of AD include pruritus, xerosis, eczematous lesions with a characteristic morphology and distribution, and a personal or family history of atopic disease. Several clinical studies have emphasized the link between AD and other atopic disorders including asthma, allergic rhinitis, and food allergies. More recent studies indicate possible links between AD and other nonatopic disorders, including ADHD, sleep disturbance, and mental health disorders, suggesting an even more profound impact of this disease. Furthermore, the social, emotional, and personal impact of AD for patients and their caregivers is substantial. Understanding both the clinical characteristics and implications of AD is critical to lessening the psychosocial, clinical, and economic burden of this disease.

Semin Cutan Med Surg 36:95-99© 2017 Frontline Medical Communications

**A**topic dermatitis (AD) is a chronic inflammatory skin disease, with a remitting, relapsing course. The fundamental diagnostic features of AD include pruritus, xerosis, eczematous lesions with a characteristic morphology and distribution, and a personal or family history of atopic disease. Numerous investigations have highlighted the association between AD and other atopy-related disorders including asthma, allergic rhinitis, and food allergies. More recently, studies suggest potential links between AD and nonatopic conditions, such as ADHD, sleep disturbance, and mental health disorders alluding to the deeper impact of the disease.

The social, emotional, and personal impact of AD for patients and their caregivers cannot be overstated. It is to be noted nearly half of AD patients are 18 years of age and younger, pointing to the significant impact on caregivers and family resources. Understanding both the clinical features and implications of AD is key to decreasing the clinical, psychosocial, and economic burden of the disease. The purpose of this review is to deliver up-to-date information regarding the diagnosis, comorbidities, and psychosocial impact of AD.

### Diagnosis

A diagnosis of AD is usually made by clinical evaluation, based upon the presence of essential, important, and associated features.<sup>1</sup> The essential diagnostic features of AD include a chronic relapsing dermatitis with pruritus, often present in an age-specific distribution. Eczematous dermatitis is primarily characterized by patches and plaques with several key secondary skin findings including erythema, excoriations, lichenification, and scaling. The cutaneous presentation varies according to race and age. The typical presentation in African American children often includes more papular or follicular disease activity. In patients with darker skin types, persistent pigmentary changes, including both hypopigmentation and hyperpigmentation, are often increasingly noted in both flaring and resolving areas.

Infantile eczema often appears initially on the scalp, cheeks, and forehead. Lesions gradually extend to involve the extensor surfaces of the extremities and the trunk. The diaper region is classically spared from involvement. Flexural extremity involvement is characteristic of childhood AD, especially in the antecubital and popliteal fossa regions. Major areas of involvement in postpubescent children include the dorsal hands and feet, face, neck, and upper back.

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*Disclosures:* Drs Davis, Waldman, LeBovidge, Ahluwalia, and Tollefson have nothing to disclose. Dr Jacob reports other from National Eczema Association, during the conduct of the study; personal fees from NEA, nonfinancial support from Dermatitis Academy, outside the submitted work. Mr Jetter is a member of the Board of Directors of the National Eczema Association. Dr Spergel reports grants from NIH, grants and personal fees from DBV Technology, grants from AImmune, personal fees from MEI, personal fees from Medscape, personal fees from Uptodate, personal fees from Rockpointe, outside the submitted work.

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Other features of AD, often present yet not required for diagnosis, include early age of onset, IgE reactivity, xerosis, and personal or family history of atopy. Commonly associated clinical findings that may aid in the diagnosis include dermatographism, keratosis pilaris, hyperlinear palms, periorbital changes (including Dennie Morgan folds), perifollicular accentuation, and pityriasis alba. The diagnosis of AD is further contingent upon the exclusion of other skin conditions including contact dermatitis, psoriasis, seborrheic dermatitis, and other cutaneous diseases that may present with eczematous eruptions.<sup>1</sup>

### Differential diagnoses

Distinguishing AD from other eczematous eruptions may be difficult, as several diagnoses may occur in conjunction with, and/or complicate, AD. The clinician should suspect an alternative diagnosis if pruritus is absent, the distribution of the rash is atypical, or conventional therapeutic management is ineffective despite patient compliance.

### Allergic contact dermatitis

Allergic contact dermatitis (ACD) is a dermatologic disorder characterized by a type IV delayed-type hypersensitivity reaction to low molecular weight haptens that come into contact with the skin and easily penetrate its barrier. Increasingly recognized, many children are becoming sensitized to contact allergens found in skin care products, prescription and over-the-counter medications, and clothing. A recent systematic review encompassing 1,507 positive United States pediatric patch tests identified 10 allergens responsible for a substantial portion of pediatric ACD. In descending order, tixocortol pivalate (a corticosteroid), propylene glycol, methylchlorisothiazolinone (MCI)/methylisothiazolinone (MI), formaldehyde, cocamidopropyl betaine, lanolin, benzalkonium chloride, fragrance and Balsam of Peru, neomycin, and nickel were identified as the most common contact allergens in the pediatric population.<sup>2</sup>

Allergic contact dermatitis may occur independently of AD; however, it is more common in AD patients. The affected skin is erythematous and pruritic, as in AD. The distribution of the eruption is helpful in differentiating between AD and ACD. Contact dermatitis should be suspected in patients with eczematous dermatitis atypical in location, geometric or symmetric in distribution, unresponsive to therapy despite compliance, or worsened by standard of care therapies. It should also be suspected in older patients (with or without a history of atopy) who develop new-onset localized, or airborne-pattern eczematous dermatitis. Identification of offending agents via patch testing, and subsequent avoidance, can put ACD into remission and improve management of AD. Avoidance of contact allergens in patients with AD is considered a mainstay of therapy.

### Seborrheic dermatitis

Seborrheic dermatitis is a common skin eruption in infants, adults with schizophrenia or Parkinson's disease, and elderly patients. This condition predominantly involves the scalp, eyebrows, nasolabial crease, central chest, and groin. The etiology of seborrheic dermatitis is postulated to result from an inflammatory reaction to the proliferation of *Malassezia* yeast on the cutaneous surface.<sup>3</sup> Often confused morphologically with AD, the characteristic le-

sions are waxy, orange to red, scaly patches. Both AD and seborrheic dermatitis frequently begin in the first 8 to 12 weeks of life, and may appear simultaneously or overlapping in the same distribution.<sup>4</sup> Initial presentation of both AD and seborrheic dermatitis characteristically occurs on the scalp. The diaper region is commonly involved in infantile seborrheic dermatitis, whereas it is classically spared in infantile AD. Unlike the dry, adherent scale of AD, the scale of seborrheic dermatitis is typically greasy. The absence or minimal concern of pruritus further differentiates seborrheic dermatitis from AD, for which pruritus is prominent.

### Psoriasis

Psoriasis, a common eruption affecting 4% of the US population,<sup>5</sup> affects both children and adults. This condition is defined by sharply circumscribed, erythematous plaques with a characteristic silvery-white adherent scale and a predilection for the extensor surfaces, scalp, umbilicus, genitalia, and gluteal cleft. Infants notably present with facial, or diaper-region involvement. Psoriasis is linked to obesity, hypertension, cardiovascular disease, insulin resistance, and smoking.<sup>6-8</sup> Psoriasis-eczema overlap (often called psoriasiform dermatitis) is characterized by either a mixture of the 2 lesions or by intermediate morphology. Distinguishing features of psoriasis include minimal or absent pruritus, positive Auspitz sign (pinpoint bleeding upon removal of scale), and Koebner phenomenon (appearance of new lesions on areas of cutaneous injury or friction). A distinctive clinical finding of psoriasis is nail involvement, including fine pits, thickening, and yellow discoloration. Family history of psoriasis and associated joint pain further supports the diagnosis; however, these findings are present in less than one-third of psoriasis cases.

### Periorificial dermatitis

Periorificial dermatitis is a common facial eruption in children and adult females and is often misdiagnosed as AD or acne. The condition is characterized by pinpoint erythematous papules and pustules, erupting around the mouth (sparing the vermillion border), chin, nasolabial folds, and glabella. Similar to AD, this rash often initially responds positively to topical corticosteroids (TCS), with recurrence upon cessation of TCS use. Two further distinguishing factors of periorificial dermatitis include lack of pruritus and cutaneous findings limited to the face. Treatment with topical metronidazole or sodium sulfacetamide lotion and/or oral cycline antibiotic for several weeks is the mainstay of therapy and often leads to complete resolution.<sup>9</sup>

### Ichthyoses

Ichthyoses represent a group of congenital disorders of keratinization, with abnormalities in skin production and desquamation. These disorders can present independently or in association with AD. Ichthyoses are characterized by excessive fine to coarse, light grey, adherent, dry scales. The first cutaneous manifestations of ichthyoses typically appear between 2-6 months of life and progressively increase until puberty. The scales are accentuated on the lower extremities, especially the shins, and often have the appearance of fish scales. Hyperlinearity of the palms and soles of ichthyosis is frequently seen. Unlike AD, patients typically do not present with pruritus, erythema, or skin inflammation.<sup>10</sup>

### Netherton syndrome

Netherton syndrome, a rare ichthyosis due to SPINK5 gene mutation, may present in infancy with a pruritic eczematous dermatitis that is refractory to conventional therapies. The typical skin manifestations of Netherton syndrome during infancy consists of severe erythroderma and prominent scale. By the age of 1-2 years, these individuals present with lesions characterized by erythema and a characteristic double-edged scale (ichthyosis linearis circumflexa). This condition may be life-threatening, due to associated dehydration, and failure to thrive. The presence of abnormal, short, brittle hair shafts, known as trichorrhexis invaginata, is pathognomonic. Due to the high risk of systemic absorption of topical corticosteroids in these patients, it is critically important to rule out Netherton syndrome prior to initiating therapy in infants with failure to thrive and eczematous dermatitis.<sup>11</sup>

### Nutritional deficiencies

Nutritional deficiencies, resulting from poor nutritional intake, malabsorption, or impaired end organ function, can present as eczematous dermatitis. Decreased zinc and biotin availability, usually due to either malabsorption or decreased intake, manifest as well-demarcated, orange, waxy plaques around the mouth and anterior genitalia. Most cases are due to either zinc or biotin deficiency and appear prior to 1 year of age. Patients with zinc deficiency (acrodermatitis enteropathica) may also develop diarrhea and emotional lability. Low serum zinc and alkaline phosphatase levels support this diagnosis. Biotin or multiple carboxylase deficiency can be distinguished by the development of anemia, lethargy, and/or seizures. Zinc and biotin supplementation leads to immediate reversal of symptoms.

### Immunodeficiencies

Immunodeficiencies, including severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome (WAS), and Hyper IgE syndrome, may manifest with specific constellations of cutaneous findings, including eczematous rash with pruritus. A comprehensive immunologic evaluation should be considered in infants and children with eczematous dermatitis and a history of chronic, recurrent infections or failure to thrive.

### Mycosis fungoides

Mycosis fungoides, the most common form of cutaneous T-cell lymphoma (CTCL), is often diagnosed via biopsy after a presumed dermatitis or tinea infection fails conventional therapies. Clinical examination varies from erythematous scaly patches and plaques to poorly circumscribed hypopigmented or hyperpigmented macules. Presentation in the pediatric population is rare, but an increasing incidence in children has been documented in recent years.<sup>12</sup> Key differentiating factors include later onset, weight loss, and lack of atopy.

### Tinea

Tinea, or ring worm, characteristically manifests as erythematous, well-demarcated annular erythematous plaques with peripheral scale and central clearing. This dermatophyte infection increases in incidence with age, and commonly presents on the hands, feet, and genitalia. Skin scraping for fungal hyphae is the gold standard for definitive diagnosis. The misdiagnosis of tinea may lead

to inappropriate treatment with TCS, resulting in an initial dampening of cutaneous inflammation. When topical therapy is discontinued, however, the pruritus and inflammation worsen, leading to additional steroid application. This results in a slow extension of the original infection with an altered appearance, known as tinea incognito.<sup>13</sup>

### Scabies

Scabies, infestation of the *Sarcoptes scabiei* mite, presents as a localized or diffuse reaction characterized by red papulovesicles with excoriations. The dermatitis can also manifest as nodules, urticarial wheals, and pustules. Often pronounced in the intertriginous regions and interdigital webs, this condition typically spares the face (except in young infants). Insidious onset of intense pruritus that is particularly prominent at night is reported by most patients. Diagnosis is made via mineral oil prep of skin scrapings of linear burrows, and identifying mites or eggs on microscopic exam.

### Comorbidities

While the skin is the characteristic organ affected in AD, there is increasing recognition that AD is a skin disease with subsequent comorbidities and psychosocial ramifications for the patient and their support network. Numerous investigations have supported the relationship between AD and infectious, atopic, systemic, and psychosocial comorbidities.

### Infectious comorbidities

The high frequency of infectious complications in individuals with AD flares is commonly recognized and documented in the literature.<sup>14,15</sup> The majority of secondary skin infections are bacterial and result from the increased prevalence of *Staphylococcus aureus* colonization in AD patients. Recent clinical investigations document *S. aureus* colonization in up to 90% of actively affected and 76% of nonaffected skin in AD patients.<sup>14</sup> This sharply contrasts with the 2%-25% frequency of colonization in nonatopic controls.<sup>14</sup> Rates of Methicillin-resistant *Staphylococcus aureus* (MRSA) vary by community.<sup>15</sup> Honey-colored crusting, pyoderma, and weeping classically distinguish the skin lesions of *S. aureus* infection. A substantial number of AD superinfections (up to 16%) are linked to Group A Streptococcus (GAS) infection.<sup>16</sup> Children with GAS superinfection have a higher frequency of more serious infectious manifestations, including hospitalization, fever, and facial involvement.<sup>16</sup> AD patients also are at a higher risk of developing disseminated viral infections, including molluscum contagiosum, herpes simplex virus, and *Coxsackie virus A6*.<sup>17</sup>

### Food allergy, allergic rhinitis, and asthma

Patients with AD and a family history of allergic disease may develop a typical sequence of other atopic diseases, including food allergy (FA), asthma, and allergic rhinitis, referred to as the "atopic march."<sup>18</sup> By age 3 years, nearly 66% of AD patients in a large-scale clinical investigation reported one or more additional forms of atopy (asthma, FA, or allergic rhinitis), and the presence of additional atopy-related conditions directly correlated with poor AD control. In all, 71% of the 66,270 AD patients investigated developed an additional atopy-related condition, and 38% reported concomitant asthma and allergic rhinitis.<sup>18</sup> Patients with

filaggrin mutations have an added risk of developing other atopy-related disorders—especially asthma and peanut allergy.<sup>19</sup> This association suggests that defects in epithelial barrier function may contribute to the development of allergic sensitization and/or systemic immune responses, resulting in the development of additional atopic disease.

Exposure to food allergens through the impaired skin barrier may lead to sensitization and possible food allergy in AD patients. Higher rates of IgE sensitization are documented in children with AD, which may be assessed through skin prick or serum IgE testing. Most of these cases do not represent true IgE-mediated food allergy, defined as “an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.”<sup>20</sup> The rate of true IgE-mediated food allergy development in 2 large clinical investigations of infants with mild to moderate AD in the US was approximately 15%.<sup>21</sup> This rate increased to approximately one-third in infants with moderate to severe AD.<sup>21</sup> The most common food allergens documented in children with AD include egg, milk, peanut, soy, and wheat.

Allergic sensitization in older children and adolescents with AD more commonly involves reactivity to aeroallergens rather than food allergens. Similar to food allergy in younger children, sensitization to aeroallergens occurs more often in AD patients with moderate to severe disease. The clinical significance of aeroallergen sensitization is variable. The most common aeroallergens include animal dander, dust mites, fungi, and pollen. One clinical study documents a 69% incidence of sensitization against aeroallergens at 5 years of age among individuals with early onset AD by 3 months of age.<sup>18</sup>

Several clinical investigations have highlighted the increased incidence of asthma and allergic rhinitis in AD patients. Depending on the study, up to 80% of children with AD will develop allergic rhinitis and/or asthma. A clinical investigation at Tucson Children’s Hospital revealed an elevated risk of asthma development among children with AD who wheeze during the first 3 years of life (OR, 2.4), versus healthy controls.<sup>22</sup> Thus, it appears that early atopy may be a critical risk factor for asthma development in children who develop airway obstruction at a young age. A systemic review of 13 cohort studies documented a 30% rate of asthma development in children with atopic dermatitis.<sup>23</sup> This trend of increased asthma development among AD patients continues into adulthood. A clinical investigation of 291 patients revealed an elevated risk of asthma development in adulthood (OR, 3.2) among patients with a history of atopic dermatitis during childhood.<sup>24</sup> Furthermore, the severity of AD is exponentially correlated to the development of asthma, as increased severity score was found to be directly associated with a higher frequency of asthma in 1 clinical investigation.<sup>25</sup> Finally, the concomitant presentation of clinically proven food allergy and AD at greater than 12 months of age correlated with a 67% rate of subsequent asthma development, providing further evidence of the atopic march.<sup>18</sup>

### Nonatopic comorbidities

Recently, several associations between AD and nonatopic comorbidities have been suggested in the literature. The most frequent comorbidity documented is sleep disturbance, affecting up to 60% of AD patients.<sup>26</sup> Furthermore, sleep disturbance may lead to neurocognitive impairment, hindering peer relations and school per-

formance.<sup>28</sup> Numerous studies involving AD children also reveal a significantly increased frequency of concurrent ADHD and additional psychiatric disorders.<sup>27-30</sup> Schmitt et al initially revealed a relationship between AD and ADHD, finding a significant association between the 2 conditions in the first population-based study.<sup>27</sup> Subsequently, a large-scale review of 6 similar studies suggested a strong link between AD and ADHD symptoms, independent of environmental factors and concurrent atopic disease.<sup>28</sup> Several clinical investigations document a positive correlation between AD severity and ADHD development.<sup>28,29</sup> Furthermore, several studies highlight an association between AD and autism, anxiety, depression, conduct disorder, and suicidal ideation.<sup>30-32</sup> Similar to the ADHD investigations, a positive correlation between AD severity and concomitant mental health disorders is strongly suggested.<sup>31,33</sup>

Emerging evidence for several systemic comorbidities including obesity, hypertension, and cancer, is highlighted in several studies, but these associations are controversial and require further investigation.<sup>32,34,35</sup> Given the numerous comorbidities linked with AD, a comprehensive assessment and a multidisciplinary therapeutic approach is warranted.

### Psychosocial impact

AD has a significant negative impact on patient and caregiver quality of life, with commonly reported areas of greatest impact including itching and scratching, sleep disturbance among both patients and parents, embarrassment about the skin, time burden, and parent-child stress associated with skincare.<sup>36</sup> Patients experience self-consciousness about the appearance of the skin, as well as avoidance of everyday activities (eg, swimming, wearing shorts) or being seen in public during a flare.<sup>37</sup> More than 25% of patients have experienced bullying because of AD, with higher rates for children (39%) and those with severe disease (33%). Reactions from others, such as staring or fear of contagion, are common.<sup>38</sup> Approximately 40% of adult patients report that their social relationships are affected, and 50% report a negative impact on sexual relationships.<sup>37,38</sup> Financial burden associated with AD is significant and includes both direct costs such as physician visits, prescriptions, and over-the-counter treatments, as well as indirect costs such as patient and caregiver absenteeism from school or work, and reduced productivity.<sup>39,40</sup> Because psychological stress is a known trigger of itch and skin flares among AD patients, the emotional burden of the disease, as well as psychological conditions such as anxiety and depression, can exacerbate the condition, creating a challenging cycle if patients and families do not receive adequate support.

### Conclusion

In conclusion, this article reviews the diagnostic criteria, differential diagnoses, and comorbidities associated with AD. A striking association between AD and atopic, psychosocial, and systemic disorders is highlighted, further emphasizing the importance of a multidisciplinary approach to care and education. Further investigations are warranted to investigate and validate comorbidities in AD.

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