Atopic Dermatitis–A New Dawn

Anne Weissler, MMS, PA-C

KEYWORDS

• Atopic dermatitis • Eczema • Topical steroids • Calcineurin inhibitors • *FLG* • Filaggrin • Th2 • Dupilumab

KEY POINTS

- Atopic dermatitis (AD) results from both abnormalities in the skin barrier including filaggrin defects, and in the immune system, involving a type 2 T-helper cell response with elevations of interleukin (IL)-4, IL-13, and other cytokines.
- Initial treatment of AD includes moisturization with baths and emollients, bland skin care, application of the appropriate topical steroid, addition of a topical calcineurin inhibitor if needed, and consideration of microbes, mimics, and comorbidities.
- Future systemic treatments may target immune abnormalities that contribute to AD, including dupilumab, an anti-IL-4.

INTRODUCTION

It may not kill you, but it can ruin your life. This phrase is used frequently in the office to describe the morbidity of uncontrolled atopic dermatitis (AD), including pruritus causing loss of sleep, school absence, and other declines in activities of daily living. AD is the most common chronic skin disease in children.[1] Early identification and successful treatment may limit the extent of the disease. The American Academy of Dermatology published updated clinical guidelines for AD but admits gaps in research.[2] The last medications approved for AD were Elidel (December 2001) and Protopic (December 2000).[3] Other medications include topical and oral steroids. Limited options have made treatment frustrating. Fortunately, there are clinical trials for both topical and systemic therapies in progress. Thought leaders have dubbed it a new dawn for AD. Information gathered as a result of this research may transform the understanding and treatment of the disease.

DEFINITION, PREVALENCE, AND RISK FACTORS

AD is characterized as a chronic inflammatory skin condition featuring pruritic, erythematous, scaly papules, vesicles, and plaques that may wax and wane or persist

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Division of Dermatology, Department of Pediatrics, Cardinal Glennon Children's Hospital, Saint Louis University, 1465 South Grand, St Louis, MO 63104, USA
E-mail address: aweissl@slu.edu

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as chronic lichenified lesions. The word eczema is often used interchangeably with AD. Eczema, however, is a more general term referring to allergic contact dermatitis (ACD), seborrheic dermatitis, psoriasis, AD, and/or other similar conditions. AD is a more specific diagnosis.

AD is often the first presentation of allergic disease. The word atopic refers to a tendency to produce immunoglobulin E (IgE) antibodies after exposure to common substances in the environment such as pollen, house dust mite, and food allergens.[4] Although not every person with AD has an elevated IgE, almost all do. The atopic march describes the sequential development of AD, sensitization to allergens, and finally, progression to asthma and allergic rhinitis.[4] Approximately one-third of patients with AD develop asthma and two-thirds develop allergic rhinitis.[5,6]

Most children with AD develop the condition before entering kindergarten: 45% during the first 6 months of life, 60% during the first year, and 85% before the age of 5.[7] The prevalence of the disease varies according to the study and region. AD affects up to 18% of children and up to 5% of adults.[8] A report from the Centers for Disease Control and Prevention analyzing the National Health Interview Survey found an increase in prevalence of eczema among US children ages 0 to 17 from 7.4% in 1997 to 12.5% in 2011. Analysis of worldwide data suggests that a plateau of around 20% may have been reached in countries with the highest prevalence. It is possible that there are a finite number of individuals susceptible to the condition.[9]

Two strong risk factors for the development of AD include a genetic defect in the filaggrin (*FLG*) gene (see later discussion) and family history of atopic disease.[10] If 1 parent has AD, asthma, or allergies, there is a 50% chance that the child will have 1 or more of the diseases. If both parents are atopic, the chance is even greater.[7]

Additional risk factors for the development of AD include a higher level of family education, a smaller family size, and residence in an urban environment.[11] These risk factors lead to the hygiene hypothesis. The hypothesis states that a lack of exposure to a variety of microbes may increase the prevalence of AD. Exposure to endotoxins, helminthes, farm animals, dogs, unpasteurized milk, and early day care may be protective against AD.[12]

PATHOGENESIS AND POTENTIAL BIOMARKERS

Although there are no unique biomarkers that help distinguish AD from other conditions, current research gives additional insight into the genetic, immunologic, and environmental influences that contribute to the disease. A review of these concepts gives context to current and future treatment modalities.

There are 2 theories to explain the cause of AD. One is the outside-in hypothesis which states that defects in the epidermal skin barrier allow for increased transepidermal water loss (xerosis) and increased penetration of allergens and microbes, causing an immune reaction. The other is the inside-out hypothesis in which immune defects cause the skin barrier dysfunction. More than likely, these theories are not exclusive. Both play a role in the pathogenesis of AD.[13]

The epidermis of the skin is made of several layers and acts as a barrier to help minimize water loss and protect the body from foreign substances, including microbes and allergens. In 2006, McLean and colleagues[14] demonstrated that the *FLG* gene has a pivotal role in skin barrier function and in the development of AD. This gene is responsible for the development of the profilaggrin protein. This protein, found in the granular layer of the epidermis, is broken down into smaller *FLG* molecules.[15] *FLG* brings structural proteins together, flattening and strengthening the cells to create a strong barrier or matrix.[15,16] This matrix with attached proteins and lipids forms the stratum