

Flexural Eczema Versus Atopic Dermatitis

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Flexural eczema and atopic dermatitis are frequently synonymized. As respiratory atopy is rarely tested for and found in these patients, systematically equating a flexural distribution of dermatitis with atopic dermatitis may too frequently result in misclassified diagnoses and potentially missed opportunity for intervention toward improving patients' symptoms and quality of life. We present a critical review of the available evidence for the atopic dermatitis diagnosis and discuss the similarities between atopic dermatitis and allergic contact dermatitis. Because neither flexural predilection nor atopy is specific for atopic dermatitis, we conclude that the term *atopic dermatitis* is a misnomer and propose an etymologic reclassification of atopic dermatitis to "atopy-related" dermatitis. Allergic contact dermatitis can induce an atopic dermatitis–like phenotype, and thus, flexural dermatitis cannot be assumed as atopic without further testing. Patch testing should at least be considered in cases of chronic or recurrent eczema regardless of the working diagnosis.

"Everyone knows how eczema looks like, yet no one knows what eczema is."—Heinrich Adolf Gottron

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As Gottron astutely identified in the late 19th century, the complexity of dermatoses within the spectrum of eczema has challenged many physicians. This is especially true for atopic dermatitis for which, even today, there is a lack of consensus on its defining criteria. One of the major requirements included in all proposed diagnostic systems is flexural involvement—an assumingly predominant and defining location for atopic dermatitis. Flexural location of eczema includes the skin crease areas in the neck, antecubital and popliteal fossae, and anterior ankle.^{1,2} However, flexural predilection is not specific for atopic dermatitis, and inclusive definitions may preclude clinicians from developing a broader differential diagnosis for patients with unclear presentations.³ In fact, flexural dermatoses may be a heterogeneous group of diseases with a common presentation but multiple genetic and environmental etiologies, the majority of which include atopic dermatitis and allergic contact dermatitis. In addition, the relationship between atopy and atopic dermatitis is more variable than previously suggested and may be a misnomer rather than a helpful diagnostic determinant.

We present an analysis of the debatable importance of atopy and flexural involvement in atopic dermatitis, as well as assess the clinical and pathophysiologic similarities to allergic contact dermatitis.

ATOPIC DERMATITIS IS NOT REALLY ATOPIC

In 1980, Hanifin and Rajka⁴ formulated a set of diagnostic criteria for atopic dermatitis. Since then, these criteria have been routinely used in epidemiologic and clinical studies in order to reduce misclassification and thus reduce outcome variability. In practice, the difficulty in application^{5–7} has led to several modifications including a UK Working Party shortened version, which has been the most validated in both clinical and investigative settings.^{8,9} Other criteria and classification systems have also been proposed; for example, the International Study of Asthma and Allergies in

TABLE 1. Diverse Diagnostic Criteria for Atopic Dermatitis and Definitions for Atopy

Hanifin and Rajka ⁴ criteria	Major features (mandatory 3 of 4): 1. Pruritus 2. Typical morphology and distribution of skin lesions: Flexural lichenification or linearity in adults Facial and extensor involvement in infants and children 3. Chronic or chronically relapsing dermatitis 4. Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis) Minor features (mandatory 3 of 23): Xerosis; ichthyosis/palmar hyperlinearity/keratosis pilaris; immediate (type I) skin test reactivity; elevated serum IgE; early age at onset; tendency toward cutaneous infections/impaired cell-mediated immunity; tendency toward nonspecific hand or foot dermatitis; nipple eczema; cheilitis; recurrent conjunctivitis; Donnie-Morgan infraorbital fold; keratoconus; anterior subcapsular cataracts; orbital darkening; facial pallor/erythema; pityriasis alba; anterior neck folds; itch when sweating; intolerance to wool and lipid solvents; perifollicular accentuation; food intolerance; course influenced by environmental/emotional factors; white dermographism/delayed blanch
UK Working Party Diagnostic Criteria ⁸	Mandatory criterion: itchy skin condition in the past 12 mo Plus ≥3 of the following: 1. History of flexural involvement (skin creases) 2. Personal history of asthma or hay fever (or in first-degree relative when <4 y old) 3. History of generally dry skin in past year 4. Onset of rash at <2 y old 5. Visible flexural dermatitis
ISAAC Questionnaire ⁶⁴	Positive response to questions 1–3 is diagnostic, 1–2 as possible case for examination: 1. Has your child ever had an itchy rash that was coming and going for at least 6 mo? 2. Has your child had this itchy rash at any time in the last 12 mo? 3. Has the itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, around the neck, around the ears or eye?
Millennium criteria ⁹	Mandatory criterion: presence of allergen-specific IgE Historical, actual, or expected (in very young children) In peripheral blood (RAST, ELISA) or in skin (intracutaneous challenge) Principal criteria (mandatory 2 of 3): Typical distribution and morphology of eczema: infant, childhood, or adult type If distribution is not typical, exclude other entity Pruritus Chronic or chronically relapsing course
American Academy of Dermatology ²³	1. Mandatory criteria Pruritus Eczema (acute, subacute, chronic): typical morphology and age-specific patterns (facial, neck, extensor in infants; flexural lesions in any age group; sparing of groin and axillary); chronic or relapsing history 2. Important features: Early age at onset Atopy: personal and/or family history; IgE reactivity Xerosis
Atopy definitions	1994: Personal or family medical history of seasonal asthma/allergic rhinitis, no history of dermatitis, and at least 1 positive prick test to a panel of 10 common aeroallergens ⁶¹ 2000: Allergic rhinitis but no asthma, no dermatitis, and at least 1 positive prick test to grass pollen but not dust mites. ⁶² 2005: At least 1 positive skin prick test, positive Phadiatop test,* total IgE >120 kU/L ³⁸

*Enzyme immunoassay for IgE-mediated allergy to grasses, trees, weeds, cat, dog, mites, and molds—a positive result indicates that the patient is allergic to one or more of these allergens.

Childhood (ISAAC) developed a questionnaire for patient-involved diagnosis, which may lead to increased subjectivity in disease determination.^{2,10} Although utilized in multiple studies, the ISAAC criteria were found to have a low positive predictive value (48.8%)¹⁰ and faced outcome errors resulting from inaccurate translations,¹¹ as well as high rates of misdiagnoses.¹²

One hallmark of atopic dermatitis is the phenotypical presentation of generalized xerosis and pruritus with chronic or relapsing dermatitis distributed along distinct anatomical sites that change with age.¹³ In a relevant study,¹⁴ the relative risk (RR) for atopic dermatitis was highest among people with dry skin (RR, 78.0), followed by the Hertoghe sign (a thinning or loss of

TABLE 2. Differential Diagnoses for Atopic Dermatitis—Other Flexural Dermatitides and Dermatoses^{24,71}

Acanthosis nigricans
Contact dermatitis (allergic, SRACD, SNAS,* SDRIFE, [†] irritant, protein)
Hailey-Hailey disease
Infantile seborrheic dermatitis
Inverse psoriasis
Immunodeficiency syndromes
Lichen planus
Molluscum dermatitis
Mycosis fungoides
Netherton syndrome
Nummular dermatitis
Nutritional deficiency (zinc, biotin)
Pemphigus vegetans
Tinea corporis
Scabies
Soft fibromas
Xanthomatosis

*“Systemic nickel allergy syndrome” (SNAS) is a rather vague term embracing SRACD by nickel and a series of unspecific symptoms (general, gastrointestinal) ascribed to alleged nickel allergy; therefore, the use of this term seems not advisable.

[†]“Symmetric drug-related intertriginous and flexural exanthema” (SDRIFE) is a term used for drug-related SRACD.

SRACD indicates systemic reactivation of allergic contact dermatitis.

the outer third of the eyebrows; RR, 46.4), white dermographism (RR = 39.6), pityriasis alba (RR, 35.0), itch with sweating (RR, 33.6), and intolerance to wool (RR, 25.7). On the other hand, the Hanifin and Rajka⁴ “major” criterion of personal or family history of atopy turned out considerably less important (RR ranging from 3.0–8.1).¹⁴

Atopy is defined by an immunoglobulin E (IgE)–mediated immunological response to minimal doses of allergens that are usually tolerated by the majority of the population¹⁵; it has been differently classified according to clinician-investigator objectives (Table 1). For example, the World Allergy Organization defines atopy as the presence of specific serum IgE antibodies or confirmatory skin prick tests.¹⁶ A confirmatory skin prick test reaction is defined by a wheal diameter equal to or greater than 3 mm to common environmental or food allergens including house dust mites, storage mites, grassy/rye pollen, hazel, alder, birch, weeds, molds, dog/cat dander, egg white, and cow milk.¹⁷ The cutaneous and systemic manifestations of asthma and allergic rhinitis are IgE induced and thus referred to as atopic. We propose that the term “IgE variant AD” would be more specific and clinically useful in categorizing patients with IgE-positive reactions and/or protein-related respiratory disease who also have flexural distribution dermatitis.

Historically, the initial naming of the disease as “atopic dermatitis” was contested as an “unfortunate choice of term” by one of the creators of its classic diagnostic criteria, Georg Rajka,¹⁸ who

stressed that not all patients diagnosed with atopic dermatitis have traits of atopy. Indeed, allergic reactions seem to not play a decisive role in every case of atopic dermatitis, and 20% to 70% of “atopic dermatitis” patients do not have an elevated total or allergen-specific serum IgE level.^{19–21} Also, Hanifin²² observed that atopic dermatitis lesions cannot be readily or consistently induced by foods and inhalants. Hanifin and Rajka⁴ classified elevated IgE and positive skin prick tests as 1 of the 23 minor diagnostic criteria, next to such nonspecific symptoms as pale face or orbital darkening. Nevertheless, in the 1998 millennium criteria of Bos et al⁹ for atopic dermatitis diagnosis, allergen-specific IgE findings were required in atopic dermatitis–diagnosed patients. On the other hand, the American Academy of Dermatology guidelines focused on the clinical aspects of atopic dermatitis and argued against the reliability of biomarkers such as allergen-specific serum IgE level²³ (Table 1). Thus, there is continued discord over the importance and relevance of atopy in “atopic dermatitis.” We propose that “atopic” dermatitis should rather be referred to as “atopy related” to stress that an IgE response is not a sine qua non component of pathogenesis.

THE ETIOPATHOGENESIS FOR FLEXURAL INVOLVEMENT IN ATOPIC DERMATITIS IS UNKNOWN

The belief that flexural eczema is equivalent to atopic dermatitis (common among many pediatricians, allergists, family practitioners, and dermatologists alike) warrants review. Through ISAAC data analysis, Flohr and colleagues³ pinpointed an epidemiologic fallacy of mistaking the association of atopy and flexural eczema for true causation. They analyzed questionnaire data and skin prick test results from 28,591 randomly selected international children 8 to 12 years old and found that the association between atopy and flexural eczema was widely variable and dependent on geographical origin. Most importantly, the combined population-attributable risk of atopy in flexural eczema across all study centers was found to be only 2.8%, meaning that less than 3% of flexural eczema can be explained by atopy alone.³

Preferential flexural involvement in atopic dermatitis may be based on general concepts such as different measurements for pH, skin thickness, and amounts and types of microorganisms and antimicrobial peptides. Because of the combination of moisture, warmth, and friction, the flexural areas become macerated and fissured, increasing the clinical response when exposed to external irritants and allergens, as well as bacterial and fungal organisms.²⁵ Regional variations in the skin surface microenvironment, including differences in bacterial growth patterns, predispose the intertriginous areas to certain infections when compared with other sites; for example, *Corynebacterium minutissimum* is found in the intertriginous areas because of its enhanced growth within a hyperhidrotic environment leading to the high incidence of erythrasma in these areas.²⁶ Overall, the differential diagnosis for

flexural dermatitis is broad and should be correlated with patient history (Table 2).

Atopic dermatitis patients have decreased amounts of antimicrobial peptides (LL-37 and HBD-2) in the superficial epidermis as compared with individuals with psoriasis; thus, atopic dermatitis patients have inherently decreased antimicrobial activity against bacterial pathogens including *Staphylococcus aureus* predisposing them to increased risk of epidermal infection.²⁷ Pertinently, the elevation of skin pH partly due to filaggrin deficiency in atopic dermatitis also affects microbial colonization.²⁸

CONTACT DERMATITIS MAY PLAY A ROLE IN ATOPIC DERMATITIS

While early onset of dermatitis in an area subject to friction and occlusion is a good marker for barrier dysfunction and inflammation due to commensal organisms, it may also predispose to percutaneous sensitization. Contact dermatitis is an inflammatory response to direct contact with a hapten (small molecule of <500 D), irritant, or protein allergen. Irritant contact dermatitis is a threshold/concentration-limited response to injury from detergents, solvents, acids, or alkali. Allergic contact dermatitis in flexures may result from the entrapment of external haptens (eg, cosmetics or textile dyes) creating a variable degree of occlusion in a moist environment supporting penetration of haptens.^{29,30} Furthermore, such close and prolonged contact between the skin and a textural material may facilitate increased penetration of haptens from the synthetic materials (dyes, finishes, and surfactants). This is especially relevant because the ability of haptens, allergens, and irritants to penetrate the skin is increased in areas with barrier deficiency, inflammation, and occlusion.³¹ Along these lines, Hann et al^{29,30} demonstrated that generalized topical exposure to a hapten (bathing with bath oil) led to a flexural site-specific allergic contact dermatitis, suggesting an increased susceptibility of allergic contact dermatitis to flexural areas and the possibility of misdiagnoses of allergic contact dermatitis as atopic dermatitis.^{12,31–37}

Many studies have failed to show a significant relationship between allergic contact dermatitis and atopic dermatitis due to methodological limitations. Misclassification bias occurs when patients are incorrectly assigned into affected and nonaffected groups. In the case of atopic dermatitis, many study participants with presumed atopic dermatitis are reflexively grouped into the affected category without the full diagnostic workup and exclusion of other diagnoses, which ultimately leads to null-favoring results.^{13,38,39} Moreover, experimental designs typically consider atopic dermatitis as a singular condition, whereas in reality it represents a wide spectrum in both clinical and immunologic dimensions. However, an association between atopic dermatitis and an increased prevalence of contact allergy has been supported by a number of different independent studies.^{13,40–43}

Studies using more stringent diagnostic criteria for atopic dermatitis such as that of Hanifin and Rajka, as compared with

those using the ISAAC questionnaire, show a higher prevalence of sensitization among atopic dermatitis adult and pediatric patients.^{44–46} Mailhol et al⁴⁷ reported a positive association between the severity of atopic dermatitis and the risk of developing contact allergy to emollients and topical drugs (odds ratio, 3.3). Paradoxically, treatment protocols for atopic dermatitis often call for large amounts of topical drugs and emollients, which involve complex formulas with a range of chemicals, preservatives, and even fragrances, which may be among the leading causes for higher allergic contact dermatitis rates in this group.⁴⁸ Almost half of all children with chronic recurrent eczema, who gave affirmative answers to the eczema module in the ISAAC questionnaire and had positive prick test (confirmed atopy), were found to have a reaction to at least 1 hapten on the European Baseline Patch Test Series.⁴⁹ A detailed examination of these children revealed that 1 in 3 (and 1 in 2 adolescents) was ultimately diagnosed with allergic contact dermatitis. Notably, a considerable proportion of those with flexural eczema (1 in 5 children and 1 in 2 adolescents) had no symptoms qualifying for the diagnosis of atopic dermatitis.¹²

SYSTEMIC HAPTEN AND ALLERGEN EXPOSURE PLAYS A ROLE IN ATOPIC DERMATITIS

Although the concept of food-provoked atopic dermatitis has been controversial, the notion of oral (food) exposure-provoked relapses in allergic contact dermatitis has been reported. Complicating this further is the fact that a number of cosmetic ingredients are used as food additives (eg propolis), whereas unprocessed foods may often contain natural allergens (eg Balsam of Peru) and/or contaminants (eg pesticides).^{50,51} Haptens are absorbed from food in the gastrointestinal tract and distributed throughout the body via blood. Once in the skin, they initiate a specific inflammatory reaction of skin-homing effector memory lymphocytes, which were resting there after previous sensitization.⁵²

Certain haptens may not form “classic” hapten-carrier complexes as normally seen in allergic contact dermatitis but may instead bind directly to T-cell receptors without first being presented by major histocompatibility complex molecules. Even though the bindings are labile, they are considered sufficient to activate T cells and thereby mimic allergic immune reactions. This may explain why some “atopic dermatitis-like” reactions to drugs or foods develop rapidly, as if bypassing the sensitization and elicitation phase. The idea of this pathomechanistic reaction to some haptens is referred to as the “p-i concept.”⁵³

Protein contact dermatitis is an inflammatory reaction to large (>10,000 D) proteins, which—in contrast to haptens—require a damaged skin barrier for penetration. Protein contact dermatitis pathogenesis greatly resembles that of atopic dermatitis in that it involves IgE-bearing Langerhans cells.^{54,55} Exposure to protein antigens is known to directly induce a T_H2-dominant response, provoking pruritus and ultimately decreasing filaggrin expression, which in turn leads to the acquired filaggrin deficiency—a highly prevalent finding in atopic dermatitis.⁵⁶

Overall, a high prevalence of missed or concurrent occurrence of allergic contact dermatitis in atopic dermatitis patients indicates that patch testing to common haptens at least should be considered in all cases of recurrent or chronic eczema in the hope of identifying an underlying allergic culprit or secondary contact sensitization complicating or altering the course of primary dermatosis.

THE FUTURE: MORE OBJECTIVE CRITERIA FOR ATOPIC DERMATITIS?

Facing the above-discussed difficulties with clinical diagnosis of atopic dermatitis, the application of nonclinical parameters may be beneficial in the standardization of the diagnosis and atopic dermatitis research. Notably, Kamsteeg et al⁵⁷ analyzed patterns of several marker proteins to help differentiate inflammatory skin conditions including psoriasis, atopic dermatitis, allergic contact dermatitis, and irritant contact dermatitis. Through analysis of genetic signatures of skin biopsies via polymerase chain reaction, immunohistochemistry, and bioinformatics, Riis et al⁵⁸ found that neuron-specific Nel-like protein 2 exhibited strong induction in atopic dermatitis, whereas CCL17 and CXCL10 mRNA and protein were found in allergic contact dermatitis as compared with control subjects. Differences in expression of fast and slow acetylators of arylamine N-acetyltransferases have been seen between atopic versus allergic contact dermatitis, thus suggesting that N-acetylation polymorphisms could serve as genetic markers for atopic dermatitis.⁵⁹ Because serum IgE regulation and other atopic dermatitis pathways are under strong genetic control, genome-wide scans of atopic dermatitis patients have been promising in elucidating specific diagnostic markers, at least for the IgE-associated variant of atopic dermatitis, which is possibly identical with protein contact dermatitis to exogenous proteinaceous allergens.⁶⁰ However, the conclusions of such studies strongly depend on their exclusive definitions for “atopic” and allergic contact dermatitis. As we herein described, atopic dermatitis does not have a precise meaning, and thus, genetic results must be conducted and interpreted cautiously as not to default in type I error because of misclassification bias. Multicenter, multigenerational, multiracial, and multiseverity study populations are necessary to validate such markers in order to provide future objective criteria and to limit the anxiety and morbidity caused by false-positive diagnoses. Difficulties in interpretation, however, can still occur in patients with both atopic dermatitis and allergic contact dermatitis.

CONCLUSIONS

Because neither flexural predilection nor atopy is specific for atopic dermatitis, we conclude that the term *atopic dermatitis* is actually a misnomer. We propose an etymologic reclassification of atopic dermatitis to “atopy-related” dermatitis to signify the importance, but not necessity of an IgE response for diagnosis. Allergic contact dermatitis to common haptens can induce an atopic dermatitis-like phenotype, and thus, flexural dermatitis cannot be

assumed as atopic dermatitis without further testing. Therefore, patch testing should at least be considered in every case of chronic or recurrent eczema regardless of the working diagnosis, as allergic contact dermatitis can only rarely be confirmed or excluded without patch testing. Sensitization can result in the development of antigen-specific IgE that may persist longer than the cutaneous or respiratory disease itself. While managing patients with dermatitis in the clinical setting, care plans for all dermatitis patients should address barrier dysfunction, infection and biofilm, irritancy, and atopic and contact allergy. Furthermore, we may need to be cognizant that “early-onset flexural dermatitis” may be challenging with regard to diagnosis and more difficult to treat because of genetic, rather than exogenous, factors.

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