

Suggestions regarding a more appropriate understanding of atopic dermatitis

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Purpose of review

The importance of consistency and accuracy of medical terminology must be recognized by all health care providers and researchers. Yet, recent publications by recognized authorities regarding atopic dermatitis seem to defy that basic tenet. I (an allergist/dermatologist) have (objectively) reviewed and (subjectively) interpreted the currently (peer reviewed) published designations etymologically, and some of their concepts scientifically.

Recent findings

Interdisciplinary, regional and international meetings have been discussing, assessing, and deliberating the newest data and observations, consistently realizing little consensus. The concluding trivial agreement denotes their individual bias. Given the same information, allergists, dermatologists, and generalists do not conceptualize, and yet dogmatically manage patients with atopic dermatitis.

Summary

Etymologically, and scientifically, atopic dermatitis can only be distinctively designated as the dermatologic syndrome, which heralds the atopic diathesis. Concomitantly, atopic dermatitis without atopy would be an oxymoron. Definitions based on anachronistic criteria demand updating. IgE, like eosinophilia, must be appreciated as epiphenomena of the transient Th1/Th2 cell reversal, which clearly differentiates 'atopic eczema' from all the 'other' eczemas. Failure to recognize the isomorphic feature of the eczema of atopic dermatitis denies patients with an essential therapeutic modality, namely 'Do not scratch, nor rub'. Education regarding the 'triggers' of itch would yield greater success (from recurrences), than prescribing immunomodulation.

Keywords

atopy, dermatitis, eczema, epiphenomenon, etymology, IgE, isomorphic phenomenon, Th1/Th2 cells

Introduction

Medical lexicons, or controlled vocabularies, are essential for the efficient, reliable, reproducible communication of patient data and medical knowledge. Researchers and clinicians need to communicate consistently and accurately with one another. The skin encompasses thousands of unique diagnostic concepts with overlapping definitions, intricate hierarchical relationships and a variety of unique clinical presentations. Ambiguity, misidentification, and misrepresentation of intended concepts are inevitable when individuals have different meanings for the same word or phrase and the medical record cannot thus accurately represent the intended concept. Dermatology, unfortunately, is plagued by the existence of a multiplicity of synonyms within its vocabulary, wherein a single word or phrase may have more than one meaning. For example, dermatitis not only has different meaning to clinicians and dermatopathologists but also is used to describe a range of unrelated conditions that neither would think of as dermatitis (e.g. dermatitis herpetiformis, dermatitis artefacta, perioral dermatitis). To be useful, words and phrases cannot have unclear meanings; each must be clear in terms of the concept that it is intended to convey. Regional and individual preferences contribute to the variety of diagnostic terms used [1]. A. Bernard Ackerman has long recognized a lack of consistent, clear terminology in dermatology [2]. He recommended greater precision and clarity in diagnostic definitions and 'a universal dictionary for dermatology'. The National Institute of Arthritis and Musculoskeletal and Skin Diseases has recently awarded a contract to the Dermatology Lexicon Project (of the American Academy of Dermatology) to lead the development of a universally acceptable and comprehensive dermatology lexicon supporting research, medical information and clinical care [3•].

Atopic dermatitis is presently managed by pediatricians, allergists and dermatologists, each having their own individual perspective on diagnosis, management and prognosis, which burdens the task of the Dermatology Lexicon Project.

Nomenclature

A word is a symbol and its meaning is constituted by the ideas, images and emotions, which it raises in one's mind.

Alfred North Whitehead

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Abbreviation

WAO World Allergy Organization

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Webster's dictionary defines 'name' as a word or phrase that establishes the distinctive designation to a person or thing. Unfortunately, many medical terms are often more descriptive than defined, frequently confounding communications.

Prurigo of Hebra may have been the first recorded description of what we recognize today as atopic dermatitis [4]. That 'label' was based on his clinical observation of 'a multiform, pruriginous, chronic, exacerbating, and paroxysmal dermatitis'. Since that time, at least 20 labels, each from the bias of the contemporary data, have been ascribed to this same entity. Besnier in 1892 [5] made a plea regarding nomenclature (for atopic dermatitis): 'to end the ambiguities and confusions ... and reclassify them in natural groups'. One hundred or more years later, we are still noting disagreement regarding the same conundrum. In 1933, Wise and Sulzberger [6], noted the association of this 'eczema' with asthma and hay fever, and introduced the term 'atopic eczema'; since then, atopic dermatitis has also been recognized as a designation which distinguishes the 'syndrome' (see below) from other eczematous conditions.

In the past 5 years, each major, professional, specialty organization has published guidelines, or parameters of their respective task forces regarding atopic dermatitis. The condition is consistently interpreted somewhat differently by each of the authoritative organizations, The American Academy of Dermatology describes it as 'a chronic inflammatory skin disease – and atopic eczema is synonymous with atopic dermatitis' [7]; the American Academy of Allergy, Asthma and Immunology identifies atopic dermatitis as 'a chronic, familiarly transmitted, inflammatory skin disease, most often the first manifestation of the atopic diathesis' [8]; the European Academy of Allergology and Clinical Immunology proclaimed it 'atopic eczema/dermatitis syndrome – not a single disease, rather an aggregation of several diseases with certain clinical characteristics in common' [9]; the International Consensus Conference on Atopic Dermatitis I and II simply find it 'a chronic inflammatory skin disease' [10]; the World Allergy Organization (WAO) accepts 'atopic eczema, on the basis for a term describing an aggregation of several skin diseases with certain clinical characteristics in common involving a genetically determined skin barrier defect' [11]; and lastly the Consensus Conference on Pediatric Atopic Dermatitis believes it is 'best viewed as a syndrome' [12]. Sadly not one of the names is a distinctive designation, in fact the 'conglomerate' seems to create doubt.

The distinctive designation (i.e. name) atopic dermatitis must be both etymologically and scientifically correct.

Is atopic dermatitis a disease, syndrome, or diseases?

Stedman's Medical Dictionary defines disease as '1. An interruption, cessation, or disorder of body functions, systems or organs. Syn. – Illness; morbus; sickness. 2. A morbid entity characterized usually by at least two criteria: a) recognized etiologic agent(s); b) identifiable group of signs or consistent anatomical alterations (see syndrome)'. The term syndrome is defined by the same source as 'the aggregate of signs and symptoms associated with any morbid process and constituting together the picture of the disease'.

The non-specificity of the WAO definition 'an aggregation of several skin diseases' is both etymologically and scientifically most imprecise for a distinctive designation. In fact, while atopic dermatitis could be considered a disease, the 'ideas, images. . . it (that label) raises in one's mind' are vague and imprecise. Thus, the lack of distinctiveness of the disease-designated definition requires refinement. Could anyone doubt the correctness of atopic dermatitis being anything but a syndrome? The 'aggregate' of signs, (e.g. xerosis; 'allergic shiners'; pityriasis alba; eczema), and symptoms, (e.g. pruritus; impaired barrier layer; elevated IgE) certainly distinguish it from all other skin disorders. Another term that is essential, for the distinctive designation is 'diathesis', which *Stedman's* defines as 'the constitutional or inborn state disposing to a disease or group of diseases, or metabolic or structural anomaly' (which certainly would include immunologic aberrations). Bearing these definitions in mind, it should be readily clear that each of the published documents lacks resolve for their directive intents. Thus, the more etymologically and scientifically appropriate distinctive designation is as follows: atopic dermatitis is the dermatologic syndrome that most often heralds the atopic diathesis.

We must therefore clearly understand the distinctiveness of the syndrome and appreciate the unique characteristics of atopy.

Is it atopic eczema or atopic dermatitis?

Descriptively, etymologically and scientifically, atopic eczema/dermatitis would be unfortunate. Eczema and dermatitis are not synonyms. Etymologically eczema from the Greek *ekzema*, (*fr ekzein, ex out + zein to boil*) which histologically is identified specifically as spongiosis, and clinically recognized as microvesicles and macrovesicles. Dermatitis is etymologically a generic term, and medically indicative of inflammation of the skin, of many causes. Since eczema (spongiosis) is not the only skin finding of atopic dermatitis, and dermatitis includes eczema, and other skin changes, this syndrome can only be distinctively distinguishable as atopic dermatitis.

Is it possible to have atopic dermatitis without atopy?

Grammatically it would be an oxymoron (an adjective modifies a noun to specify a thing as distinct from something else). 'Atopy' specifically distinguishes this dermatitis from all other dermatitides.

Unfortunately, there is no universally accepted definition for atopy, and thus this diathesis continues to be almost exclusively acknowledged by epiphenomena, such as its immunologic aberrations (i.e. elevated IgE levels, eosinophilia) [13], inconsistently ascertainable by positive skin prick tests, or in-vitro IgE antibody tests; allergic rhinitis; and some asthmas.

While atopics are most often identified as 'IgE antibody high responders', not all high IgE responders are atopic, nor does a normal IgE level exclude (atopic) allergic disease [14]. Elevated IgE levels have been noted in patients with helminth infestations; allergic bronchopulmonary aspergillosis; staphylococcal enterotoxin (super antigens); some viral infections, such as HIV [15] and cytomegalic virus; hyper-IgE syndrome [16] (Job's syndrome); Wiskott-Aldridge syndrome, and rarely in Hodgkin's disease; multiple myeloma and exposure to 'chemicals' such as tobacco smoke and in patients who are alcoholics, and those suffering from graft versus host disease.

What is the difference between the (genetically predetermined) epiphenomenon of elevated IgE in atopy and the same (acquired) epiphenomenon in the other entities? IgE synthesis occurs exclusively in one's B-cells, initiated by two signals. Signal one is cytokine-dependent (IL-4, IL-13), and signal two is delivered by T-cells (CD40) through a complex series of interactions.

In the atopic, the first signal to produce the epiphenomenon comes from allergen-specific mast cells, basophils, and Th2 cells, which secrete the cytokines (IL-4, IL-13). While for the non-atopic, the first signal comes from non-allergen-specific T-cells, which also produce IgE, but the latter IgE is polyclonal, rather than allergen specific [17]. The predominant proportion of the IgE response in the other hyper-IgE states is polyclonal. Allergen-specific IgE-mediated hypersensitivity reactions are rare in patients with chronic helminth infections [17]. The highest levels of (polyclonal) IgE are detected in some parasitic infections. It has also been noted that IgE production in these patients is concomitantly associated with suppressive IFN- γ (IgG4) levels [18] (which has not been noted in the atopic diathesis). Elevated (polyclonal) IgE levels are also considered the hallmark of the Th1/Th2 reversal occurring in advanced HIV infection [9]; in fact those IgE levels are used to follow the progression of AIDS in HIV-infected adults [19].

It is indeed surprising that the WAO concludes, 'In children and young adults of atopic constitution, the underlying inflammation is dominated by an IgE-antibody associated reaction' [20], instead of recognizing IgE as merely one of many 'triggers' of inflammation in the atopic (see below). Is the WAO suggesting that the 'localized' eczema that occurs (only) in the antecubital fossa, or eyelids, in atopic patients is dominated by an IgE-antibody associated reaction?

Not all atopic patients with elevated, allergen-IgE antibodies react clinically to their respective, specific exogenous antigen (particularly in patients with atopic dermatitis). Yet it is well known that IgE-mediated hypersensitivity reactions may at times be responsible for an exacerbation of atopic dermatitis, without being central to its pathogenesis. For example, histamine release during food hypersensitivity reactions may result in a transient increase in itching of atopic dermatitis, causing the patient to scratch, which then elicits the eczema [21]. Specific allergens have also been known to provoke flares of other existing etiologically unrelated dermatitis in susceptible persons.

Ongoing epidemiologic studies support the view that production of IgE can often be a prerequisite for the recognition of atopy ('allergic symptoms'). The role of genetics in IgE regulation has been well-documented [22]. Many, if not all, of the known factors for IgE regulation and IgE-dependent reactions carry a polymorphism, associated with specific atopic phenotypes.

The biphasic pattern of T cell behavior has been accepted specifically for atopic inflammation, strongly purporting that the atopic syndrome is Th2 cell driven [23–25]. Results of T cell studies consistently confirm the central role for IL-4 and IL-10 in the regulation of both IgE and non-IgE-mediated responses. This clearly reflects the shift in the Th1/Th2 paradigm. The development of IgE antibody-mediated immediate type hypersensitivity to common allergens is frequently associated with allergic symptoms, though sensitization to allergens without symptoms is more frequently observed. There is clearly no correlation between titers of IgE antibodies and symptoms. Indeed, there are some patients with severe asthma with low to no titers of allergen-specific IgE antibodies, and emerging evidence that other systemic regulatory mechanisms are associated with their disease activity (J.A. Woodfolk, presented at the World Allergy Forum at the AAAAI 60th Annual Meeting; 21 March 2004; San Francisco, California).

It should be evident, given the vagaries of IgE levels, that this epiphenomenon cannot be the distinguishingly distinct feature of atopy. Thus, absence of antigen-specific IgE cannot rule out the atopic diathesis. While

the source of the epiphenomenon seems to be the more consistent denominator of the atopic diathesis, the unique behavior of the transient Th1/Th2 cell behavior must be the hallmark of atopy.

I have suggested the following definition for atopy: Atopy is the expression of an array of polygenic and phenotypic immunologic aberrations, in which a spectrum of inflammatory reactions may occur in various organ systems, induced by the cytokinal profile of a transient Th1/Th2-cell reversal. These effector cells can be activated by both immunologic and non-immunologic secretagogues, and it is the genetic propensity for the Th2 cell dominance and presence of specific high affinity IgE receptors on Langerhans' cells, and hyper-releasable basophils, that differentiates them from non-atopics. Elevated IgE levels and eosinophilia are but epiphenomena of Th2 cell activation.

The 'eczema' of atopic dermatitis

D.Y.M. Leung clearly demonstrated that both the involved and uninvolved skin of patients with atopic dermatitis has an increased number of Th2 cells. The acute Th2 cell infiltration in atopic dermatitis [26], and its cytokinal increase of IL-12 in chronic atopic dermatitis skin lesions, along with its expression on eosinophils or macrophages that initiates the switch to Th1 cell development in chronic atopic dermatitis [27].

Acute atopic dermatitis lesions are characterized by intracellular and intercellular edema of the epidermis (spongiosis). In the dermis, a marked perivenular infiltrate of T cells and some monocytes-macrophages are present. Eosinophils, mast cells, and neutrophils are rarely present in acute atopic dermatitis lesions. In chronic atopic dermatitis, the epidermis is hyperplastic and hyperkeratotic with increased epidermal Langerhans' cells. Cellular infiltrate in the dermis consists of predominantly macrophages and eosinophils and, thus, the cytokinal release from the various cell types in atopic dermatitis skin lesions that produce the noted skin inflammation [28].

As has already been noted, the immunologic (i.e. cytokinal) hallmark of atopic dermatitis is the result of the Th1/Th2 imbalance. Several determinants are required for Th2 cell development early in atopic skin; these include the cytokinal milieu, the host's genetic propensity, pharmacologic factors, costimulatory signals, the site of antigen entry, and antigen presenting cells [29].

There is little doubt that T helper cells are the effector cells for all spongiotic dermatoses, with Th1 cells producing (the vesiculo/bulla) of allergic contact, and 'other' dermatitides, and Th2 cells inducing and impacting the (vesicular but never bullous) spectrum of atopic eczemas. Perhaps some day, histopathology will be able

to differentiate the Th1 cell eczemas from the Th2 cell driven eczemas.

While there is no published documentation of T-cell activation in atopic dermatitis, by non-IgE secretagogues, from our clinical observations regarding the behavior of atopic dermatitis, we can conclude that non-IgE provoking exacerbations of atopic dermatitis, including xerosis, irritants, sweating, scratching, infection, do so by triggering the T-cells. It is not just allergens that activate the T-cells.

Another important, specific pathophysiologic factor regarding the eczema of atopic dermatitis, which has been overlooked, is its isomorphic reactivity. Koebner described this phenomenon in 1872, when he noted the elicitation of respective lesions (psoriasis, lichen planus), induced by a variety of traumatic insults, such as scratching [30]. L.E. Holt recognized, circa 1950, that the variable distribution of the eczema of infants with atopic dermatitis was dependent on their ability to (initially) rub, and (subsequently) scratch their itch [31]. The accepted dictum that 'atopic dermatitis is an itch that erupts, rather than an eruption that itches' should be questioned. Many of us believe there is no 'primary lesion' of atopic dermatitis; instead it is pruritus that initiates the rubbing, or scratching, which brings out the eczema. Thus, promoting treatments that address this pathophysiologic mechanism would be essential in the management of patients with atopic dermatitis (see below).

A corollary of the isomorphic reaction would be the rationalization that localized eczema (i.e. 'eyelid' dermatitis, 'nipple' dermatitis, nummular eczema) in atopic patients may all be a variant in the atopic dermatitis syndrome.

The pruritus of atopic dermatitis

Pruritus is universally recognized as the cardinal symptom of atopic dermatitis. Unfortunately, it continues to be rationalized merely as the result of the atopic patient's 'lowered threshold' of itch. Whereas Wahlgren *et al.* [32] recognized it more appropriately as 'the atopic's innate perception of mechanical stimulation as "itch" rather than touch'. They also noted that once an itch begins in patients with atopic dermatitis, there is an increased liability of the surrounding skin to react to slightly mechanical, otherwise non-itching stimuli with itch (a phenomenon they call 'alloknesis'). A possible explanation for the hypersensitive reactivity of atopic skin is the presence of hyperplastic nerve fibers with enlarged axons, noted in the skin by Sugiura *et al.* [33] and Rapp and Kopp in this issue. In a questionnaire given to immunotherapy patients in my office, without a past or present history of atopic dermatitis, 46% ($n = 128$) reported their skin was

itchier than other, compared with 12% of non-atopic patients ($n = 144$).

Pruritus is most often the initial symptom of eczema in patients with atopic dermatitis. Yet the mediators of itch in atopic dermatitis have not yet been positively identified, although many putative candidates have been suspect. Histamine, a most important recognized pruritogen, is unlikely to play the major part because of the lack of clinical efficacy of non-sedating antihistamines [34,35]. With histamine being the key mediator of itch for IgE-dependent allergic reactions [36] and with the anecdotal lack of success of omalizumab (anti-IgE) therapy in atopic dermatitis, a primary role for IgE in atopic dermatitis remains debatable.

Moreover, naltrexone, an opiate antagonist, was found to significantly reduce both itching and alokneses in patients with atopic dermatitis [37] but other studies found the effect of the drug less convincing [38]. Stander and Steinhoff [39] attribute the lack of response to opioid antagonists in all patients with atopic dermatitis, to the fact that both immunological and non-immunological factors must be contributing to their itch [39]. Interestingly, topical calcineurin inhibitors, which inhibit the release of cytokines (i.e. IL-2, IL-3, IL-4, IL-5, GM-CSF, and TNF- α) from Th2 cells, clearly reduce the itch severity of patients with atopic dermatitis [40]. Thus, the release of the cytokines, which instigate the pruritus, like IgE levels, is another epiphenomenon of Th2 cell activation, by either or both immunologic and non-immunologic stimuli. Avoidance of every 'trigger of itch' [41], especially the scratching, should be the primary objective of management of patients with atopic dermatitis: anti-inflammatory medications are merely 'band-aids'. Suppressing the inflammation (the eczema) without elimination of the triggers, ensures a recurrence.

Conclusion

Current conceptual precepts produce change slowly. Von Hebra would certainly have argued against the possible role of immunoglobulins, cytokines, and T cells in his *prurigo diathesiques* in 1892. While Sulzberger, might have been intrigued in 1933. In 1981, the Hanifin–Rajka classification for the diagnosis of atopic dermatitis resolved so much of the ambiguity, that despite its pre-T cell/cytokine foundation, it is still quasi-universally guiding our researchers. One hundred years after Besnier, we have so much more science to decipher, in a computerized milieu, and yet be held responsible by an international congregation.

Perhaps appropriately, George Bernard Shaw facetiously noted that 'science is always wrong – it never solves a problem without creating ten more'. In the present-day knowledge explosion, it must create one hundred more.

In this article, I have questioned much of the present-day dogma, and offered some, I believe, etymological and scientifically appropriate, practical variations on the theme, that is, atopic dermatitis.

As an epilogue, I see atopic dermatitis as the dermatologic syndrome which heralds the atopic diathesis. Essential for making that diagnosis are atopy, the polygenic, phenotypic cause of immunologic aberrations; pruritus, the instigator of scratching/rubbing, activating Th cells; and eczema, the Th2-cell driven spongiosis. A full understanding of those essentials would direct management of patients with atopic dermatitis to prophylaxis rather than merely relieving symptoms. Emphasizing the recognition and then evading the triggers of those instigators of trauma, to the defective epidermis, should supplant the urge to contain the ensuing inflammation. Unfortunately, we continue to be directed by our ability to suppress inflammation, which to date surpasses our willingness to preclude its recurrence.

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