Contact dermatitis in atopic individuals

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Purpose of review
Both atopy and diseases from the spectrum of dermatitis and eczema are among the most frequent clinical problems worldwide; nevertheless, they are still poorly defined and too frequently misdiagnosed. In the present review, studies pertinent to this topic were systematized and critically assessed with particular attention to definitions of relevant diseases.

Recent findings
The overall message from the research done to date is that various types of dermatitis frequently coexist. Atopy and contact allergy seem independent, while there is insufficient data to state upon the relationship between atopy and allergic contact dermatitis. Furthermore, it seems at present that atopy does not, whereas atopic eczema does constitute a risk factor for irritant contact dermatitis.

Summary
The interplay between atopy and diseases from the spectrum of dermatitis and eczema is not fully understood; nevertheless, their coexistence and overlapping are not rare. Therefore, every patient with eczema – regardless of age, sex or atopic status – should undergo an extensive diagnostic programme including each atopic eczema, irritant contact dermatitis, allergic contact dermatitis, and protein contact dermatitis. Better definitions and well designed studies are necessary to achieve detailed information on the complex relationships between each atopy, atopic eczema, and the three contact dermatitides.

Keywords
allergic contact dermatitis, atopic eczema, atopy, irritant contact dermatitis, protein contact dermatitis

Motto: The world of atopy is definitely shrinking as the experimental work on allergic sensitizations expands.

R. L. Mayer (1957) [1]

INTRODUCTION

Irritant contact dermatitis (ICD), allergic contact dermatitis (ACD), and protein contact dermatitis (PCD), together with atopic eczema (AE) belong to the clinical spectrum of dermatitis/eczema. These diseases are sometimes depicted as mutual opposites; however, their clinical features and pathomechanisms overlap to an extent making any clear-cut differentiation virtually impossible. When looking at studies of the relationships between atopy and the dermatitides, difficulty of drawing general conclusions becomes apparent, mainly due to imprecise definitions and incompatible outcome measures. In the present analysis, special attention is paid to differences between relevant terms as defined below.

Atopy is a tendency to produce IgE antibodies in response to low doses of allergens (usually common environmental proteins), to which the majority of people in similar exposure would not produce IgE. According to the present understanding, the term 'atopy' should not be used until an IgE sensitization has been confirmed by detecting specific IgE antibodies in serum or by positive skin prick tests [2].

Contact allergy (delayed-type hypersensitivity, type IV allergy) is an acquired readiness to cell-mediated inflammatory reactions against specific haptens (exogenous chemicals of molecular weight below 500 Dalton that can penetrate through intact epidermal barrier), to which most people in similar exposure would not react. The presence of contact allergy is connected with a tendency to developing a range of diseases – most typically ACD [3].

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KEY POINTS

- Atopy and contact allergy appear as independent phenomena and may coexist in individuals in a random manner.
- Clinical features of atopic eczema and contact dermatitides overlap to an extent compromising results of clinical studies.
- At present it seems that atopy does not, whereas atopic eczema does constitute a risk factor for irritant contact dermatitis.
- Data from available studies are insufficient to state upon the relationship between atopy and allergic contact dermatitis, however, it is apparent that both conditions frequently coexist.

Atopic eczema (synonym: atopic dermatitis) is a chronic inflammatory skin disease that commonly begins in early infancy, runs a course of exacerbations and remissions, and is associated with a characteristic distribution and morphology of skin lesions. Furthermore, pruritus and subsequent sleeplessness are hallmarks of this disease [4].

Contact dermatitis (synonym: contact eczema) is a collective term for three dermatitides with various causes, whose common feature is the development of skin inflammation in response to direct contact with the provoking agent: irritant contact dermatitis; allergic contact dermatitis; and protein contact dermatitis [5].

ICD is acquired inflammatory skin disease caused by chemical or physical insults leading to direct cellular injury. Most ICD cases are associated with detergents, solvents, acids or alkali. Acute ICD (toxic dermatitis) develops rapidly (minutes to hours) after exposure to potent irritants, whereas chronic, cumulative variants of ICD develop gradually in response to repeated contacts with milder irritants [6]. ICD is essentially an injury; therefore, everyone will develop this disease after an individual threshold of resistance to irritants is exceeded [7].

ACD is an inflammatory skin disease initiated by specific immune reactions to a hapten. It occurs in individuals with previously acquired contact allergy following re-exposure to the sensitizing hapten [8]. In contrast to ICD, only a minority of people exposed to a particular hapten will respond with dermatitis.

PCD is acquired inflammatory skin disease initiated by specific immune reactions to allergens – proteins with molecular weight exceeding 10000 Daltons – usually of animal or plant origin [9,10]. As molecules of this size cannot pass through the intact skin barrier, preexisting skin damage seems to be a prerequisite. The pathogenesis of protein contact dermatitis remains unclear: at present, type I and type IV hypersensitivity reactions are discussed, along with a possibility of delayed reaction initiated by IgE-bearing Langerhans cells, in which PCD strikingly resembles present concepts of atopic eczema [11].

CONTACT DERMATITIS IN ATOPIC INDIVIDUALS

In line with the above definitions, the question of contact dermatitis in atopic individuals must be divided into several more specific ones, that is, what is the relationship between atopy and each ICD, ACD, or PCD? Inclusion of atopic eczema into this discourse as a counterpoint to atopy seems necessary, as these two terms are too frequently misused as synonyms [12]. An overview of definitions of atopy used in former studies (Table 1) [13–20,21▪,22–25] is a good illustration of difficulties with obtaining unequivocal answers to the above questions.

IRRITANT CONTACT DERMITITIS IN ATOPIC INDIVIDUALS

The relationship between atopy and ICD has been quite extensively studied in experimental settings, and with the exception of one early study [13], no increased skin susceptibility to model irritants sodium lauryl sulphate (SLS) or dimethyl sulfoxide (DMSO) has been observed in people with respiratory atopy, elevated total IgE, as well as past (inactive) atopic eczema [14–16,18,19]. On the contrary, there was only one epidemiological study looking into this relationship [17], in which 72% of patients diagnosed with occupational ICD were 'atopics' as compared with 30% estimated in the general population; also the mean latency period from employment to first symptoms of occupational ICD was shorter in 'atopics' than 'nonatopics' (64 versus 72 months). Unfortunately, the group deemed by the authors as 'atopics' consisted of undefined proportions of people with 'respiratory atopy' and atopic eczema – either past (inactive) or present (active), which hampers any sound discussion of the disagreement between acute experimental and epidemiological observations.

IRRITANT CONTACT DERMITITIS IN ATOPIC ECZEMA

The overall conclusion from a series of experimental studies is that of increased susceptibility to irritants in active atopic eczema (recently reviewed in [26▪]). Filaggrin deficiency was postulated as a possible

Table 1. The various definitions of atopy used in studies of topics within the scope of the present review, ordered chronologically. Note that in two recent studies [23,24] the term `atopy' was used in the actual meaning of `atopic eczema'

Publication year	Definition of 'atopy' (or 'atopic' patients)
1994	'Positive personal and family history of seasonal asthma or allergic rhinitis and no history of dermatitis, and one or more positive prick test responses to a panel of 10 common aeroallergens' [13].
1996	'Patients with allergic asthma or rhinitis (or both)' [14].
1998	'(...) atopics (defined broadly by high IgE reactivity)' [15].
1999	'Respiratory atopy: individuals with a typical history of rhinoconjunctivitis or atopic asthma and showing at least 1 positive prick test to a relevant aeroallergen' [16].
	'Erlangen Atopy Score' (a combination of skin and respiratory symptoms, family anamnesis, and IgE) [17].
2000	Patients 'with allergic rhinitis but no asthma, without a personal history of dermatitis and with positive prick test responses to grass pollen but not to house dust mites, showing symptoms exclusively during the pollen season' [18].
2002	'Respiratory atopy patients' [19].
2005	'Positive skin prick test results, positive Phadiatop test results, and total IgE levels greater than 120 kU/L were used as atopy markers' [20].
2011	'(...) atopy, defined as positive skin prick test to one or more common airborne or food allergens' [21▪].
	'(...) atopic individuals (AIs) according to a current history of at least one of AD, AR, or AA' (where, AD – atopic dermatitis, AR – allergic rhinoconjunctivitis, AA – allergic asthma) [22].
	'atopic pediatric patients' = patients who 'had met Hanifin and Rajka criteria for a diagnosis of atopic dermatitis' [23].
	'(...) atopic patients (according to Hanifin and Rajka criteria)' [24].
	'The participants were considered atopic when at least two of the following criteria were present: having a clinical history of atopic dermatitis, allergic rhinitis, allergic asthma, or food allergies; each confirmed by prick test' [25].

'molecular link' between atopic eczema and ICD [27,28]. There are also other relevant components of the skin barrier, for example, claudins – transmembrane proteins pivotal to the tight junctions between cells, including keratinocytes: a reduced expression of claudin-1 and 23 in patients with atopic eczema was recently reported [29]. Nevertheless, the increased susceptibility to irritants may also be an unspecific effect of skin barrier damage due to inflammation, irrespective of its actual cause [16].

CONTACT ALLERGY IN ATOPIC INDIVIDUALS

When analyzing published research results, one has to realize the substantial, yet sometimes overlooked difference between contact allergy (altered immune reactivity detected with patch tests) and the actual disease 'allergic contact dermatitis'. The relationship between atopy and contact allergy was discussed elsewhere, with the overall conclusion that these are independent phenomena that may coexist randomly in the same person [20].

CONTACT ALLERGY IN ATOPIC ECZEMA

In an experimental sensitization study [30] utilizing a potent contact sensitizer dinitrochlorobenzene (DNCB), only 33% of patients with severe atopic eczema could be sensitized, as compared with respectively 100 and 95% of patients with mild and moderate atopic eczema, indicating a diminished contact sensitivity in severe atopic eczema. In an epidemiological observation, however, the severity of atopic eczema appeared as a significant risk factor (odds ratio, OR = 3.3) for developing contact allergy to topical drugs [31]. This discrepancy between acute experiment and epidemiology may have various explanations: perhaps a massive, long-term exposure to haptens from external drugs overcompensates for the decreased ability to develop contact sensitization in severe atopic eczema, or alternatively contact allergy may be acquired during remissions of the disease. Other cross-sectional studies of this relationship lead to discordant conclusions, possibly due to usage of different definitions of atopic eczema and contact allergy (Table 2) [23,32–36]. Regardless of these discrepancies, the core message from these studies remains clear: contact allergy should be considered in every patient with atopic eczema, and topical drugs along with emollients are frequent sensitizers and should be included in routine patch testing in this group.

ALLERGIC CONTACT DERMATITIS IN ATOPIC INDIVIDUALS

In the previously mentioned epidemiological study [17], 60% of patients with diagnosed occupational

Table 2. An overview of recent studies on the relationship between atopic eczema and contact allergy

Study population	Definition of atopic eczema	Definition of contact allergy	Summary of main results and source
1146 Danish schoolchildren (12–16 years) [32]	Questionnaire by Schultz Larsen, Diepgen and Svensson [33]	At least one positive reaction to patch tests on day 3	No association between AE (lifetime prevalence) and CA
3202 random Danish adults (18–69 years) [34]	UK Working Party's diagnostic criteria (self-reported history of an itchy skin condition plus a minimum of two of four minor criteria) [35]	At least one positive reaction to patch test on day 2	CA more frequent among participants who reported AE (13.6%) than those who did not (9.5%, significant difference, $P=0.018$)
101 Californian paediatric patients (6-18 years) [23]	Hanifin and Rajka criteria [36]	At least one positive reaction to patch tests on day 3 or 7	CA in 89% patients with AE, as compared 66% of those without AE (significant difference, Z-score 2.78)

AE, atopic eczema; CA, contact allergy.

ACD were 'atopics', as compared with 30% in the general population, also the mean latency period was shorter for 'atopics': 71 versus 84 months in 'nonatopics'. The reader, however, is reminded of the above-discussed problematic definition of 'atopy' in this study.

ALLERGIC CONTACT DERMATITIS IN ATOPIC ECZEMA

Among paediatric patients with physician-diagnosed atopic eczema (based on Hanifin and Rajka criteria), concomitant ACD was found in 33% of children and 73% of adolescents [37▪]. This demonstrates that comorbidity of ACD is frequent among atopic eczema patients and increases with age, confirming previous observations [38]. Moreover, it seems probable that a considerable number of adult patients with 'persistent atopic eczema' suffer, in fact, from undiagnosed secondary ACD sustained by external drugs or emollients.

PROTEIN CONTACT DERMATITIS IN ATOPIC INDIVIDUALS

Until now, there are no systematic epidemiological data addressing directly the relationship between atopy and PCD; however, clinical observations indicated on a possible connection [39–41]. In a recent study [42▪] of 27 patients diagnosed with PCD, 52% had a history of atopy. A characteristic 'atopic marsh' including PCD was described in a patient, who in a period of 16 years suffered at various stages from occupational allergic rhinitis, PCD, asthma, allergic conjunctivitis, and finally contact urticaria – all due to IgE-mediated allergy to cow dander [43]. Altogether, these scarce data seem to place PCD within the spectrum of atopic diseases.

PROTEIN CONTACT DERMATITIS VERSUS ATOPIC ECZEMA

Recently proposed diagnostic criteria for PCD include the presence of chronic or recurrent eczema due to contact with protein-containing material and positive prick test reaction to this material [44▪], thus making the entity PCD 'atopic' by definition. As history of atopic eczema is found in every second PCD patient [45,46], it seems probable that PCD may, in fact, be a subtype of atopic eczema – actually, the subtype that fits best into the spectrum of atopy-related diseases, next to allergic rhinitis or asthma. At present, however, we know too little about aetiologies of both PCD and AE to verify these conjectures.

FUTURE RESEARCH NEEDS AND LIMITATIONS

For reliable research of the relationships between atopy, atopic eczema and contact dermatitides, well defined criteria are necessary that would enable accurate differentiation between analysed conditions and diseases. Nowadays, we seem to have unequivocal clinical criteria for atopy (positive sIgE or skin prick tests to common allergens). The identification of contact allergy with the use of patch tests seems also relatively straightforward and well validated, nevertheless, one has to keep in mind that the diagnostic effectiveness of patch tests depends on the composition of test series (more extensive series detect more people with contact allergy) [47,48▪]) and time of reading (prolonged observation detects more contact allergy) [49,50,51▪]). Even the method of application may influence the results: for example, patch test applied with IQ Chambers shows better sensitivity than T.R.U.E.

test [52], which in turn seems more sensitive than testing with Finn Chambers [53]. Good identification of ACD in future studies seems quite feasible through combining a positive patch test with confirmation of its clinical relevance [3]); however, the assessment of relevance may be biased by an investigator's competence and technical facility for detecting suspect haptens in the patients' environment [54].

The level of difficulty substantially increases with ICD: this disease is relatively easy to reproduce in acute experiments with known irritants, like SLS or DMSO; however, the clinical (and thus epidemiological) diagnosis is made by exclusion of other eczemas, owing to the present lack of confirmatory diagnostic tests for ICD. This implies a considerable amount of subjectivity and a resulting risk of misdiagnoses that could jeopardise results of any epidemiological study. Moreover, a range of various ICD types are distinguished [55] – it seems possible that atopy may be relevant to some of them, but not to others. In the end, the difficulty with designing credible epidemiological studies reaches a level of virtual impossibility in case of atopic eczema – a conspicuous, yet ephemerid entity, as to which there is still no agreement whether it should be regarded as a condition, a disease or a syndrome [56,57,58▪▪]. Flexural eczema – almost a 'diagnostic fetish' in past epidemiological studies of atopic eczema has been ultimately discredited [59], not least so because this clinical feature is also not uncommon in ACD [37▪,60,61,62▪,63▪,64]. Cases of ACD-related flexural eczema have been misdiagnosed as atopic eczema for decades [65–67], which may be due to the fact that in most ACD literature, flexural eczema is part of a wider picture referred to as 'hematogenous contact eczema', 'systemic allergic dermatitis', 'systemically induced ACD' or 'baboon syndrome', and only exceptionally gains more visibility while being referred to as 'flexural exanthema' [68]. Interestingly, the pattern of 'flexural allergic contact dermatitis' was described in a series of patients externally exposed to a sensitizing hapten (ingredient of a bath oil) over the entire body, suggesting that the skin of flexural areas is more vulnerable also in ACD [69].

The above-mentioned problems with definitions of diseases may be solved by applying nonclinical criteria in future research. Highly promising in this respect seem results of a study [70] showing that immunohistochemical staining of skin biopsies for five marker proteins associated with epidermal activation (hBD-2, elafin and KRT16), cellular proliferation (Ki67) and infiltration by cells of haematopoietic origin (CD45) may suffice for the differentiation between psoriasis, atopic eczema, allergic contact dermatitis and irritant contact dermatitis. Determination of CCL17 and CCL27 may further help with distinguishing between ACD and atopic eczema [71]. Another interesting option is genetic markers of atopic eczema [72], a concept that actually had been employed recently in epidemiological research [73]. After multicentre validation of such markers in well defined groups of patients, they might provide a relevant step forward for the benefit of both science and patients.

CONCLUSION

Skin diseases from the spectrum of dermatitis and eczema are difficult to differentiate, based merely on clinical and histological features. This creates a considerable risk for misdiagnoses in both clinics and research, resulting in a great deal of confusion and misconceptions. Future studies should be aimed at overcoming the present methodological problems – especially the ephemerid and internally conflicted definition of 'atopic eczema' and the vague and devoid of any confirmatory feature definition of irritant contact dermatitis. Nevertheless, even with the present limitations, a clear message from completed studies is that various kinds of eczema/dermatitis frequently coexist in both atopic and nonatopic individuals. Therefore, an extensive diagnostic work-up covering all above-discussed kinds of dermatitis should be employed in every eczema patient, regardless of the preliminary diagnosis or atopic status.

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Conflicts of interest

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