

Review article

Polysensitization and increased susceptibility in contact allergy:
a review

Genetic factors presumably play a role in contact allergy (CA). There is, however, a lack of conclusive evidence from clinical studies. This may be on account of the strongly competing or modifying impact of exogenous factors, namely the potency of allergens and the intensity of exposure, and the fact that – in principle – everybody can be sensitized. Regarding phenotype, in contrast, polysensitization (PS) seems to indicate a subset of individuals at greater risk. In human sensitization experiments with dinitrochlorobenzene, induction was facilitated in PS, and elicitation enhanced. Recent clinical epidemiological data, taking confounders for PS, such as age, sex, and other skin diseases into account, demonstrated the following: (i) PS was the greatest risk factor to be sensitized to a number of (even weak) index allergens, indicating higher susceptibility on the level of induction; (ii) patch test reactions in PS patients were generally stronger indicating higher susceptibility on the level of elicitation. These findings are complemented by reports on polymorphisms of TNF- α and IL-16 in PS patients. Future studies on the genetics of CA should be performed in subgroups with PS, focussing on polymorphisms relevant for CA-specific and nonspecific (inflammatory) processes.

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The role of genetics in the development of atopic diseases was extensively studied during the last decade (1). The type of inheritance is multifactorial with many genes and environmental factors contributing to the observed phenotypes. In contrast, there is a lack of conclusive evidence regarding the role genetics in contact allergy (CA) as summarized in (2). This may at least partly be because of an insufficient operational definition of a susceptible individual or a phenotype inherently at greater risk – a general problem in the study of complex disease genes. Here, we review evidence indicating that polysensitization (PS) to contact allergens may be regarded as a phenotype of increased susceptibility to CA, and not merely the result of multiple allergen exposure.

Contact allergy

Contact allergy is an exaggerated reaction of the individual's immune system following dermal exposure to low molecular weight chemicals by employing the tools of normal cell-mediated immune mechanisms. It can thus be considered as an untoward side-effect of an otherwise well-functioning immune system (3). As in allergic diseases in general, two sequential phases can be distinguished: In the case of CA it is first the induction phase leading to sensitization of the individual, with hapten-specific T-lymphocytes as 'hidden witnesses' of the first

happen encounter. This is followed by the effector or elicitation phase after re-exposure to the hapten, with eczema (allergic contact dermatitis; ACD) as the clinically evident manifestation of CA. As in the case of other allergic diseases, CA may remain 'mono-phasic', if sensitization has been proven, normally by diagnostic patch testing, but where clinical symptoms, that is previous eczema, has not been observed so far.

Susceptibility

In medicine, the term susceptibility is widely used, namely in the sense of 'predisposition to a disease', yet normally without referring to a general concept or definition. Hence, its meaning is revealed only in the different actual applications of 'susceptibility'. Implicitly to this notion, it is postulated that some or many individuals are 'unsusceptible' (dichotomous classification), or may be more or less susceptible (graded ordinal classification). This predisposition may be acquired, may develop and may be on account of genetic variation for which certain phenotypes or genotypes or both are indicative. There are many examples for each of these conditions: Susceptibility to opportunistic infections in patients infected by HIV is acquired. Susceptibility to osteoporosis and cancer increases (develops) with age, but may have, at the same time, a genetic basis. Susceptibility for UV-light induced

skin cancer is increased in individuals with pale skin (a phenotypic classification with a probably complex underlying genotype) and is dramatically increased in patients with Xeroderma pigmentosum (autosomal recessive inheritance).

Similarly, different pathways of susceptibility may also exist in CA. Susceptibility is clearly acquired in patients with venous insufficiency and leg dermatitis (4), or with chronic hand eczema caused by wet work, or mechanical, or chemical irritation (5). Susceptibility may develop over time, e.g. together with endocrinological changes, like in women under the influence of female hormones (6). In contrast, susceptibility to CA may decrease with age. Despite an increase of the frequency and number of sensitizations with age, probably on account of an increased opportunity to be exposed to allergens during life (4, 7), the capacity for (new) sensitization and elicitation may be diminished in older ages (7, 8).

However, the phenotype and the genotype of inherent increased susceptibility to CA are largely unknown. Sulzberger and Rostenberg had shown in an experimental study that individuals with a 'recent or active proven eczematous dermatitis' were more readily sensitized to dinitrochlorobenzene (DNCB) and *p*-Nitroso-N,N-dimethylaniline (NDMA) than individuals without past or present allergic eczema (9). Numerous studies in patients with manifest eczema corroborate these findings (10). A decreased threshold against irritating substances (which, at the same time may act as sensitizers) was a common finding in various studies (10). However, this increased reactivity to chemicals (irritation or sensitization) does not necessarily indicate inherent and permanent susceptibility, as it may merely be a temporary state 'status eczematicus'. It would thus be acquired, and return to normal after clearance of eczema (11). Additionally, an inherent increased nonspecific irritability of the skin may be relevant as an inborn trait of individuals who develop ACD more easily (12). It cannot be decided which out of above both factors (acquired and/or inherent) had played the crucial role in the above induction experiments. Nevertheless, the important role of (nonspecific) inflammation in the pathogenesis of ACD (13) resulted in the modern concept of the 'danger model' (14).

However, in our view, it would be premature to explain the fact of being sensitized to one chemical merely by the individual's inherent susceptibility. An intense exposure may be sufficient, because (almost) everybody with a normal immune system can be sensitized by a sufficiently high induction dose. This has been proven by several induction experiments (15, 16) (see below: experimental findings). In a twin study in individuals allergic to nickel, only a slight, nonsignificant association with genetic factors was observed (21). Furthermore, important exogenous factors increasing the risk of CA exist, which may blur the view on possible genetic influences. These comprise the inherent sensitizing potency of a chemical, which differs considerably between chemicals (17), and

exposure to the chemical as expressed by dose (single and cumulative), and time (18). In addition, these exogenous factors may interact with individual inherent factors: family studies have shown that children could be experimentally sensitized to the strong allergen DNCB regardless of sensitization in their parents, whereas using the weaker allergen NDMA children were sensitized significantly more often if their parents were sensitized (19). This could indicate that increased susceptibility may play a role in sensitization to weaker allergens, whereas the influence of susceptibility is overridden in the case of stronger allergens. This view is supported by a twin study in which monozygotic and dizygotic twins were sensitized with equal success to the strong allergen DNCB (20). Nevertheless, the current view of a possible gene-environment interaction in CA ascribes the dominant role to allergen exposure and not to genetic factors (21).

Are atopic dermatitis patients more susceptible to CA? The discussion on this question has been controversial for a long time (22). A decreased as well as an increased baseline risk to become sensitized to 'delayed type' contact allergens has been postulated. A fresh, differentiated look on this controversy seems appropriate. Susceptibility to sensitization to contact allergens may vary, e.g. with the clinical severity of atopic dermatitis (AD) and was remarkably low in patients with serum IgE levels above 1000 IU/ml. Furthermore, the group of patients with AD has been found to be heterogeneous as regards to their responses to immediate type hypersensitivity allergens (23, 24) – such heterogeneity may also exist with regard to CA. Contact allergy, in particular PS to contact allergens, may be a characteristic of those AD patients who have a continuing problem with their AD. In an unselected patch test population ($n = 456$), those patients with AD averaged 2.7 relevant positive patch test responses compared with 2.0 in the nonatopic group ($P = 0.02$). Reviewing the literature on sensitization experiments, clinical and population-based studies, biochemistry, and functional aspects of atopic skin (barrier function) and immunological findings in atopy, Schnuch et al. (22) concluded that possible mitigating effects of AD on the pathogenic process of ACD on the immunological level may be compensated by the established barrier dysfunction facilitating the penetration of haptens in AD. Therefore, it appears reasonable to assume a largely similar susceptibility to CA in persons with and without AD (22).

Polysensitization

Both in (type I) – inhalant allergies and in (type IV) – contact allergies the term PS (syn.: multiple sensitization, polyvalent sensitization) describes sensitization to more than one allergen, verified by appropriate tests (e.g. skin prick test, specific IgE assays and epicutaneous patch testing, respectively). Polysensitization is not necessarily

associated with manifest symptoms (8). Although concomitant sensitizations may be on account of different causes (exposure-related, cross-allergen-related, test-related – see below), PS is used here as a synonym for ‘concomitant reactions’.

Polysensitization in atopic diseases is associated with increased severity of allergic diseases (25, 26), with an immunological profile different from that found in mono-sensitized (24), and a familial coincidence suggesting a genetic basis (27, 28). However, PS in atopic diseases is beyond the scope of this review focused on PS in CA.

Background: polysensitization in contact allergy

In a population-based and in a clinical study, PS was observed significantly more often than what might be expected compared to the occurrence of single sensitivities (29, 30). Moreover, there was an increased risk in terms of a high ratio of observed to predicted prevalence of sensitization associated with the number of sensitivities (30). In several patch test studies high percentages of individuals turned out to be polysensitized (>1 allergic reaction), namely, in population-based studies 15–36% (31, 32), and in most clinical studies about 40–50% of those who reacted allergic (30, 33–36). In a recent study from Denmark almost 15% of those reacting allergic had three or more than three contact allergies (37). Thus, PS may not simply occur by chance, but it may be a phenomenon in its own right. Several factors may contribute to this phenomenon.

Exposure

The most important (and trivial) reason for PS may be simultaneous or successive exposure to multiple allergens. Exposure to allergens at the same time or the same occasion may cause sensitization to the allergens encountered in the specific environment. Examples can be found in certain occupations like hairdressers, or in subgroups of patients exposed to topical drugs. Exposure to allergens often used or found together may also be the cause of PS as in the case of fragrances (almost always mixtures of many single compounds), cosmetics (containing fragrances and preservatives), or tools and jewellery (metals). Conversely, no specific pattern of exposure may be discernible, when multiple sensitizations have been acquired on several unrelated occasions over time (8, 38). However, case reports on PS in young children under the age of 10 may indicate that PS is not always linked to long term, cumulative exposure to allergens, but may apparently be related with individual susceptibility factors (39, 40).

Cross/concomitant reactions

Polysensitization (concomitant reactions) may be on account of cross-reactivity because of structural similarity

of the allergens (41). Some allergic reactions tend to remain singular [monosensitization (MS), e.g. to thio-mersal or nickel (36)], others occur in specific clusters, such as aminoglycoside antibiotics (42) or para-substituted aryl compounds like paraphenylenediamine (PPD), paraaminoazobenzol, or benzocaine (88). Non-immunological cross reactions, also called ‘false cross sensitivity’, may be on account of the presence of the same hapten in different allergens, e.g. limonene in different ‘cross-reacting’ essential oils, or the formation of the same hapten by a number of allergens, e.g. formaldehyde by formaldehyde releasers. In other cases, however, where the molecular structure is very similar and thus is suggestive of cross-reactivity, as in eugenol and isoeugenol, the association is rather weak, because the mechanism of sensitization through isoeugenol is thought to depend on the formation of an orthoquinone, whereas eugenol may react via a phenolic radical mechanism (43). It is sometimes difficult to clinically prove true cross-reactivity, as co-exposure cannot always be excluded, as in the case of co-reacting aminoglycoside antibiotics (42), or sesquiterpene lactones from *Frullania* and *Compositae* (41).

Patch test related aspects – reproducibility

It cannot be excluded that at least some of the reactions found in polysensitized individuals could be interpreted as false positive ones if these reactions have not been confirmed by another test: In one study, approximately 40% of the reactions (68% of + and 23% of ++/+++) were nonreproducible (44). However, these figures, which would cast serious doubts on the reliability and even the validity of patch testing, were not confirmed by others (45, 46). Furthermore, it was shown that reproducibility varies between allergens and patch test systems used (37, 47), and decreased when more than four positive reactions were seen at the same time and with another positive reaction in close vicinity to an allergic reaction (48).

Nonreproducibility of allergic reactions (especially after longer-time intervals) was explained by ‘loss of sensitization’ (49, 50). This basically ill-understood phenomenon may mainly occur with weak reactions, weak allergens or borderline irritants (37, 44, 49, 51, 52). Patients not strongly sensitized may have developed a positive reaction to a standardized patch test under extraordinarily favorable conditions resulting in a temporarily increased reactivity of the skin, to which altered skin absorption or seasonal variations may have contributed. In the absence of such enhancing factors, these patients may remain in a state of subclinical sensitization (because of a low induction dose) requiring a higher dose to reproduce the former result (16, 53) (for further details see below). Nielsen et al. emphasized that because of unexplained high variation in patch test reactivity, as was shown e.g. by Hindsen et al. (54), a negative patch test

reaction does not exclude CA to the allergen in question without fail (55). Instead of regarding this phenomenon as a patch test artefact, Katsarou et al. (50) assumed hyposensitization to have taken place in those with 'lost sensitization', as (allergen)-specific circulating T-cells were suppressor cells (CD4+ CD45RA+), whereas allergen-specific T cells of patients with persistent reactivity were memory cells (CD4+ CD45RO+).

The distinction between true PS and a phenomenon called 'angry back' (AB) (56) or 'excited skin syndrome' (ESS) (57) may prove difficult (58). Some or many of these reactions were considered false positive, as they could not be reproduced in subsequent patch testing. Retesting patients who had previously multiple reactions resulted in a loss of 40–60% of reactions (52, 56, 59). In some cases of ESS, full reproducibility may be achieved, whereas in others, it may drop to 20% (58).

Mitchell stated that a 'single strong positive patch test reaction creates an AB', or, as Max Jessner has put it several decades earlier, a 'crazy back' (60), which means a back 'hyper-reactive to other patch test applications' (56). Maibach broadened the term to the 'ESS' suggesting that it is the entire skin, not just the back, which is hyper-reactive (57). In addition, Bruynzeel et al. (61) reported on the so-called spill-over effect. When marginally irritant concentrations of sodium lauryl sulphate (SLS) were applied at various distances from a strong positive allergic reaction, the intensity of SLS-reactions was significantly higher in SLS patches situated adjacent to the allergic reaction. The notion and (modern) explanations of 'status eczematicus' (see above) may apply to these phenomena (62).

However, ESS seems to be rather rare both in patch test patients seen in clinics (63) and in population-based studies (55). In a 4-year-period, Cockayne and Gawkrödger (63) observed only 17 cases of ESS (out of approximately 1600 patients patch tested), among them 10 with exacerbation of AD. In eight of 10 cases, the reactions were considered relevant, i.e. not false positive. Recently, we reported that only <1% of $n = 58\,268$ patients tested exhibit more than six allergic reactions (Fig. 1) (64).

One of the hypothetical explanations of the AB is the influence of a patch test reaction or preparation on the adjacently applied patches. In several studies, we found that neither adjacent negative (65) nor neighbouring positive reactions enhance a positive reaction (66), and that a high-positive 'patch test load' (reflecting the number as well as strengths of synchronous positive reactions) correlates with further positive reactions irrespective of their location (67). The latter finding concurs with the experimental findings of Kligman and Gollhausen (60), but is in contrast to the observation of a spill-over effect (61). On the other hand, it may be compatible with a temporarily enhanced general reactivity of the skin (in its exaggerated form 'excited skin'), but may also be on account of individual factors (67). In a number of

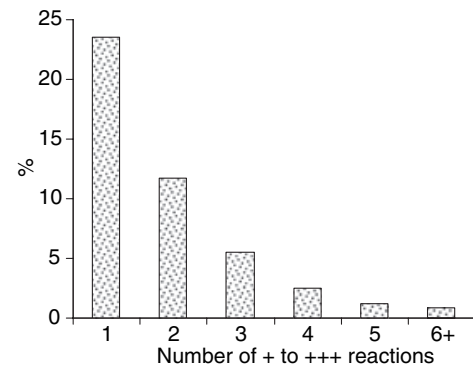


Figure 1. Distribution of the number of positive reactions (+, ++, or +++) to allergens of the standard series. 6+: 6 or >6 reactions. Total number of patients $n = 58\,268$. Number of patients with no positive reaction to standard series allergens: $n = 31\,865$ (54.7%) (64).

experiments, Kligman and Gollhausen (60) as well as Memon and Friedman (68) found that neither local nor general reactivity of the skin was increased by a strong patch test reaction.

While not denying the existence of transiently elevated skin reactivity (on account of pre-existing dermatitis, status eczematicus), the authors categorically reject the concept of AB and ESS (hyperirritability caused by one strong patch test reaction). Memon and Friedman (68) favor the idea that patients with multiple positive reactions 'are indeed genuinely allergic to multiple allergens'.

PS, prognosis and severity of ACD

High severity of a disease and frequent relapses may generally indicate a high degree of susceptibility. A higher frequency of relapses in PS may simply reflect the increased probability to encounter the culprit allergens, whereas severity may indeed be influenced by susceptibility as an individual factor. Studies on the prognosis of ACD (69) and in particular its impact on the quality of life (70) did not explicitly and systematically address the question whether PS differed from MS with regard to severity and prognosis. Nevertheless, PS often develops after a primary sensitization, e.g. to colophony (71). In one follow-up study on formaldehyde allergy, there was no difference between patients with and without PS, with respect to frequency of eczema eruption or eczema severity (72). However, PS patients were found to be affected more often by a generalized eczema (73), to have a long persistence of hand dermatitis (74), were more often re-tested several times after the first patch test than MS patients (37), and exhibited a stronger allergic reaction (75). The prognosis (e.g. the chance to remain symptom-free or to continue with the original profession) was considered bad in PS (76, 77). It is, however, difficult, to get a clear picture of the fate of PS patients, as PS may

not always be reproduced and 'loss of sensitization' is still debated (see above).

Experimental findings

With a number of experiments Friedmann, Moss and co-workers contributed essentially to the concept of susceptibility in CA (16, 30). Individuals were sensitized with doses of DNCB between 62.5 and 1000 μg . Four weeks after induction challenges with doses ranging from 3.125 to 25 μg were performed. All participants who had been sensitized with 500 μg or higher doses reacted to a challenge with 12.5 μg . When sensitized with 62.5 μg , only <10% reacted. The dose required to sensitize 50% was estimated as 116 μg . Furthermore, with increasing challenge doses in groups with a given induction dose, the reactivity increased. Even with the lowest induction dose (62.5 μg) a response could be provoked provided the challenge dose was high enough. Therefore, the elicitation dose depends on the induction dose, and it is inversely correlated with the latter. And at any sensitizing dose below the 100% effective dose, there was a wide range of responses, indicating different susceptibility.

In view of the clinical observation that some individuals appear to develop contact sensitivities readily to a wide range of environmental substances, the authors wondered whether patients with PS (with at least three positive patch test reactions to distinct contact allergens) differed in their response to DNCB (30). The same experiments as described above were performed. It was found that at each sensitizing dose, more subjects with PS than subjects without PS could be sensitized and that the 100% sensitizing dose was lowered to 250 μg in subjects with PS. The PS subjects were also more responsive than 'normal' subjects, the challenge dose-response curve being shifted upwards compared with those of the normal subjects (Fig. 2). Furthermore, an augmentation (a non-linear increase) of sensitivity produced by any (linear) increase in sensitizing dose was noted (Fig. 3).

The authors further addressed the question whether the acquisition of one single contact sensitivity increases the susceptibility to further sensitization (30). When people who had only a single contact sensitivity to nickel were tested with the same protocol, the response to challenge with DNCB was significantly increased only in PS, whereas in the nickel-sensitized patients, it was only slightly and not significantly increased (Figs 2 and 3). As the only remarkable finding, the 100% sensitizing dose was lowered to 250 μg , indicating that individuals sensitized to one allergen may be slightly more susceptible (30). Those patients, however, with PS on account of a well-defined exposure (occupational or therapeutic related) did not show an increased response to DNCB, which led the authors to conclude, that increased susceptibility is in fact the cause and not the result of PS. It could further be concluded that exposure can be an

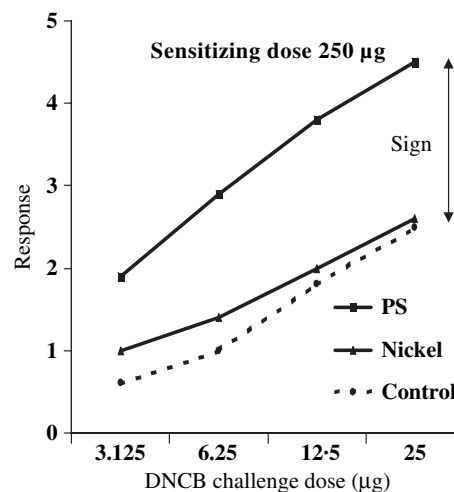


Figure 2. Relationship between DNCB challenge and response [measured as skinfold thickness (mm) after a sensitizing dose of 250 μg in all three groups (healthy controls, monosensitized to nickel, and PS (30), modified)].

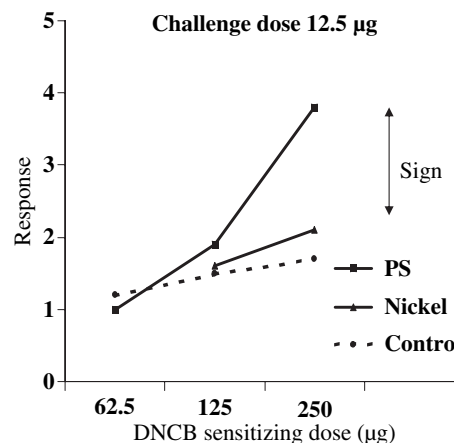


Figure 3. Relationship between DNCB sensitizing dose and response [measured as skinfold thickness (mm) to challenge with 12.5 μg of DNCB in three groups (healthy controls, monosensitized to nickel, and PS (30), modified)].

important determinant for PS, overruling factors of susceptibility.

Friedmann recognizes sufficient evidence to support the idea that there is a broad range of susceptibility to CA within the general population, 'high responders' lying at one tail of the distribution, the other tail presumably being the 'low responders'.

One question remains: is the hypothesized distribution of susceptibility compatible with the graded distribution of the number of sensitization (see Fig.1), does an increasing number of sensitization correlate with increasing susceptibility? Using the ratio between observed vs predicted prevalence as an indicator of risk, it was found ($n = 21$ individuals) that with the 'risk' increasing the

response to different challenge doses (susceptibility) increased, the correlation ranging from 0.54 to 0.48 (all significant).

Moss et al. (30) summarized the results of their study, performed > 20 years ago, but still highly relevant and of utmost importance: 'Patients with multiple allergies are more readily sensitized experimentally, and to a greater degree than normal, by DNCB, an unrelated antigen'.

The spectrum of concomitant reactions (PS)

Several studies analyzed the pair-wise associations between positive reactions to distinct allergens (34–36, 78, 79). According to these studies, the number of significant positive associations between a positive reaction to a given allergen with positive reactions to other allergens of a standardized patch test series strongly depends on the given allergen. The highest numbers of associations were seen with fragrance mix ($n = 23$), colophony ($n = 20$), thiuram-mix ($n = 20$), PPD ($n = 19$), and potassium dichromate ($n = 19$), and low numbers were seen with thiomersal ($n = 4$) and nickel ($n = 9$) (36). To describe the associations quantitatively, a 'Multiple sensitivity index', ranging from -1 (allergen without associations) to $+1$ (allergen always associated with another allergen) was proposed (35). Further analyses of frequently occurring associations revealed that the probability of specific associations differs broadly (34, 36, 78, 79). The association of the rubber ingredients, e.g.

thiuram-mix and zinc diethyldithiocarbamate displayed the highest degree of association (OR: 166.4) (36), probably on account of a common metabolite. One may consider several reasons not only for the association as such, but also for the high (or lower) odds ratios (Table 1). The relation to allergen exposure is heterogeneous: The two allergens in question may occur together, in a mixture (fragrance) or a material (rubber) (exposure internally related). The two allergens do not occur in the same material together, but are often used separately in similar or identical areas of exposure (externally related). A painter is exposed to different allergenic materials (e.g. biocides and resins) (80), a hairdresser to different unrelated hair-cosmetics (81), a patient with AD or leg dermatitis to topical drugs and emollients (4, 82). The strength of association may be enhanced through an increased susceptibility, as in the case of leg dermatitis (see above).

The degree of association is normally high if two allergens cross-react or become identical after being metabolized. These different scenarios, of which some are proven, others only plausible, are used in Table 1.

Polysensitization and evidence from clinical epidemiology

The existence of a large pool of clinical data – patch test, clinical and demographic data – namely, the collection of the Information Network of Departments of

Table 1. Selected associations of positive patch-test reactions with OR >6, significant ($P < 0.05$) after adjustment for multiple testing [see (36)] and possible reasons for concomitant reactions (for further explanation see text)

Associated reactions	OR	95% CI	Association related to				Comment
			Struct	Exp IR	Exp ER	Exp Susc	
Thiuram mix–ZDEC	116.4	113.84–243.30	X	X			Rubber ingredients, thiurams metabolized to dithiocarbamates
Mercapto-mix–IPPD	16.9	11.03–25.91		X			Rubber ingredients
Benzocain–PPD	26.9	22.37–32.33	X			X	Rapid N-Acetylators ? (98)
IPPD–PPD	10.9	8.30–14.28	X			X	Rapid N-Acetylators ? (98)
Colophony–Turpentine	10.2	8.69–11.99	X	X			Common source (<i>pinus</i> species) of the resin (C.) and the volatile oil (T.)
Fragrance mix–Colophony	6.8	6.03–7.61	X				Association could be extended to Compositae mix
Chromat–Cobalt	12.5	10.97–14.25		X			Exposure: cement
Nickel–Cobalt	10.8	9.74–12.03		X			Cheap jewellery
Formaldehyde–CI/MI	10.3	8.28–12.77			X		Biocides in industrial applications
MCI/MI–MDBGN	6.2	5.09–7.62			X		Biocides used in cosmetics
Fragrance mix–Balsam of Peru	8.85	8.14–9.63		X	X		Fragrance compounds
Cetylalcohol–Paraben	27.7	21.18–36.17		X	X	X	Allergens frequent in leg dermatitis
Cetylalcohol lanolin alcohols	16.6	13.16–21.01	X	X	X	X	Dito
Cetylalcohol–Neomycin	13.4	10.25–17.56		X	X	X	Dito
Nickel–Balsam of Peru	0.90	0.80–1.00					Negative association
Nickel–Lanolin alcohols	0.85	0.72–0.99					Negative association

OR, odds ratio; CI, confidence interval. Struct/Metab, structure/metabolism related; Exp IR, exposure 'internally' related (mixtures like perfumes or material like rubber); Exp ER, exposure 'externally' related (areas of exposure where allergens are often but separately used, e.g. hairdressers); Exp Susc, exposure in patients with enhanced susceptibility (e.g. leg dermatitis); ZDEC, zinc diethyldithiocarbamate; IPPD, isopropylparaphenylenediamine; PPD, paraphenylenediamine; MCI/MI, methyl (chlor)isothiazolinone; MDBGN, methylidibromoglutaronitril. Bold indicates outstanding results; ? indicates a hypothetical role.

Dermatology (IVDK, <http://www.ivdk.org>; accessed 12 November 2007) allows for the detailed analysis of 'polysensitization'. The main advantage of such sufficiently standardized, quality-controlled data is the sheer number of patients included. This enables (i) analysis of relatively rare allergens, such as paraben mix; (ii) estimation of prevalences, odds ratios or other descriptive measures (of association) with sufficient precision; (iii) statistical testing with adequate power; and (iv) most importantly, consideration of potential confounding factors (83). In the context of PS, age, sex, and leg dermatitis appear as the most important confounders (4, 37), as they are associated both with outcomes of interest (such as reactions to weak allergens) and PS as risk factor of interest.

Confounding can, in this context, best be counteracted by restriction (exclusion of cases with a certain demographic or clinical profile), by standardization or by adjustment, most commonly in terms of multifactorial analysis. In multifactorial analyses, the association between a dichotomous outcome (for different definitions see below) and several factors of interest or confounders is quantified in such a way that the risk estimate for each factor is adjusted for the impact of all other factors. This means that, in theory, the 'pure' effect of any given factor is estimated, notwithstanding possible residual confounding by other factors not included in the model. Among different regression types, defined by the function used to link the outcome with the set of risk factors, logistic regression analysis and Poisson regression analysis have been most widely used. The former yields estimates quantifying risk as OR, the latter as prevalence ratio which can be interpreted as an estimate of relative risk, in contrast to the OR, where this is possible only in case of rare outcomes (<1% prevalence). All estimates are accompanied by the respective confidence intervals (CIs), usually 95% CI, to indicate precision.

As an example, the results of a Poisson regression analysis are given in Table 2 (42). It becomes evident that PS is by far the most important risk factor, compared with other confounders included.

Induction

In several multiple regression analyses, PS was used as an explanatory variable, in addition to other well-known risk factors, such as sex, age, AD, or anatomical site (e.g. leg dermatitis) (42, 84–86). The risk of being sensitized to neomycin, bufexamac (a topical NSAID), the fragrance mix or to nickel and chromate steadily and significantly increases with the number of additional positive reactions to other standard series allergens (Table 3).

Elicitation

In some earlier studies, we noted that the strength (+ vs + + / + + +) of patch test reactions to allergens may be

Table 2. Results of a Poisson regression analysis with positive (+ to +++) patch test reaction to neomycin sulfate (20% pet.) on the third day reading as outcome (dependent variable) I (positive in 2.5%)

Risk factor		%	PR	95% CI
Atopic dermatitis	Past or current	16.7	1.07	0.88–1.29
Gender	Female	61.8	0.97	0.86–1.09
Year of patch test	1998/1999	36.7	1.00	(Reference)
	2000/2001	33.1	0.96	0.84–1.10
	2002/2003	30.2	0.83	0.72–0.96
Main anatomical site	Trunk	3.6	1.00	(Reference)
	Hand	27.4	0.82	0.59–1.18
	Arm, excl. flexures	3.6	0.82	0.51–1.29
	Foot	3.5	1.00	0.65–1.53
	Leg, excl. flexures	11.4	1.73	1.26–2.44
	Face	15.1	1.12	0.80–1.60
	Neck	1.1	1.09	0.56–1.98
	Head n.e.c.	2.6	0.89	0.52–1.49
	Flexures	0.5	0.85	0.20–2.35
	Axillae	0.7	0.40	0.10–1.09
	Generalized	8.8	0.74	0.50–1.10
	Anogenital	2.7	0.80	0.46–1.34
	Other	7.0	0.94	0.64–1.40
	Missing site	12.1	0.90	0.64–1.31
Age group (years)	<10	0.6	1.47	0.66–2.80
	10–19	5.0	0.43	0.26–0.68
	20–29	13.5	0.38	0.27–0.53
	30–39	16.4	0.72	0.57–0.92
	40–49*	17.1	1.00	(Reference)
	50–59	17.9	1.18	0.96–1.46
	60–69	15.4	1.53	1.25–1.88
	70–79	9.8	2.13	1.73–2.63
Occupational causation	80+	4.5	1.76	1.36–2.26
	Certain or probable	14.2	0.76	0.59–0.97
	None	52.8	1.00	(Reference)
	1	24.2	2.70	2.28–3.20
	2	12.3	3.83	3.19–4.59
Number of further positive reactions to other standard series allergens	3	6.0	6.19	5.10–7.49
	4+	4.8	8.33	6.95–9.99

The percentage in the third column denotes the frequency of the demographic or clinical attribute in the entire group of patients (42).

PR, prevalence ratio; CI, confidence interval.

*The median age group was chosen as reference to better illustrate the peculiar, nonlinear shape of the risk curve.

related with further sensitization. Patients with + + / + + + reactions to nickel showed more often reactions to the other metals cobalt and palladium than those with only a + reaction (87). In an analysis of allergic reactions to the group of para-substituted aryl compounds such as PPD, we observed that with increasing intensity of the reaction to PPD the probability of reactions to other 'para-compounds' increased (88). This prompted us to study this relation systematically, specifically alluding to the hypothesis of increased susceptibility (89). We found that with increasing strength of a positive reaction to nickel or to fragrance mix the likelihood of (i) further positive reactions to unrelated contact allergens and (ii) the strength of these reactions increased significantly (Table 4). In other studies, a relation between stronger patch test reactions and disease severity or clinical

Table 3. The risk of being sensitized to neomycin, bufexamac (a topical NSAID), the fragrance mix or to nickel and chromate increases with the number of additional positive reactions to other standard series allergens

Risk factor		Neomycin (Po)		Bufexamac (Po)		Fragrance mix (Io)		Nickel–chromate (Io)	
		PR	95% CI	PR	95% CI	OR	95% CI	OR	95% CI
Number of further positive reactions	None				1.00 (reference)				
	1	2.7	2.3–3.2	1.2	0.9–1.5	2.7	2.6–2.9	2.4	1.8–3.2
	2	3.8	3.2–4.6	2.1	1.7–2.7	4.7	4.4–5.0	4.8	3.6–6.6
	3	6.2	5.1–7.5	2.9	2.1–3.9	6.8	6.3–7.4	4.6	3.3–6.5
	4 (≥)	8.3	7.0–10.0	4.8	3.6–6.3	12.8	11.7–13.9	n.c.	

Results of Poisson (Po) and logistic (Io) regression analyses, respectively; several separate analysis (42, 84–86) are summarized. OR, odds ratio; PR, prevalence ratio; CI, confidence interval; n.c.; not calculated. Bold indicates an essential figure.

Table 4. Risk of further reactions and their increased intensity depending on the strength of reactions to the fragrance mix (89)

Reactions to the fragrance mix								
Risk factor	+		++		+++		Nonpositive	
	PR	95% CI	PR	95% CI	PR	95% CI	PR	95% CI
Number of further positive reactions								
0			1.0 reference				1.0	Reference
1	2.5	2.4–2.7	2.8	2.5–3.0	2.9	2.4–3.5		
2	4.2	3.7–4.8	6.0	5.2–7.1	6.5	4.9–8.7		
3	5.9	4.2–8.2	11.0	7.5–16.0	9.8	4.7–20.4		
4	17.9	5.6–56.7	25.1	6.7–93.9	25.8	3.0–222		
Intensity of reactions to further allergens	1.77	1.71–1.84	2.11	2.01–2.21	2.27	2.08–2.47		

OR, odds ratio; PR, prevalence ratio; CI, confidence interval.

relevance was shown (90, 91). Together with our results, this could serve as an indirect hint that PS and disease severity are associated, adding to the above mentioned reports.

Sensitization to weak allergens

Finally, we wondered whether patients with sensitization to a weak allergen are more likely to be polysensitized and are thus showing an increased susceptibility as compared with patients sensitized to a strong allergen (64). Such a hypothesis is supported by experimental findings in genetic studies (19) (see above). Moreover, we have noticed that patients reacting to strong allergens like oak moss or isoeugenol reacted less often to other fragrances than patients sensitized to weak allergens, such as geraniol or alpha-amylcinnamic aldehyde (92). Therefore, we wondered whether patients sensitized to one strong index allergen, methyldibromoglutaronitril (MDBGN) and 1-weak index allergen, the paraben mix, respectively, differed with regard to PS [for references to the notion of ‘weak’ and ‘strong’ see (64)]. We could demonstrate that individuals sensitized to the weak allergen carry a greater risk to become polysensitized (to react to additional standard series allergens) than those reacting to the strong allergen (Table 5).

Conclusion and perspectives

From experimental and clinical findings, sufficient evidence indicates that PS is a clinical sign of heightened susceptibility:

- 1 Polysensitized patients are more easily sensitized to the experimental sensitizer DNCB and PS patients are more often found sensitized to weak allergens. PS is also the greatest risk factor to be sensitized to an index allergen-like neomycin. PS therefore indicates a high susceptibility on the level of induction of CA.
- 2 PS is associated with stronger reactions and with a greater degree of sensitization to the experimental sensitizer DNCB. PS is therefore related with a high susceptibility on the level of elicitation of CA.

These findings add further quantitative elements to the notion of CA as a ‘graded phenomenon’ (93), depending not only on exposure dose and allergen potency, but also on graded susceptibility.

Finally, in the course of our studies on cytokine polymorphisms in contact allergic patients we observed polymorphisms in the promoter regions of the cytokines IL-16–295 (C/C) and TNF- α -308 (A/A) being overrepresented only in the PS group, compared with controls and the MS patients (94, 95). These studies may

Table 5. Increase of risk for additional sensitization in the group sensitized to a weak allergen relative to the group sensitized to a strong allergen, the factor being the quotient of the respective odds ratios

Reactions (++) to index allergens		+ to +++ reactions additional to index allergens		
'Weak allergen'	'Strong allergen'	≥2	≥3	≥4
Paraben-mix	MDBGN + PE	OR	OR	OR
++/+++	—	7.8	8.0	10.3
—	++/+++	3.0	2.8	2.8
Increase of risk by factor of		2.6	2.9	3.7
		++/+++ Reactions additional to index allergens		
++/+++	—	7.4	10.1	17.0
—	++/+++	3.5	4.1	3.7
Increase of risk by factor of		2.1	2.5	4.6

In order to avoid confounding by weak (+) false positive reactions, only stronger reactions to the index allergen were considered for selection. In this analysis, the association between polysensitization and reaction strength is again obvious (see above) (64).

MDBGN, methylidibromoglutaronitril; PE, phenoxyethanol.

cautiously be taken as first hints that the PS phenotype as a clinical sign of increased susceptibility may have a genetic basis. Further studies on polymorphisms in PS patients are needed to gain sufficient insights in the genetics of CA. For further studies on the issue of susceptibility, we suggest a patient to be regarded as 'polysensitized' if sensitization to three or more allergens of the standard series is present that are unrelated with regard to cross-reactivity.

However, PS may not only indicate increased susceptibility to CA, but may be a sign of a generally increased inflammatory reactivity to xenobiotics. After having noticed a relation between CA to fragrances and an increased reactivity of the airways to aerogenic exposure to fragrances (96), Elberling et al. (97) addressed the

question if patients allergic to different contact allergens (e.g. nickel) reported also more often mucosal symptoms, when exposed to chemicals unrelated with contact allergens (laser printer, drying paint, car exhaust, newspaper). Having at least one positive patch test was associated with symptoms of the airways (OR: 1.7, 95% CI: 1.2–2.5), and, interestingly, the OR increased with the number of positive patch tests. The results of this study may point to PS as an indicator for a more general trait other than those expressed by specific polymorphisms of e.g. cytokines, and not exclusively linked to CA. Future studies on polymorphisms in PS patients should focus also on mechanisms playing a role in inflammatory processes in general, or in the skin in particular.

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