Chapter 9

Individual Predisposition to Irritant and Allergic Contact Dermatitis

9

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Contents

9.1 Introduction

Contact dermatitis is a skin disease that is either caused or exaggerated by environmental factors. However, development of contact dermatitis requires the combination of environmental factors and a susceptible host. While some individuals may develop contact dermatitis after only brief contact with irritants or allergens, other individuals may continue to remain unaffected even under extreme exogenous conditions. This chapter will focus on the susceptibility of the host to the development of irritant and/or allergic contact dermatitis.

9.2 Irritant Contact Dermatitis

Irritant contact dermatitis is a complex disease, with a multifactorial pathogenesis, to which individual as well as environmental factors contribute. Within the individual, the response to irritant stimuli depends on the skin barrier function, the inflammatory reactivity of the skin and – addressing chronic irritant contact dermatitis – its regeneration ability. Individual-related variables that influence these factors, and attempts to identify "sensitive skin," will be discussed in the following.

9.2.1 Can "Sensitive Skin" Be Identified?

9.2.1.1 Sensitive Skin

Exposed to the same exogenous conditions some individuals develop an irritant eczema while others do not. The group that develops eczema may be expected to have increased skin susceptibility or increased skin reactivity compared to the rest. Whether the concept of "sensitive skin" in fact exists has been debated. In his pioneering study of primary irritants, Björnberg found no correlation between the intensity evoked by 11 different primary irritants, and stated that the response to one particular irritant does not necessarily predict the response to another irritant [1]. This statement was supported by later studies [2, 3]. However, Frosch and Kligman [4] reported a statistically significant correlation between the skin response to particular irritants, and a group of individuals with sensitive skin could be identified by assessment of skin susceptibility to skin test with seven different irritants and assessment of minimal erythema dose (MED) [5]. For preselection of hyper-reactors, Frosch and Kligman [6] for practical reasons

used a 24-h forearm chamber exposure to 5% sodium lauryl sulfate (SLS).

The contradiction between reports that no correlation between irritant responses exists and that hyper-reactors can be identified may be specifically explained by choice of irritants, dose, test region, and test method. The different penetration abilities of particular irritants may account for discrepancies in the intensity of the evoked skin response. Use of high doses of irritants, eliciting severe reactions, may tend to equalize skin responses. Regional variation also exists [7].

9.2.1.2 Skin Irritancy Test

The identification of subjects with increased susceptibility to irritants would play an important role in the prevention of irritant contact dermatitis. Based on the original alkali test by Burckhardt [8], numerous pre-employment tests have been suggested [9–11]. However, reproducibility of the screening methods is low and the inter-individual variation high, and none of the tests has hitherto been found satisfactory for the purpose of pre-employment tests for sensitive skin.

9.2.1.3 Noninvasive Measuring Methods for Identification of Sensitive Skin

A number of noninvasive bioengineering methods have been used in an attempt to evaluate the biophysical properties of skin.

Experimental data, mainly based on SLS-induced skin irritation, indicate that measurement of baseline transepidermal water loss (TEWL) may be helpful for identification of sensitive skin. Tupker et al. [12] studied the role of baseline TEWL in skin susceptibility to weak irritants in healthy volunteers and found that barrier damage and inflammation evoked by the irritants were strongly related to baseline TEWL. In a group of 70 nonatopic healthy volunteers challenged with SLS, baseline TEWL was found to contribute significantly to a multiple regression analysis model using TEWL after exposure as the dependent variable [13], and, in the same study, subjects with high visual scores after SLS exposure had increased baseline TEWL compared with those who had low visual scores. Only a few studies have utilized individual baseline TEWL values for prediction of risk of irritant contact dermatitis. Repetitive measurements of baseline TEWL in workers in the metal industry in Singapore indicated that high TEWL values obtained from the back of the hands may predict later development of irritant contact dermatitis [14]. This finding was supported by a recent study of apprentice hairdressers and apprentice nurses, reporting a trend toward a relationship between increased baseline TEWL and risk of hand dermatitis [15]. Findings were however not statistically significant. This indicates that baseline TEWL is only one of a number of factors influencing skin susceptibility, and the particular significance of this parameter may be overruled by other factors. Recently, the irritant threshold for an SLS patch test applied for 4 h was illustrated to correlate well with TEWL values obtained from SLS-irritated skin, indicating that the irritant threshold technique may be helpful in predicting the development of occupational contact dermatitis [16].

Attempts to identify sensitive skin have also been performed by other bioengineering methods. Measurements of skin hydration by electrical capacitance and electrical conductance measurements are generally considered of limited value as indicators of sensitive skin [17]. Measurement of skin color has been reported to be helpful in the evaluation of skin sensitivity to irritants [13, 18], but intermittent exposure to UV light may interfere with the accuracy of measurements. Biophysical properties such as pH values, skin lipids, and skin thickness as measured by ultrasound need further investigation with respect to their usefulness as indicators of sensitive skin [16]. Today, none of the bioengineering methods can by themselves identify sensitive skin. Further studies using varying experimental designs are necessary, and final conclusions depend on large-scale epidemiological studies.

9.2.2 Individual-Related Variation in Skin Susceptibility

9.2.2.1 Genetic Factors

Apart from the relationship between atopic dermatitis and development of irritant contact dermatitis, which is discussed below, the knowledge of influence of genetic factors is sparse, and systematic studies in this field are few. Holst and Möller studied the cutaneous sensitivity to benzalkonium chloride, SLS, and potash soap in twins [19]. Comparing the intra-pair reaction strength a higher degree of concordance was found among monozygotic than among dizygotic twins for one irritant, but not for all irritants tested. This indicates that a genetic predisposition to irritant susceptibility may be specific for each irritant (Table 1). In a recent questionnaire investigation in-

Table 1. Influence of individual related factors on skin reactivity to irritants and allergens

	Reactivity to irritants	Reactivity to allergens
Genetic factors	Yes	?
Sex	No	?
Age	Yes	?
Ethnic factors	?	?
Regional differences	Yes	Yes
Atopic dermatitis	Yes	?
Medication	Yes	Yes

cluding 6666 twins, hereditary risk factors were found to play a significant part in the development of hand eczema in the general population, when no extreme environmental exposure was present [20]. A subsample of the same twin material was studied with regard to contact allergy, atopic dermatitis and wet work, and the results indicated that a hitherto unrecognized genetic risk factor for hand eczema independent of atopic dermatitis and contact allergy is important for development of irritant contact dermatitis localized on the hands [21].

9.2.2.2 Sex

Hand eczema and contact dermatitis are known to occur more frequently in women than in men [22, 23]. This may, however, very well reflect differences in environmental hazards rather than endogenous differences between the sexes. Results from the above-mentioned twin study indicated that the high frequency of hand eczema in women in comparison with men was caused by environmental and not genetic factors [21].

Most experimental investigations have found no sex-relation in skin susceptibility [13, 24, 25].

Hormonal influence on skin reactivity in relation to the menstrual cycle has been discussed. Increased skin reactivity prior to and during the menstrual phase was initially reported by Halter in 1941 [26], and was supported by later casuistic reports [27, 28]. In an experimental study, skin reactivity to SLS was found to be significantly increased at day 1 in the menstrual cycle as compared to days 9–11 in non-menstruating women [29]. No cyclic variation in baseline TEWL has been reported. In experimental settings and in attempts of predictive patch testing, the influence of menstrual cycle on skin reactivity may be of some importance, but the clinical implication of the finding is uncertain.

9.2.2.3 Age

Increased susceptibility to irritants in childhood has been reported [30], as well as an increased susceptibility to SLS in young compared to elderly females [31]. Irritation, however, seemed to be more prolonged in the older group [32], indicating less skin reactivity but a prolonged healing period in older people. Barrier properties in aged skin (>80 years of age) were recently studied [33], and an abnormal barrier integrity and repair function as compared to young skin (20–30 years) was reported. These abnormalities were attributed to a deficiency in key stratum corneum lipids in old age.

9.2.2.4 Ethnic Factors

An inclination toward increased skin susceptibility to SLS in black and Hispanic skin was reported [34, 35], but a statistically significant difference was found only for particular concentrations of the irritant, and only when tested on pre-occluded skin. Decreased transcutaneous penetration was reported in black persons.

9.2.2.5 Regional Differences

Susceptibility to irritants differs between anatomical regions. In most studies skin susceptibility to irritants is ranked as extremities < back < forehead [36, 37]. Baseline TEWL with respect to anatomical sites can be ranked as back = abdomen = arm < dorsum of hand<forehead<palm [38]. However, a linear relationship between TEWL and skin reactivity to exogenous substances cannot be generalized, neither to all anatomical sites nor to every substance.

9.2.2.6 Atopy

The significance of a history of atopic dermatitis for the development of irritant hand eczema has been comprehensively demonstrated [21, 39, 40]. In experimental studies baseline TEWL has been reported to be increased in uninvolved skin in patients with atopic dermatitis [41–43], and patients with atopic dermatitis were reported to react more severely to irritants than healthy controls [43, 44]. The characteristic functional abnormalities as found in atopic dermatitis were not found in baseline conditions or after irritant exposure [45] in patients with respiratory atopy without atopic dermatitis.

9.2.2.7 Coincidental Diseases (Other Than Atopy)

In a recent study, the ability of individuals who perceive stinging to experience irritant reactions in the skin was examined. It was concluded that the ability to perceive stinging is not correlated to irritant susceptibility or other types of nonimmunological skin responses [46].

Hyper-reactive skin with an exaggerated response to irritants has been proven in patients with current active eczema [18, 23]. Hyporeactive skin with a decreased response to irritants was reported in patients with severe cancer [47].

9.2.2.8 Medication

Cortisol treatment is known to reduce skin responsiveness to irritants [48]. The influence of other drugs has not been thoroughly studied.

Core Message

- ICD is a complex disease, to which individual as well as environmental factors contribute.
  Atopic dermatitis (previous or current) is a major individual risk factor for development of ICD.

9.3 Allergic Contact Dermatitis

The development of contact allergy is dependent on individual susceptibility and exposure to potential allergens (Table 1).

9.3.1 Individual Predisposition to Contact Sensitization

9.3.1.1 Genetic Factors

Sulzberger and co-workers [49, 50] in human sensitization experiments with *p*-nitroso-dimethylaniline (NDMA) and 2,4-dinitrochlorobenzene (DNCB) established an individual variation in susceptibility to contact sensitization, and further showed that individuals who were highly susceptible to sensitization with one chemical showed little or no susceptibility to sensitization with other chemicals. More recent studies suggest that individual susceptibility occurs by a non-antigen-specific amplification of immune sensitization [51].

Twin studies on allergic contact sensitization are sparse. In a twin study of reactivity to DNCB and tuberculin no difference in concordance rate for dizygotic and monozygotic twins was reported [52]. Contradicting this, a study of nickel allergy in twins suggested that genetic influence over contact sensitization to nickel is likely [53]. In a recent Danish study including 630 female twins of whom 146 had a positive patch test to nickel, it was concluded that allergic nickel contact dermatitis is caused mainly by environmental factors and only to a lesser degree by genetic factors [54].

Numerous studies of the HLA genes in contact sensitization have not disclosed any consistent pattern [55]. The lack of association between the HLA genes and contact sensitization does not exclude the importance of genetic factors. Hitherto unknown HLA genes may be associated with allergic contact dermatitis, there may be heterogeneity in allergic contact dermatitis, and/or allergic contact dermatitis may not be associated or linked to the HLA region.

In conclusion, it seems that some individuals are more easily sensitized than others to common haptens due to their genetic background, but the total number of sensitized individuals in the population depends upon the degree of cutaneous exposure.

9.3.1.2 Sex

Women have higher immunoglobulin levels (IgM and IgG) than men, and stronger cell-mediated immune responses [56]. Both in animal studies and in humans, there is a preponderance of autoimmune disease in women compared to men.

Walker et al. [57], however, found that men are more susceptible to DNCB sensitization compared to women in a large well-controlled study. A similar study on patch sensitization to *p*-amino-diphenylamine and isopropyl-*p*-diphenylamine disclosed a significantly increased number of women sensitized as compared to men [58]. The authors suggest that women, through more frequent contact with para substances than men, may achieve subclinical sensitization. Rees et al. [59] report an increased reactivity to challenge with DNCB in DNCB-sensitized women compared to DNCB-sensitized men.

The main reason for female preponderance in clinical patch test studies is the high number of nick-

el- and cobalt-sensitive women. This is most likely a consequence of different exposure, with ear piercing the main risk factor for nickel allergy in women. A recent study of nickel allergy in men with pierced ears confirmed the role of ear piercing as a risk factor for nickel sensitization also in men, but the frequency of nickel allergy in men with pierced ears was lower than the frequency reported in women [60].

The influence of sex hormones on induction and elicitation of contact allergy is largely unknown. In a pilot study the response to DNCB was enhanced in women receiving oral contraceptive hormones [61] and a preliminary report indicates that the cutaneous reactivity to patch testing differs within the menstrual cycle [27]. The limited knowledge in this field is inconclusive, and deserves further systematic evaluation [62].

9.3.1.3 Age

The exposure pattern to environmental allergens differs between age groups. The most frequently recognized contact allergies in children are thiomersal, nickel, fragrance mix, and isothiazolinones [63] – and, in the United States, poison ivy and poison oak. Young people are more exposed to industrial and cosmetic chemicals than the elderly, who are more exposed to topical medicaments. The elderly may have one or more contact allergies reflecting exposure 30–40 years earlier, with the positive patch test being of historical interest only. Prevalence of contact allergy would be expected to increase with increasing age. In a recent study including 1501 8th-grade schoolchildren, as much as 15% were reported to have one or more positive patch tests [64]. In epidemiological studies of contact allergy, age is therefore an important confounder, which should be handled adequately, for example by stratification or multivariate analysis. Loss of sensitivity over the years – or reduction of the contact allergy to below a clinically relevant threshold – has been debated [65], and figures such as 20% to 50% have been suggested. However, these studies have not considered a possible overestimation of contact allergies in the primary studies due to excited skin syndrome.

9.3.1.4 Ethnic Factors

In an experimental study from 1966, black people were found to be less susceptible to contact sensitization with poison ivy and DNCB compared to white [66]. Newer data are not available.

9.3.1.5 Regional Differences

As mentioned above, exposure to allergens and ability of the allergens to penetrate the epidermis are essential factors for contact sensitization. These factors are influenced by regional variation. Sensitization is increased by traumatizing the skin, and skin exposed to irritants, for example on the hands, may often be traumatized. The barrier abilities of stratum corneum change from one region to another, as reflected by differences in TEWL values [38], and penetration abilities for different allergens may likewise change.

Occlusion promotes percutaneous penetration, and contributes to sensitization from topical medications in stasis dermatitis and perianal eczema.

Reactivity to diagnostic patch testing differs greatly according to anatomical site. Skin responsiveness is more pronounced on the back than on the arms and thighs, and only the upper back is recommended for routine diagnostic patch testing.

9.3.1.6 Atopy

Atopics downregulate Th1 cells, which explains their tendency to severe viral infections, particularly with herpes simplex [67]. Because of this Th1-cell downregulation, a decreased propensity to contact dermatitis is expected. Clinical studies addressing this problem are contradictory, but most find a decreased tendency to contact sensitization [68–71]. Some studies suggest that especially patients with severe atopic dermatitis have a decreased ability to develop contact allergies [72, 73]. In a population-based study no correlation, either positive or negative, was found between the presence of a positive patch test and IgE sensitivity [74]. Respiratory symptoms may also be of importance, and different subgroups of atopic patients with respect to contact sensitization may exist.

Another possible bias is the increased number of irritant patch test results in atopic patients, especially when testing metals, e.g., nickel, cobalt, and chromate [75]. Recent studies do, however, indicate that atopics seem to have an increased frequency of nickel sensitization [76]. Because of these uncertainties, patch test results should specify the number of patients included with atopy.

9.3.1.7 Coincidental Diseases (Other Than Atopy)

Patients with acute or debilitating diseases such as cancer (Hodgkin's disease and lymphoma) have im-

paired capacity for contact sensitization [47]. Patients with psoriasis are generally considered to have fewer contact allergies than others, but, due to the intensive treatment of psoriasis patients with topical agents, this impression may not be correct [77].

9.3.1.8 Medication

It is a general clinical experience that systemic prednisolone in a dose exceeding 15 mg/day may diminish or suppress allergic patch test reactions, as may topical corticoid treatment. Antihistamines and disodium cromoglycate do not seem to significantly influence the allergic contact dermatitis reaction. The influence of azathioprine and nonsteroidal anti-inflammatory drugs on the outcome of patch test reactions is unexplored.

Exposure to ultraviolet light, especially UVB [78, 79] and PUVA [80, 81], may reduce risk of sensitization and temporarily diminish the ability to elicit allergic reactions in sensitized individuals.

Suggested Reading

Björnberg A (1968) Skin reactions to primary irritants in patients with hand eczema. Isacson, Göteborg

Rystedt I (1985) Factors influencing the occurrence of hand eczema in adults with a history of atopic dermatitis in childhood. Contact Dermatitis 12:185–191

The thesis by Björnberg from 1968 was chosen as a classical reference, since the knowledge today about irritants and skin irritancy testing is still dependent on the results from this great work.

The epidemiological studies performed by Rystedt in the 1980s are still of current interest, and are the basis for the advice that we give today to atopic patients to prevent development of ICD.

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