

The relation between the localization of foot dermatitis and the causative allergens in shoes: a 13-year retrospective study

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The purpose of this retrospective study was to test whether the initial pattern of clinical presentation of shoe dermatitis could indicate the causative allergen(s) and to estimate the odds on foot dermatitis in patients with a positive patch test versus those with a negative patch-test result. Between 1990 and 2002, 8543 patients were patch tested with the standard series (and additional allergens, if appropriate). Of them, 1168 (14%) had been referred because of foot dermatitis and 474 of these patients (5.5% of the total group) presented a positive reaction to one or more substances related to shoes. We found that 6 standard allergens in the male group and 8 standard allergens in the female group were statistically significant for the shoe dermatitis group. The data showed a relationship between the distribution pattern of the foot lesions and most of the allergens. These results have clinical applications since the gender of the patients and the localization of the foot eruptions can, indeed, indicate what allergen is involved.

Key words: contact dermatitis; foot; footwear; gender; localization; odds ratio; regions; shoe.
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Foot dermatitis is a diagnostic and therapeutic challenge. As for other body sites, there are many differential diagnoses to be considered (1), including allergic contact dermatitis (ACD), irritant contact dermatitis (ICD), dyshidrosis, psoriasis, tinea pedis, lichen planus, juvenile plantar dermatosis and id-like spread reactions (2). When considering the possibility of ACD, potential allergen sources such as shoes, socks, cosmetic and topical pharmaceutical products have to be taken into account (1).

Dermatitis of the feet presents with specific characteristic clinical patterns at, for example, contact sites with the shoe tips, the upper and side parts, and the sole of the shoes. The dermatitis rarely appears on the sides or in the plantar flexure creases of the toes (3). The lesions are usually symmetric, but may be patchy and even unilateral. Moreover, in chronic cases, the specific pattern of the disease may no longer be present. For example, allergens can leach out of the shoe to affect parts of the foot that are not normally in contact with it.

Local factors are particularly favourable to the development of allergy, such as friction, sweating, pressure and occlusion. In agreement with the

assessment in *Fisher's Contact Dermatitis* (4): 'The extraordinary thing about shoe dermatitis is its relative rarity. The hot, humid environment within the shoe, combined with hundreds of chemicals, creates an ideal situation for the development of allergic or irritant contact dermatitis'. Indeed, highest prevalence rates have been recorded in warm climates (5, 6).

However, among patients suffering from ACD, reactions to shoe materials are fairly common (7, 8), the most frequent causes being chemicals found in leather, rubber, adhesives, dyes and to a less extent biocides and decorations.

It is useful for a dermatologist to know about footwear manufacture and composition, in order to assist the allergic patient in finding shoes that can be worn without difficulty (4). This knowledge is, however, not easy to acquire or to apply because of the constantly changing design and complex composition of shoes and reluctance of the manufacturers to divulge all the ingredients present that may or may not have been reported to be allergens (2).

Currently, patch testing for shoe allergy is performed not only with chemicals from the standard series, but also with a shoe series (with

varying composition), and pieces of or extracts from the shoes worn by the patient. Many cases of shoe allergy can be diagnosed from the standard series (9), and most of the patients do present, in general, multiple positive tests.

The diagnosis of shoe allergy is difficult to make without patch testing, and a prepatch test diagnosis is often misleading, such as in the case of a mycosis which may mimic ACD.

The aims of this retrospective study were:

- (1) To determine which are the most common allergens causing shoe dermatitis.
- (2) To establish whether there is a relation between the primary location of the dermatitis and the causative allergen(s).
- (3) To estimate the odds on ACD of the feet in patients with a positive patch test versus those with a negative patch-test result.

Materials and Methods

Between 1 January 1990 and 31 December 2002, 8543 patients were patch tested in the Contact Allergy Unit of the Katholieke Universiteit Leuven, of whom 1168 (14%) had been referred because of foot dermatitis. The patients studied presented with eczematous dermatitis located on their feet. They were patch tested with a European standard series (Hermal, Reinbeck, Germany) with Belgian additions (Table 1) and (when indicated) also with other allergens, depending on the patients' history. A shoe series (Table 2) and pieces of or extracts from the shoes worn by the patient were included in order to detect the cause of the ACD. Thin pieces of shoe material about 1.5 cm² were moistened with saline, attached to Micropore[®] tape (3M Health Care, Borken, Germany) and applied on the back. Often parts of many shoes were tested.

The patch tests were administered with Van Der Bend patch-test chambers (Van Der Bend, Brielle, the Netherlands) applied on the back with Micropore[®], and fixed with Fixomull (Beiersdorf, Germany) and later with Mefix (Mölnlycke Health Care, Göteborg, Sweden) as adhesive tape. The patch-tested readings were performed according to

Table 1. Belgian additions to the European standard series

Substance	Concentration (%) in petrolatum
Propylene glycol	10 (aqueous)
Euxyl K400	1.5
Tosylamide/formaldehyde resin	10

Table 2. Shoe series (K.U. Leuven)

Substance	Concentration (%) in petrolatum
Acrylic monomer	2
Benzoylperoxide	1
2,2,4-Trimethyl-1,2-dihydroquinoline	1
Dibutylthiourea	1
Dibutylphthalate	5
Carba-mix	3
<i>N,N</i> -Dimethyl-4-toluidine	5
Dodecylmercaptan	0.1
Diethylthiourea	1
Glutaraldehyde	2
Acid yellow 36	1
Tricresylphosphate	5
Diphenylmethane-4,4-disocyanate	2.5
Resorcinol monobenzoate	2
<i>p-tert</i> -butyl-catechol	0.25 (formerly 0.5)
Phenol formaldehyde resin	5
4,4-Diaminodiphenyl-methane	0.5
4-Aminoazobenzene	0.25
Disperse Orange 3	1
Disperse Blue 106	1
Disperse Blue 35	1
Acid Red 359	5
Chloroacetamide	0.2
2-Thiocyanomethyl benzothiazole	0.1

the international guidelines by the International Contact Dermatitis Research Group after 2 days, 3 days (exceptionally) but mostly 4 days and sometimes later, if necessary.

All data were retrieved from, and evaluated with, a computer database developed in our department. The data were split up by gender. All the statistical analysis were performed on the two separate groups (female/male). A Chi-square method for proportions was performed. A *P*-value <0.05 was considered statistically significant.

All the allergens identified were reported. However, since we did not have enough data available for all possible allergens, we restricted the statistical analysis to the standard allergens. For each of these standard allergens, we estimated the association between the outcome of the test and the presence of dermatitis. Associations were measured by an odds ratio (OR) and a corresponding 95% confidence interval. To compute these ORs, the SAS software system version 9.1 (SAS Institute, Cary, NC, USA) was used.

To display the frequency of foot lesions on the one hand, and standard allergens identified in patients with shoe dermatitis on the other hand, a histogram was used.

Results

Of the 1168 patients referred with eczematous dermatitis of the feet, a positive reaction to one

or more substances related to footwear was recorded in 474 (41%). This represented 5.5% of the total population (8543). With regard to the gender distribution, there were 331 (70%) females and 143 (30%) males. The mean age of the entire group was 36 years (range 3–83 years) (Fig. 1). There were 16 patients below the age 16 (9 girls and 7 boys).

Table 3 represents the relevant patch-test reactions observed to allergens of the European standard and the shoe series in 1168 patients with foot dermatitis: chromate, cobalt, PPD, rubber additives, colophony and PTBPF resin are the most important shoe allergens. For those that do react to rubber additives (103 in total), mercapto mix and mercaptobenzothiazole (MBT) are the most commonly observed. Dodecyl mercaptan produced the highest number of positive reactions in the shoe series followed by 2-thiocyanomethyl benzothiazole (TCMTB), 4-aminoazobenzene and *p*-*tert*-butylcatechol (PTBC).

In order to specify the standard allergens that were significant for shoe dermatitis, we compared the results of patch testing in the group with contact allergy to shoes and the results in patients with contact allergy not due to shoes. Positive reactions due to nickel sulfate were not included in the results because it was in most cases not involved as a relevant allergen related to shoe dermatitis. The frequency of atopy was not included because this was not considered relevant to this study.

For the females, potassium dichromate, *p*-phenylenediamine (PPD), cobalt chloride, colophony, mercapto mix, *p*-*tert*-butylphenol formaldehyde (PTBPF) resin, MBT and thiuram mix were significantly associated with footwear dermatitis.

As to the males, the significantly associated allergens in this regard were potassium dichromate, colophony, mercapto mix, MBT, thiuram mix and PPD.

The same allergens (except PPD and IPPD) were found in the 16 children investigated, but the number was too small to allow a comparison between boys and girls.

The strength of the association between foot dermatitis and the result of the test is computed by ORs. The odds of dermatitis is the ratio of the probability of having dermatitis to the probability of not having dermatitis. An OR larger than 1 means that the odds of having dermatitis when having a positive patch-test result is larger than the odds of having dermatitis when having a negative patch-test result. These results are presented in Table 4.

The patients examined presented with lesions on different parts of the foot, including (exceptionally) the interdigital sites of the toes. The most relevant allergens in the standard series which were positive in relation to the regions on the foot affected are visualized in Fig. 2.

Potassium dichromate and cobalt chloride were most often found in relation to dermatitis of the whole feet superficies, however, with a small predominance for the dorsal parts. This also applies to PPD, colophony and PTBPF resin. The rubber chemicals, MBT and mercapto mix, and to a lesser extent thiuram mix, were associated with the soles of the feet, in particular.

48 patients presented with positive reactions to their own shoes materials, most of them being females (69%). The dorsal region was involved in 56% of the patients, plantar regions 19% and both regions 25%. The most common allergens associated in decreasing order of frequency were potassium dichromate, colophony, PTBPF, TCMBT, PPD, mercapto mix, PTBC, cobalt chloride, MBT and thiuram mix. Only 7 patients presented with positive reaction to shoe material only. Miconazole nitrate was found as a relevant allergen in two patients; thus it can be considered to be a contaminant of the shoes materials.

Discussion

In general, ACD of the feet is seen much less commonly than ACD of the hands, and in both cases the dermatitis is usually more severe over the dorsal aspects (10, 11). Like the palmar hand,

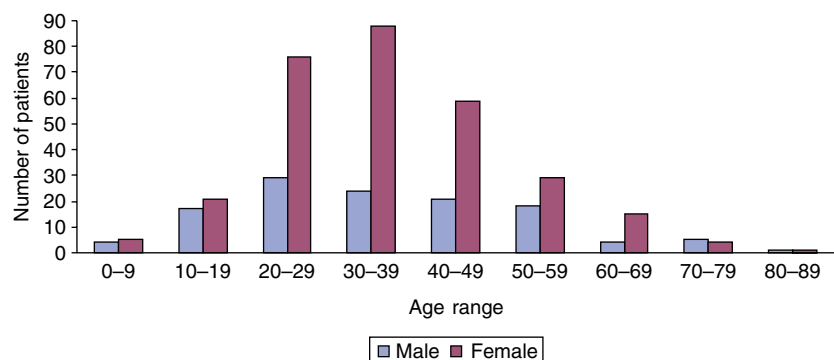


Fig. 1. Ages of patients with allergic contact dermatitis to shoes.

Table 3. Relevant results of patch testing in 1168 patient with foot dermatitis*

Allergen	No. of patients	Description
Potassium dichromate†	253	Leather tanning
Cobalt chloride†	132	Concomitant to chromium
PPD†	106	Dyes
Colophony†	89	Pine resin extract; glues, finish
PTBPF resin†	63	Adhesives in shoes
Mercapto mix†	58	Rubber accelerator‡
MBT†	47	Rubber accelerator‡
Thiuram mix†	40	Rubber accelerator‡
IPPD†	10	Rubber antioxidant
Dobecylmercaptan§	47	Polymerization inhibitor-Neoprene glues
2-Thiocyanomethyl benzothiazole§	35	Biocide in leather
4-Aminoazobenzene§	21	Dye (cross-reacts with PPD + other azodyes)
<i>p-tert</i> -butyl-catechol§	20	Cross-reacts with PTBP resin
Benzoylperoxide§	11	Catalyst (glues), plasticizer
Disperse Blue 106§	10	Textile dye
Carba-mix§	9	Rubber chemical mix
Disperse Orange 3§	9	Textile dye
Diethylthiourea§	8	Rubber accelerator (in neoprene glues)
Black rubber mix§	6	Rubber antioxidants
Disperse Blue 35§	3	Textile dye
Dibutylphthalate§	1	Plasticizer in various plastic materials

PPD = *p*-phenylenediamine; IPPD = *N*-isopropyl-*N*-phenol-4-phenylenediamine; MBT = 2-mercaptobenzothiazole; PTBPF = *p-tert*-butylphenol formaldehyde; PTBP = *p-tert*-butylphenol.

*Some patients had more than 1 relevant allergic reaction.

†European standard series.

‡The total number of subjects reacting to rubber accelerators was 103.

§Shoe series.

if the plantar foot is the only portion contacting the allergen, the dermatitis will be restricted to this area (10). The most common allergens in decreasing order of frequency in our series were potassium dichromate and cobalt chloride (concomitant to chromium), followed by PPD, rubber components, colophony and PTBPF resin.

The occurrence of shoe dermatitis in our patch-tested patients (5.5%) is within the range

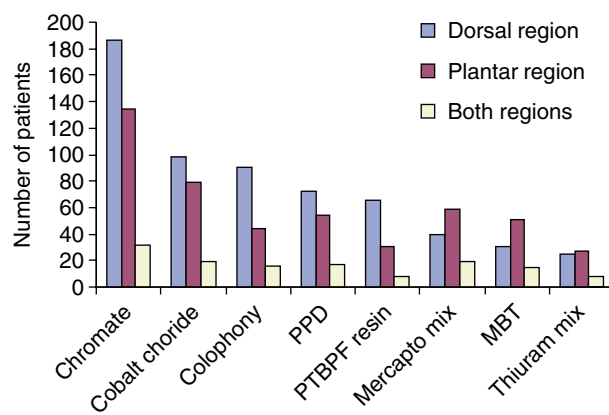
Table 4. Association analysis of the significant allergens from the standard series for shoe dermatitis in females and males

Allergens	Odds ratio	95% CI
Females		
Potassium dichromate	21.8800	(16.3381;29.3018)
Thiuram mix	1.7672	(1.0780;2.8971)
PPD	1.8214	(1.3101;2.5322)
Cobalt chloride	4.4550	(3.3600;5.9069)
Colophony	2.7790	(2.0067;3.8485)
Mercapto mix	9.2672	(5.8804;14.6052)
PTBPF resin	8.6389	(5.8309;12.7991)
MBT	10.3461	(6.3155;16.9491)
Males		
Potassium dichromate	3.1166	(1.8683;5.1988)
Thiuram mix	1.9785	(1.0630;3.6827)
PPD	1.7637	(1.1218;2.7729)
Colophony	2.8769	(1.7297;4.7849)
Mercapto mix	6.1546	(3.2730;11.5732)
MBT	5.6606	(2.7742;11.5502)

MBT = 2-mercaptobenzothiazole; PPD = *p*-phenylenediamine; PTBPF = *p-tert*-butylphenol formaldehyde.

There was no significant association between shoe dermatitis and the other standard allergens.

reported in the literature (between 3% and 12.5%) (12). In Freeman's study, the incidence of shoe dermatitis was almost equal in both genders (females 47% and males 53%) (11), whereas, in our series, ACD due to footwear was more frequent among women than men (female : male ratio, 5 : 2), which is in agreement with some reports (13, 14), although the majority of the studies reported that it predominates in men (2, 5, 15–17). To us, a female predominance seems logic because women between the ages of 20 and 50 often do not wear stockings in the



Most relevant allergens in the standard series

Fig. 2. Visualization of frequency of allergens versus regions.

summertime and are thus in direct contact with the potential allergen(s).

It is well known that dorsal foot dermatitis normally points to an allergen in the shoe upper, which is generally made of leather or synthetics. In our study, potassium dichromate was the most important allergen found, followed by cobalt chloride, PPD, colophony and PTBPF resin.

Chromium compounds are used to dye both leather and non-leather synthetic uppers of the shoes (9, 18). In contrast to earlier results (2, 11), chromium has gained importance as a shoe allergen, especially in Europe (14, 18–20), the highest predominance being observed in females prone to wear leather shoes. Leather finishing processes involve the use of selected biocides by the manufacturer (9), one of them being TCMTB (Busan 30L[®]), used for preservation of both chrome and vegetable tanned leather (19). TCMTB was included in our shoe series, where it was the second most frequent allergen. However, TCMTB is not tested any longer since it has been abandoned in the process of leather finishing. Besides, it does cross-react with MBT compounds: among the 35 patients with a positive reaction to TCMTB, 69% and 57% also had a positive reaction to mercapto mix and MBT, respectively.

Cobalt allergy is often associated with chromate dermatitis due to leather shoes (21, 22), the reason for this not being obvious. Cobalt compounds may be used as dyes or pigments for shoes (21), or as catalysts (e.g. cobalt naphthenate) in polyester adhesive. On the other hand, cobalt and concomitantly nickel can cause lesions on the dorsum of the foot due to its presence in the decoration and trim. The relevance of nickel and cobalt are difficult to characterize though, because they are ubiquitous allergens, especially in women (13).

PPD-positive reactions often indicate a cross allergy to azo dyes, rubber additives (e.g. diaminodiphenyl methane) or other *p*-aminobenzene compounds. According to earlier reports (10, 23), shoe dermatitis from dyes is extremely rare, which is attributed to the firm fixation of the dyes to the leather. However, re-dyed shoes and dyes in fabric that may bleed can cause dermatitis. In our shoe series, several subjects reacted to *p*-aminoazobenzene as a marker for azo-dye sensitivity. PPD has been found to be a frequent allergen in Southern Italy; however, it is also likely that a proportion of the positive reactions to PPD were in fact due to stocking dyes (18).

Adhesives are used throughout the shoe and often come in direct contact with the foot, particularly when used to fix the soles and insoles, or the linings of the shoe, in place. Colophony may be present as a tackifier in heel and toe counters

in latex adhesives (9), in shoe polish, plastics and as a leather tanning or finishing agent (24). In our series, it was an equally significant allergen both in women and men.

In our series, potassium dichromate, cobalt chloride, PPD, colophony and PTBPF resin also involve the foot sole, because most of the substances used in the shoe uppers are used for shoe soles and insoles as well. However, the rubber allergens MBT and mercapto mix, as well as thiuram mix, albeit to a lesser extent, are particularly significant for foot sole dermatitis. This is also shown by the OR results, both for males and females (Table 4). The soles and insoles may be made of rubber, and the linings of shoes can be secured by glues containing rubber components. In the United States and Australia, where sport shoes are frequently worn, the most common shoe allergens are rubber components (accelerators) (2, 11). It is noteworthy that perspiration enhances skin penetration, hence exposure and sensitization to rubber allergens (2). No matter where the rubber is in the shoe, it is important to remember that when the shoe becomes wet after being worn, the suspect chemicals can migrate to distant parts of the shoe (4).

Patients with ACD to shoe components are usually advised to wear shoes made of 'hypoallergenic' material, which has proven to be effective in some cases (7). Indeed, in our experience, the results obtained with extracts from 'hypoallergenic' leather vary greatly between the subjects tested. In these cases, the following recommendations can be made: wearing wooden or plastics shoes, wearing good-quality new leather shoes and discarding them after a few months (thus preventing the allergens from leaching out) and wearing extra pairs of socks in shoes that are too large (thus preventing contact with the allergens). These simple measures can, according to certain authors (7, 12), result in clearance of half the cases of allergic shoe eczema due to an unknown allergen.

Socks can cause contact dermatitis due to components such as dyes and rubber additives. Moreover, they are also able to act as allergen carriers, for mercaptobenzothiazole in particular, which may leach out from sweat-contaminated cotton socks; single washing or boiling does not eliminate the contamination (25).

Eczema around the heels and toes suggests an allergy to the heel and toe stiffeners or counters, which are used to enable the shoe to retain its shape. The simplest and least problematic type is a layer of hot-melt adhesive. The other types consist of a polyester or cotton material impregnated with a variety of resins. These counters expose people to a number of potential allergens (9),

including colophony and PTBPF resin. In our study, however, no allergens were found to correlate specifically with contact dermatitis of the heels.

Special situations always have to be kept in mind. Hyperhidrosis, occlusive footwear and socks, which may lock in wetness and retain some of the allergens after washing, may exacerbate the lesions (26–28) (occasionally, controlling hyperhidrosis will allow a patient with minimal problem to wear allergy-causing shoes for short periods of time) (4). Moreover, topical medication can induce primary foot dermatitis or exacerbate an existing one (2). Indeed, despite the identification and discontinuance of a topical medication, the dermatitis may persist because of contamination by allergens of the leather or fabric of the shoe, and of the socks, even after washing (29), hence the usefulness of testing with material from the patient's own shoes.

Conclusion

In this retrospective study of patients suffering from shoe dermatitis, we could determine that 8 standard allergens correlate particularly well with shoe dermatitis, that there are gender differences with regard to the allergens identified and that the localizations of the foot eruptions can, indeed, indicate which allergen is liable to have caused them. However, in order not to miss a contact allergic dermatitis from footwear, in agreement with other authors (30, 31), other allergens that are not present in the standard series, as well as the patient's own footwear, also need to be tested.

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