

Report

Foot contact dermatitis: nitrofurazone as the main cause in a retrospective, cross-sectional study over a 16-year period from Turkey**Esen Özkaya, MD, and Algun Polat Ekinici, MD**

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Abstract

Background The major causative agents in allergic contact dermatitis of the foot may differ from country to country. Sufficient data on foot eczema in patients from Turkey are lacking.

Objective To identify the clinically relevant contact allergens in foot eczema and determine the role of patch test series and patients' own materials in the detection of the responsible allergens.

Methods Among 1753 patients patch tested between 1996 and 2012 in our clinic, 53 with suspected allergic foot eczema were enrolled in this retrospective, cross-sectional study. Forty nine patients were patch tested with the extended European baseline series, 49 with supplemental series including rubber, leather, topical drugs, textile, cosmetic series containing preservatives and emulgators and varnish/plastic/glue series, and 37 with their own substances.

Results Thirty of the 53 patch tested patients showing sensitization to at least one clinically relevant allergen were diagnosed with allergic foot eczema. The main eliciting agent was nitrofurazone ($n = 8$), followed by leather shoe allergens, ie, potassium dichromate ($n = 6$), p-tert-butylphenol formaldehyde resin and formaldehyde, in the second range. Rubber shoe allergens were less frequently observed ($n = 3$). In more than 1/3 of the patients, the causative agent could only be identified by testing the patient's own substances and/or supplemental series.

Conclusion Nitrofurazone was the leading causative agent followed by leather shoe allergens. Pediatric patients were frequently sensitized with shoe allergens. Patch testing with patient's own substances had a critical value in the detection of the causative agent in a significant number of patients.

Introduction

Allergic contact dermatitis (ACD) of the foot is a common dermatosis affecting males and females of all ages, including pediatric patients. Hot and humid environments and pressure and occlusion within shoes and socks are regarded as the main predisposing factors.^{1,2} Shoe allergens including rubber, leather, adhesives, some chemicals of footwear materials such as dyes, and topical medications have been reported as the major causative agents of ACD worldwide.^{1,3} Detecting the causative allergen with patch testing is essential for effective treatment and prevention of the dermatitis. Causative allergens may change from country to country depending on local factors such as habits, traditions, and climate conditions. Unfortunately, comprehensive data on ACD in Turkish patients are lacking. We therefore aimed to identify the clinically relevant contact allergens as well as the role of patch test series and contact

materials in the detection of the responsible agents in a large series of patients in Turkey during a 16-year period.

Materials and methods

In this retrospective, cross-sectional study, files of 1753 patients who underwent patch testing between June 1996 and December 2012 in the allergy unit of our clinic for clinically suspected ACD were evaluated. Of these, 53 patients with primary involvement of the foot were enrolled in the study.

Patch testing was performed after written or oral consent of patients, or legal guardians in children. Test allergens were applied in IQ® Chambers (Chemotechnique Diagnostics, Vellinge, Sweden) to the upper back for 48 hours. Patch tests were occluded with Hypafix® tape (BSN medical GmbH, Hamburg, Germany). Test sites were evaluated at days (D) 2, 3, 4, and in some patients at D7 as well, according to the criteria of

the International Contact Dermatitis Research Group.⁴ Patients' own materials such as shoes, topical medications, or others were properly tested depending on the physical and chemical structures of the materials.⁵ Topical preparations were tested "as is." Shoes were tested as pieces of 3 × 3 cm or 5 × 5 cm, soaked in water for 15 minutes, and occluded for 72 hours. Forty-nine patients were patch-tested with our extended European baseline series, and with supplemental series of allergens supplied by Brial Allergen (Greven, Germany) and Chemotechnique Diagnostics and in the earlier years by Hal-Brial (Leiden, The Netherlands). The tested supplemental series were rubber (*n* = 6), leather (*n* = 23), topical drug (*n* = 2), textile (*n* = 4), cosmetic (*n* = 21) including preservatives and emulgators, and varnish/plastic/glue (*n* = 2). Thirty-seven patients were additionally tested with their own substances including pieces of leather/rubber shoes, topical medicaments, and creams used on the foot. The dimethylglyoxime test (Chemo Nickel Test; Chemotechnique Diagnostics) was used to reveal evidence of nickel release from metal objects if necessary.

Results

Fifty-three of 1753 patch-tested patients (3%) had suspected allergic foot eczema confined to the foot. Thirty-five of them (66%) had at least one positive patch test reaction. A total of 30 of the 53 patch-tested patients (56.6%) (19 female and 11 male) with confirmed sensitization to clinically relevant allergens were diagnosed with ACD of the foot while the rest of the patients' diagnosis was mainly consistent with irritant contact dermatitis. The mean age of patients having ACD was 31 years (range: 3–80 years). Seven of them (23.3%) were pediatric patients (≤18 years). The median duration of lesions was 12 months (range: 1–120 months). Most of the patients (*n* = 20) had no atopic background, while five had atopic dermatitis or mucosal atopy. History of atopy was unknown in the remaining five. The most frequently observed morphological pattern of eczema was erythematous-squamous (*n* = 13), followed by dyshidrosiform (*n* = 8), combined type (*n* = 7), and others (not specified) (*n* = 2). The dorsum of the foot was the most commonly affected area (*n* = 11), followed by the plantar area (*n* = 10), the whole foot (*n* = 6), lateral parts of the foot (*n* = 2), and plantar surface of the toes (*n* = 1). The characteristic features of these patients are shown in Table 1.

Patients were mainly sensitized to topical preparations (*n* = 13), followed by leather shoe allergens (*n* = 11), and others (Table 2). Concomitant sensitization with shoe allergens and topical medications was observed in two patients. As shown in Table 2, the main causative topical medicament was nitrofurazone (*n* = 8) (Fig. 1), followed by antifungals, antiseptics, and others. The main causative shoe allergens were leather components (*n* = 11), predominantly potassium dichromate (*n* = 6) (Fig. 2), followed by rubber allergens (*n* = 3), and nickel in shoe metal accessories (*n* = 2). The involvement was

Table 1 Characteristics of 30 patients with allergic contact dermatitis of the foot

	Number of patients (<i>n</i> = 30)
Gender	
Female/male	19 : 11
Age	
Median (minimum–maximum)	31 (3–80)
Localization	
Bilateral/unilateral	21 : 9
Morphologic pattern	
Erythematous-squamous	13
Dyshidrosiform	8
Combined	7
Others (not specified)	2
Affected area of the foot	
Dorsum	11
Plantar	10
Whole foot	6
Lateral parts	2
Plantar surface of the toes	1
Patch test with:	
The extended European baseline series	29
Supplemental series	24
Patients' own substances	23
Relevant allergen in:	
The extended European baseline series	18 ^a
Supplemental series and/or patients' own substances (mainly topical preparations, and shoes)	14 ^a

^aThe total number of patients is >30 as two patients had concomitant relevant contact sensitizations to two allergens from different series.

exclusively bilateral in shoe dermatitis. Shoe dermatitis affected all parts of the foot including dorsal (*n* = 6), plantar (*n* = 5), and lateral (*n* = 2) sites, and the whole foot (*n* = 3) without interdigital involvement. The dorsum of the foot was prominently affected in those with contact sensitization to leather, i.e., potassium dichromate, whereas plantar involvement was mainly seen in rubber allergy. Pediatric patients (*n* = 7) were mainly sensitized with shoe allergens (*n* = 4; leather shoe in 3, and rubber shoe in one), followed by nitrofurazone (*n* = 1), mercurial antiseptic (*n* = 1), and nickel in shoe metal accessories (*n* = 1).

Unexpected rare causes of allergic foot eczema included nickel in metal foot file and razor in each one patient, used for scratching the heel, and para-phenylenediamine in a new carpet dye in another patient. Foot eczema did not recur after avoiding the culprit agent.

In 60% of the patients (*n* = 18), the responsible allergen/agent was identified by testing with the extended European baseline series alone, and in the remaining 40% (*n* = 12) by testing with the patients' own substances and/or supplemental series, mainly comprising topical preparations and their

Table 2 Relevant allergens/materials in 30 patients with allergic contact dermatitis of the foot

Relevant allergens/materials (% vehicle)	No. of patients	Allergen source (n)
Nitrofurazone (1% pet.), ^a NCO (as is)	1	Topical preparations (13)
Nitrofurazone (1% pet.), ^a NCO (as is), polyethylene glycol 400 (100% pet.)	1	
Nitrofurazone (1% pet.), ^a NCO (as is), fucidic acid (2% pet.)	1	Main allergens: Nitrofurazone/NCO (8)
Nitrofurazone (1% pet.), ^a NCO (as is), potassium dichromate (0.5% pet.)	1	
Nitrofurazone (1% pet.), iodine (5% pet.)	1	
^a NCO (as is)	2	
^a NCO (as is), carbamix (3% pet.)	1	
Iodine (5% pet.)	1	
Ammoniated mercury (1% pet.)	1	
Antifungal cream (as is, contains clotrimazole+hexamidine)	1	
Antifungal cream (as is, contains 1% isoconazol nitrate), isoconazole nitrate (1% pet. and 1% in ethanol)	1	
Moisturizing cream (as is, contains Amerchol, wool alcohol), wool alcohols (30% pet.), Amerchol (50% pet.)	1	
Potassium dichromate (0.5% pet.)	4	Leather shoe (11)
Potassium dichromate (0.5% pet.), nitrofurazone (1% pet.), NCO (as is)	1	
Potassium dichromate (0.5% pet.), ^b own leather shoe	1	Main allergen: Potassium dichromate (6)
4-tert-Butylphenol formaldehyde resin (1% pet.), ^b own leather shoe	2	
Formaldehyde (1% aq.), ^b own leather shoe	1	
^b Leather shoe material	2	
Thiuram mix (1.0% pet.), mercapto mix (1.0% pet.), mercaptobenzothiazole (2.0% pet.)	1	Rubber shoe (3)
Carbamix (3.0% pet.), NCO (as is)	1	
Mercapto mix (1.0% pet.), mercaptobenzothiazole (2.0% pet.), ^b rubber shoe material	1	
Nickel sulfate (5.0% pet.)	1	
Nickel sulfate (5.0% pet.), palladium chloride (1.0% pet.)	1	Metal shoe accessories (2)
Nickel sulfate (5.0% pet.)	2	
p-Phenylenediamine (1.0% pet.), Disperse Orange 3 (1.0% pet.), aminophenol (1.0% pet.)	1	Metal foot file/ razor (2)
		Carpet dye (1)

Patients' own substances are underlined.

Total number of patients presented in Table 2 is >30 as two patients had concomitant relevant contact sensitizations, i.e., one to nitrofurazone and potassium dichromate, and the other one to nitrofurazone and carbamix.

^aNCO, nitrofurazone containing ointment contains nitrofurazone + polyethylene glycol.

^bLeather/rubber shoe material is tested for 72 h in pieces of 1 × 1 cm or 3 × 3 cm, obtained from different parts of the shoe, soaked in water.⁵

**Figure 1** Nitrofurazone-induced allergic contact dermatitis on the dorsum of the right foot

ingredients, and own shoe material (Fig. 2). The dimethylglyoxime test revealed evidence of nickel release from metal shoe accessories in two patients and metal foot file in one patient.

Discussion

To our knowledge, this is the largest series on ACD of the foot reported from Turkey. The prevalence of foot contact dermatitis shows a wide variation from 1.5 to 24% in previous reports from different countries,^{2,3,6,7} which is probably related to local differences in climate, weather, traditions, or to personal factors such as occupation, habits, and lifestyle, and to constitutional factors such as hyperhidrosis. The frequency of confirmed ACD of the foot among patch-tested patients was 1.7% in our study.

The female predominance in our study was consistent with previous reports, which was attributed to the greater variation of footwear in females and to the habit of wearing shoes without socks.^{7,8} On the other hand, a male predominance was reported in an increasing number of recent studies, being attributed to more occlusive male footwear particularly in certain



Figure 2 Leather shoe-induced allergic contact dermatitis of the feet. Note the symmetrical involvement of the dorsal and medial parts of the feet. Positive patch test reactions to potassium dichromate and own shoe material (particularly upper parts of the shoe)

occupational groups such as military personnel and factory workers.^{2,3,9} One of our patients was a bakery worker, working in a hot and humid environment, whereas an occupational relationship was not observed in the rest of the group.

The mean age of our patients represents a relatively younger group than those reported by other studies.^{1,3,9} This could be attributed to a more active and faddish lifestyle of individuals at these ages leading to exposure to different shoe allergens. The rate of atopy background in this study (16%) was lower than that (24.9%) of a previous study from our clinic on patch test results of patients with suspected ACD.¹⁰ Although hand dermatitis is known to be significantly associated with an atopic background, atopy itself is not regarded as a risk factor for foot eczema.^{3,9}

Topical preparations particularly nitrofurazone were the most common cause of allergic foot eczema in our study, mainly presenting with unilateral involvement and dyshidrosiform morphology. Although potent sensitizing capacity of nitrofurazone is very well known worldwide,^{11,12} it is still the most preferred antibacterial topical agent in Turkey, particularly in surgical branches. We believe that its use is a tradition in our country, which seems difficult to break. Therefore, we are afraid that nitrofurazone-induced ACD would continue to be a remarkable problem in Turkey. As seen in our patients (Table 2), active and/or inactive ingredients of topical preparations, e.g., emulgators, preservatives, and fragrances, may be the culprit agent in ACD. Therefore, it is necessary to patch test with all ingredients of a topical agent.

Shoe-related dermatitis of the foot is associated with traditional, occupational, and behavioral factors in the selection of shoes, and the use of different chemicals and substances during manufacturing. In our study, the dorsum of the foot was predominantly affected in those with contact sensitization to

leather, i.e., potassium dichromate, whereas plantar involvement was predominantly observed in the patients with rubber allergy. Plantar surface of the toes,¹³ dorsum of the toes, and/or the foot^{1,8} were the most frequently involved sites in shoe contact dermatitis in previous reports.

Shoe components, mainly leather, rubber, adhesives, preservatives, or dyes, are known as other important causes in ACD of the foot. The North American Contact Dermatitis Group and an Indonesian report indicated rubber additives as the most common shoe allergens,^{1,14} whereas the European and Indian groups found leather allergens, i.e., chromium salts, as the main cause.^{3,7,15,16} In a previous case series from Turkey, two patients were reported to have allergic foot eczema from potassium dichromate in leather.¹⁷

Leather shoe allergens were in the second range in our study. It was mainly caused by potassium dichromate, the most frequently used tanning agent for leather. Use of chromium-tanned leather during shoe manufacture plays the most important role in exposure to chromium salts.¹⁸ p-tert-Butylphenol formaldehyde resin, another important leather allergen,³ is a well-known adhesive, which is used as a glue and found in the structure of neoprene, and has been used in the manufacturing of both leather and rubber shoes.^{14,19} Formaldehyde, both a preservative and tanning agent for leather, is known to be another potential leather allergen. Formaldehyde was considered the most likely agent in one patient in our study. Nowadays, it is recommended to test formaldehyde at 2% aq.; however, our patient reacted positively with formaldehyde 1% aq. Dimethyl fumarate, an effective mold growth inhibitor, is a recently introduced new and extremely potent contact sensitizer for, in particular, leather furniture or leather shoe-related ACD.²⁰ Patch test results with dimethyl fumarate (0.1 and 0.01% in pet.) were negative in two of our tested patients.

Rubber shoe allergens were detected as a minority in our study (Table 2). Two of the three patients with rubber shoe-related ACD showed positive patch test reactions to more than one rubber additive. Cross-reactivity is usually expected between thiuram mix and carbamix; however, interestingly, one of our patients showed a positive patch test reaction only to carbamix. Mixed dialkyl thioureas should also be patch-tested together with common rubber allergens such as thiurams, carbamates, mercaptobenzothiazole, mercapto mix, and black rubber mix when rubber-induced ACD is suspected.²¹ Thiourea compounds were negative in four of our patients tested with the related rubber series.

Another shoe-related ACD source is metal shoe accessories, which were found to be responsible for shoe allergy in two patients in our study and in one patient in the previous case series from Turkey.¹⁷ The dimethylglyoxime test helped to identify nickel release from the metal shoe accessories in our patients.

p-Phenylenediamine, that may be an indicator of sensitization to azo dyes in leather shoes, was found to be the culprit allergen in one of our patients with plantar eczema. Testing the insoles of her shoes was negative; however, interestingly, the eczema could be attributed to walking barefoot on a new carpet at home. Concomitant sensitizations were observed with Disperse Orange 3 and p-aminophenol. Carpet dye was suspected as the eliciting agent. Nowadays, a textile dye mix is available for screening purposes of azo-dye sensitization.²²

Finally, unexpected causes of allergic foot eczema from nickel were observed in two patients with plantar eczema; one from a metal foot file and the other from an old razor, both used for scratching or rasping the heel.

It is also noteworthy to remind that shoes and socks could be contaminated with the allergens, e.g., topical medicaments, rubber or leather allergens, which persist there and could not be rinsed off.^{23–25} Therefore, patients should be advised to avoid them permanently.

Another important finding of this study was that the responsible allergen/agent could only be identified with testing the patients' own materials and/or supplemental series in a significant number of patients (40%). These comprised mainly patients' own topical preparations and their ingredients not present in the baseline series, e.g., nitrofurazone, iodine, antifungals, moisturizing cream, etc., and shoes. In the remaining, the extended standard patch test series was sufficient to reveal the causative allergen.

Patch testing with a shoe series is usually recommended for patients with suspect of allergic foot eczema. A minimum of shoe allergen series should include potassium dichromate, p-tert-butyl phenol formaldehyde resin, formaldehyde, colophonium, azo dyes, adhesive resins, preservatives including dimethyl fumarate, rubber additives including thioureas, which are the main allergens in common. Topical medicaments and cosmetic products and their active and inactive ingredients

(fragrances etc.) should be added to this series according to the history of the patient. According to the results of the present study, it seems essential to investigate the use of nitrofurazone-containing topical medications in every patient with foot eczema in Turkey as well.

Conclusion

Nitrofurazone-containing antibacterial ointment was the leading causative agent in ACD of the foot in our patients, followed by leather shoe allergens, predominantly potassium dichromate. Pediatric patients were frequently sensitized with shoe allergens. Nickel, either in metal accessories or in metal tools used for scratching the heels, seems another important cause of foot eczema. Plantar eczema in a patient from carpet dye was striking. As shown in our study, patch testing only with the currently available shoe series may not suffice to detect ACD of the feet reliably. Patch testing with the patient's own substances had a critical value in the detection of the causative agent in a significant number of patients, particularly in those with contact allergy to topical medications and/or shoes.

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