

ORIGINAL ARTICLE

Fragrance contact allergy in Iran

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Abstract

Background Fragrances are considered as one of the most common causes of allergic contact dermatitis. About 1–4% of the general population suffer from fragrance contact allergy (FCA).

Objectives To determine the frequency of FCA and its clinical relevance in a sample of Iranian patients with history of contact and/or atopic dermatitis from January 2004 to December 2008.

Methods Standardized patch testing with 28-allergen screening series recommended by the German Contact Dermatitis Research Group and European Standard Series was used at six dermatological clinics in Iran. Fragrance allergens comprised of fragrance mix I (FM I), *Myroxylon pereirae* (MP; balsam of Peru), Lyrall[®], turpentine and FM II.

Results Fragrance contact allergy was detected in 7.2% of the patients. The frequency of positive reactions to FM I, MP and FM II were 3.7% (41/1105), 2.8% (32/1135) and 1.1% (3/267) respectively. 82.4% of the reactions to fragrance allergens were clinically relevant. The most common involved areas were hands (68.4%) and face (35.4%). Fragrance allergy predominantly affected women aged more than 40 years ($P = 0.008$). Positive reaction to more than two allergens was significantly higher in FCA patients compared with other contact dermatitis patients ($P < 0.0001$), and FM I, nickel and MP were the most frequent allergens in these patients.

Conclusions Despite less frequency of FCA in comparison with some European countries, its clinical relevance in Iranian patients seems to be high. It mostly affects the hands and the face predominantly in women aged more than 40 years.

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Keywords

allergic contact dermatitis, fragrances, Iran, patch test

Conflict of interest

None declared.

Introduction

Fragrances are considered as one of the most common causes of allergic contact dermatitis (ACD). It is estimated that 1–4% of the general population and between 6% and 14% of the contact dermatitis patients suffer from fragrance contact allergy (FCA).¹ Natural or manufactured fragrances are present in our environment and can be found in cosmetics, perfumes, cleansers, medications, foods and industry.^{2–4} More than 2500 fragrance constituents are used in the composition of perfumes of which at least 100 substances have been proved as contact allergens.⁴ ACD to fragrances is considered as a consequence of repetitive environmental exposure along with the age-related vulnerability parameters.⁵ Fragrance allergy most frequently involves the face, upper extremities, behind the ears, neck and the axillae, although generalized contact dermatitis has also been reported.^{2,3}

Three principal allergen mixtures have been used in the patch test screening series to detect FCA:

- 1 Fragrance mix I (FM I), originally introduced in 1977, is comprised of eight fragrance compounds (*Evernia prunastri*, isoeugenol, eugenol, cinnamal, geraniol, hydroxycitronellal, cinnamyl alcohol and amyl cinnamal). Patch testing with FM I can result in positive reactions in up to 70% for patients with FCA.⁶
- 2 *Myroxylon pereirae* (MP; balsam of Peru) which may be positive in up to 50% of fragrance allergic individuals.⁷ Although originally a combination of FM I and MP was expected to detect up to 90% of patients with fragrance ACD, because of concomitant reactions between FM I and MP and an increase in the use of the industrial fragrances, positive reactions to these two substances have decreased to 60–70%.^{6,8}
- 3 Fragrance mix II (FM II) has been recently introduced as a complementary mixture, which can detect one-third of patients sensitive to fragrances overlooked by FM I.⁹ It contains six commonly used constituents of perfumes:

hydroxyisohexyl 3-cyclohexene carboxaldehyde citral, farnesol, coumarin, citronellol and hexyl cinnamal.¹⁰

Hydroxyisohexyl 3-cyclohexene carboxaldehyde citral (LyrallTM; International Flavors & Fragrances Inc., New York, NY, USA) is included in the British Standard patch test series both in FM II at 2.5%. Due to a high rate of positive patch test reactions in European patients, LyrallTM is included in the aforementioned series at 5% concentration too.¹¹

The aim of this study was to determine the frequency of FCA and its clinical relevance in a sample of patients with the history of contact dermatitis and/or atopic dermatitis (AD) admitted to the referral dermatology clinics in six major cities of Iran.

Patients and methods

Participants and primary evaluation

Data from patients evaluated by patch testing in Iran were retrospectively studied for allergy to fragrance allergens including FM I, MP, Lyrall[®], turpentine and FM II. From January 2004 to December 2008, a total of 1137 patients with a clinical diagnosis of contact dermatitis and/or AD (according to the UK Working Party diagnostic criteria¹²) were evaluated by patch testing. The study protocol was reviewed and approved for ethical clearance by the Ethical Committee of the Center for Research and Training in Skin Diseases and Leprosy, Tehran University of Medical Sciences. Primary evaluation consisted of obtaining medical history and performing a thorough physical examination. A questionnaire consisting of patient's demographical characteristics, location of dermatitis, drug history, probability of occupational dermatitis, personal and familial history of AD, asthma, allergic rhinitis or urticaria was filled for each patient. Those who had taken oral corticosteroids at a dosage of >20 mg/day within 2 weeks prior to the study were excluded.

Patch test methods

Patients were tested with the 28-allergen screening series recommended by the German Contact Dermatitis Research Group (DKG) (469 patients) or European Standard Series (ESS)¹³ (668 patients) provided from Hermal, Reinbek, Germany. The allergens were used in the upper back using Finn ChambersTM on Scanpor[®] tape (Epitest, Tuusula, Finland) for 24–48 h and readings were noted at 48 and 72 h according to the guidelines of International Contact Dermatitis Research Group.¹⁴ The clinical relevance was defined as the history of contact with any fragrance containing the material showing positive reaction in patch testing at the same location of the dermatitis as stated by the patients.

Data analysis

Data analysis was performed using Statistical Package of Social Sciences version 16.0 (SPSS Inc., Chicago, IL, USA). Interval and ratio variables were described as mean $\pm$ standard deviation (SD) and categorical data were presented as proportions. Independent

t-test and chi-squared test were used for comparing mean values in quantitative variables and proportions in categorical variables respectively. *P*-value <0.05 was considered statistically significant.

Results

During a 5-year period, FM I, MP, Lyrall[®], turpentine and FM II were tested in 1105, 1135, 1137, 469 and 267 patients respectively. The proportions of the patients with at least one positive patch test reaction to any allergen and with at least one positive patch test reactions to the aforementioned allergens are presented in Fig. 1. The mean age of the entire study population was 31.5 ± 12.6 years. The mean age of patients with ACD was not significantly different from the mean age of those without ACD (31.1 ± 11.9 vs. 31.9 ± 13.1 years). The mean age of patients with FCA was significantly higher than that of patients allergic to other substances (35.2 ± 13.6 vs. 30.3 ± 11.3 years, *P* = 0.003).

Fifty-three (64.6%) of patients with FCA were women. Fourteen of 92 (15.2%) male participants who were 40 years old or younger had at least one positive reaction to a fragrance allergen. This proportion for male patients older than 40 years was 14/57 (24.6%) (*P* = 0.156). Thirty-five of 281 (12.5%) female participants who were 40 years old or younger had a positive reaction to at least one fragrance allergen. This proportion in female patients older than 40 years was 17/67 (25.4%) (*P* = 0.008).

Table 1 shows the percentage of positive patch test results for various fragrance allergens (91 positive reactions in 82 patients) in the whole study. The MOAHLFA Index¹⁵ of patients with and without FCA is illustrated in Table 2. With the exception of the proportion of the patients older than 40 years of age, no other component of MOAHLFA Index differed significantly between the

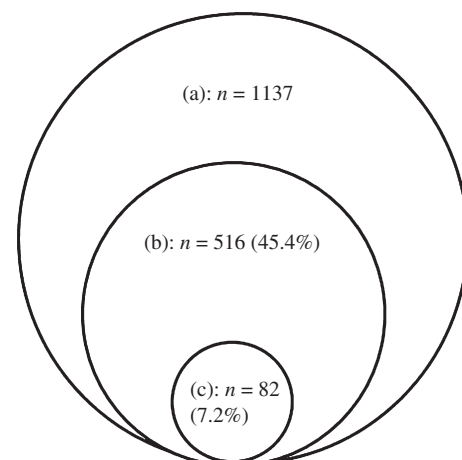


Figure 1 Proportions of positive patch test results in different patient groups. (a) Total patch tested patients. (b) Total patients with at least one positive patch test result. (c) Patients with at least one positive patch test result to one of the perfume allergens (fragrance mix I, balsam of Peru, Lyrall, turpentine and fragrance mix II).

Table 1 Number of positive patch test results to various fragrance allergens in patients with fragrance contact allergy (FCA) and their percentage in patients with allergic contact dermatitis (ACD) and whole study population

Allergen	No. patients with FCA*	% Patients with FCA in all tested patients (n)
FM I	41	3.7 (1105)
MP	32	2.8 (1135)
Lyrall®	8	0.7 (1137)
Turpentine	7	1.5 (469)
FM II	3	1.1 (267)

FM I, fragrance mix I; MP, *Myroxylon pereirae* (balsam of Peru); FM II, fragrance mix II.

*For the total of 91 positive test results in 82 patients.

Table 2 Demographical variables of the patients with and without FCA according to MOAHLFA Index

	All tested patients (%)	ACD but not FCA (%)	FCA (%)
Male	378/1137 (33.2)	128/431 (29.7)	29/82 (35.4)
Occupation	201/939 (21.4)	98/377 (26.0)	16/70 (22.9)
Atopic dermatitis	220/990 (22.2)	76/395 (21.7)	12/73 (16.4)
Hand involvement	788/1095 (72.0)	306/421 (73.1)	54/79 (72.7)
Leg involvement	330/1097 (30.1)	129/423 (30.5)	22/79 (27.2)
Face involvement	370/1095 (33.8)	140/421 (33.3)	28/79 (34.6)
Age >40 years	254/1091 (23.3)	93/417 (22.3)	31/80 (38.8)

ACD, allergic contact dermatitis; FCA, fragrance contact dermatitis.

*Significant difference between FCA and ACD but not FCA ($P = 0.002$).

Table 3 MOAHLFA Index for different fragrance allergens

FM I (%)	MP (%)	Lyrall [®] (%)	Turpentine (%)	FM II (%)	
Male	36.6	37.5	25.0	42.9	33.3
Occupation	21.6	29.2	0.0	14.3	66.7
Atopic dermatitis	16.1	36.4	0.0	16.6	0.0
Hand involvement	66.7	77.4	37.5	57.1	100
Leg involvement	33.3	32.3	12.5	14.3	33.3
Face involvement	38.5	41.9	25.0	42.9	33.3
Age >40 years	46.3	35.5	25.0	42.9	50.0

FM I, fragrance mix I; MP, *Myroxylon pereirae* (balsam of Peru); FM II, fragrance mix II.

two groups. In Table 3, MOAHLFA Index for different fragrance allergens is demonstrated. No statistically significant difference existed. Past or present clinical relevance of positive reactions to fragrance allergens was 82.4%. Among patients with ACD, 380 (88.4%) had positive patch test reactions to one or two allergens and 52 (11.6%) had positive reactions to three or more allergens.

In patients with FCA, 52 (63.4%) had positive patch test results to one or two allergens, while 30 (36.6%) had positive reactions to three or more allergens. Therefore, polysensitization (reaction to more than two allergens) was significantly higher in patients with FCA ($P < 0.0001$). FM I, nickel and MP were the most frequent allergens in these patients. Polysensitization may reflect the fact that FM I and MP have isoeugenol and eugenol in common, while turpentine and MP have terpenes in common, and so they share the same allergens.

Discussion

In this study, we determined the frequency of FCA and its clinical relevance in a sample of Iranian patients with a history of contact dermatitis and/or AD. Among 1137 patch tested patients, 516 (45.4%) had at least one positive patch test reaction, which is compatible with our previous studies.^{16,17} FCA was detected in 7.2% of the patients in the present study, which is less frequent in comparison with the report by Nardelli *et al.*,¹⁸ in which 14.5% of patients had positive reaction to at least one fragrance substance. In the study of Nardelli *et al.*, FM I and FM II recognized 9% and 2.1% of FCA patients respectively.¹⁸ Van Oosten *et al.*,¹⁹ found that 10.3% of their patients had FCA, and the frequency of positive reactions to FM I and FM II were 5.8% and 9.3% respectively. In the present study, FM I and FM II were detected in 7.6% and 2.3% of patients with positive patch test reactions.

Previous reports^{16,20} showed that the hand and the face were the most commonly affected anatomical areas in patients allergic to the fragrances. However, some studies have suggested different patterns of involvement.^{6,21} In the presence of several materials containing fragrances such as household products, cleansers, waxes, polishes and almost all cosmetics, which are used by the hands, it is not unexpected that hands are the most common site of involvement.¹⁸ Our study also supports this idea by showing hand involvement in almost two-third of the FCA patients.

As mentioned previously,⁵ the mean age of the patients with FCA was significantly higher than that of the patients allergic to other substances. In the present study, FCA was significantly more frequent in the female patients older than 40 years. The female predominance in patients with FCA and the increase in fragrance sensitivity with the increase in age have been reported previously.^{11,22,23} This can be explained by the greater exposure of women to various sources of fragrances such as household products, cosmetics or perfumes.⁵

Myroxylon pereirae is an eminent marker for FCA.²⁴ It has been reported that up to 50% of patients susceptible to fragrance allergy might react to MP.²⁵ Similar to the report of Nardelli *et al.*,¹⁸ 2.8% of our patients reacted to MP, which is comparable with our previous report.¹⁶

In a previous study, Lyrall® has been tested, both separately and as a constituent of FM II in British standard series.¹¹ In the present study, 0.7% of the patients were reactive to Lyrall®, which is >0.4% reported in a study conducted in the US.²⁶

The prevalence of AD ranges from 14% to 27% in patients with FCA.⁶ In this study, the prevalence of AD in FCA patients was 16%. Consistent with that reported by Nardelli *et al.*,¹⁸ no significant association between fragrance allergy and AD was found in the present study. While, the proportion of the patients with positive patch test reactions to FM I among those who had AD [19/220 (8.6%)] is comparable with another study [141/1839 (7.7%)],²⁷ in the present study, a statistically significant difference between the proportion of patients with positive patch test reactions to FM I among non-atopics [22/917 (2.4%)] and the proportion observed in atopics [19/220 (8.6%)] was detected ($P < 0.0001$). This difference may be partly explained by a higher proportion (>50%) of atopic cases that were patch tested by Buckley *et al.*²⁷ in their clinic.

Past or present clinical relevance of positive reactions to fragrances was 82.4% in this study, which is compatible with previous reports.^{16,28,29} The findings of this study should be interpreted in the context of some limitations. Patch testing with standard series of allergens finds fewer patients with FCA and cannot distinguish definite fragrance substances. Adding specific fragrance series to the conventional screening series will increase the likelihood of detection of FCA.

In conclusion, although FCA is less commonly observed in Iran in comparison with what has been reported from European countries, its clinical relevance in Iranian population seems to be high. Less frequent observation of FCA in Iran may be explained by either less frequent use of fragrances that are commonly used in Europe and the US in general or using some local fragrance with different ingredients. Hands and face were the most frequent involved areas and women were affected more frequently. Comparing women older than 40 years with younger women, a higher proportion of patients with positive patch test reactions to at least one fragrance allergen was observed. Moreover, positive reactions to more than two allergens were significantly higher in patients with FCA compared with other patients with ACD.

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