

A clinical and patch test study of patients with positive patch test reactions to fragrance mix in China

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The clinical and patch test (PT) features of patients with positive PT reactions to fragrance mix (FM) were studied. 378 consecutive eczema outpatients patch tested with a modified European standard series were analysed. 60 patients (15.9%) reacted to FM. No significant differences could be found between the ages of FM PT-positive and PT-negative patients [median age 40.5 (range from 18 years to 69 years) versus median age 37.5 (range from 5 years to 81 years), rank sum test, $P=0.301$]. FM PT-positive rate in confirmed non-cosmetic allergic contact dermatitis patients was 30.4%, which was similar to that in confirmed cosmetic allergic contact dermatitis patients (30.4% versus 30%, χ^2 test, $\chi^2=0.0010$, $P=0.972$). The FM PT-positive rates were 10.8% in males and 18.2% in females (χ^2 test, $\chi^2=3.3443$, $P=0.067$). 76.7% of the patients with fragrance contact dermatitis were allergic to Chinese traditional medicine, which is much higher than that for cosmetic allergy (76.7% versus 43.3%, χ^2 test, $\chi^2=6.9446$, $P=0.008$). The positive PT rate to colophonium in the patients with positive PT reactions to FM is higher than that in the FM PT-negative patients (18.9% versus 3.0%, χ^2 test, $\chi^2=15.5471$, $P<0.01$). 62.5% of the patients reacted to colophonium were positive to FM. These results show that age has little effect on fragrance contact allergy. Other fragrant products besides cosmetics are also important sources of fragrance contact allergy. Chinese traditional medicine was an important factor in fragrance allergy in China. Patients with positive PT reactions to FM are more likely to react to colophonium.

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Fragrance is widely distributed in cosmetics, toiletries, foods, industrial products and pharmaceutical products (1). Contact allergy to fragrance is common. The positive patch test (PT) rate of fragrance mix (FM) is about 1% in the general population (2) and 5.9%–19.5% in eczema patients (3, 4). Reactions to fragrances include contact dermatitis, contact urticaria and photo-allergic reactions. Fragrance allergy has a serious impact on patients' daily life. Patients allergic to fragrance have not been fully studied in China. The aim of this study is to analyse the clinical and PT features of Chinese patients with positive PT reactions to FM.

Patients and Methods

Diagnostic criteria

Eczema. Eczema was diagnosed and classified according to standard textbooks (5, 6). Specific

types of eczema, such as contact dermatitis, atopic dermatitis (AD), asteatotic eczema, seborrhoeic dermatitis etc., were clinically diagnosed accordingly (5, 6), and the remaining unspecified eczema was diagnosed as unclassified eczema.

Contact dermatitis. Contact dermatitis was diagnosed clinically by the disease history and clinical examination based on a standard textbook (6). Specific types of contact dermatitis, such as allergic contact dermatitis (ACD), irritant contact dermatitis etc., were clinically diagnosed accordingly (6). If similar ACD was elicited at least $\times 2$ by the same contact allergen, ACD was considered clinically confirmed.

Cosmetic allergic contact dermatitis (CACD). CACD was suspected by the disease history and clinical examination based on a standard textbook (6). Only patients with strong evidence supporting the diagnosis were included. If the patients with

suspected CACD could apply the suspected cosmetics again later without any reactions, CACD was excluded. If patients with suspected CACD also fulfil the following criteria, i.e. positive usage test and/or positive PT results with the suspected cosmetics as is or positive repeated open application test, CACD was clinically confirmed.

Cosmetic irritant contact dermatitis. Cosmetic irritant contact dermatitis was diagnosed by the disease history and clinical examination based on the standard textbooks (5, 6).

Atopic dermatitis. AD was diagnosed by using the UK diagnostic criteria (7).

Atopic diathesis. Atopic diathesis was considered when any of the following diseases, i.e. allergic rhinitis, allergic asthma or AD, could be found in the patients' personal or family history.

Study population

All eczema patients patch tested from July 2000 to February 2003 were included. There were 120 males and 258 females, with age range from 5 years to 81 years. All patients were Chinese Han races.

Investigation of suspected environmental agents by questionnaire

The suspected causal agent was investigated by using a questionnaire (8). In the questionnaire, patients' personal data, present illness (patients' description, date of onset, effects of weekends, effects of vacation and previous therapy), contacts existed in work, clothes, toiletries, household and treatment, atopic diathesis as well as medications (taking presently or within last 3 months) were included.

Patch testing

Patch testing was performed with a modified European standard series of allergens and IQ Chamber supplied by Chemotechnique Diagnostics, Malmö, Sweden (Table 1). Allergens were applied to the upper back, and the results were recorded at 2 and 3 days according to ICDRG grading (9).

Statistical analysis

The data were processed by χ^2 test and rank sum test with statistical software spss 11.0.

Results

60 patients (15.9%) were FM PT positive. The final diagnosis of these patients and the results of FM PT

are summarized in Table 2. The highest positive rate (30.4%) of FM PT was found in confirmed non-cosmetic ACD (NCACD) patients. No significant difference could be found in FM PT-positive rates between confirmed CACD and confirmed NCACD patients (χ^2 test, $\chi^2 = 0.001$, $P = 0.972$) (Table 2).

Of the 60 patients, 13 were male and 47 were female. There was no significant difference in FM PT-positive rate between the 2 groups (10.8% versus 18.2%, χ^2 test, $\chi^2 = 3.344$, $P = 0.067$).

No significant differences could be found between the ages of FM PT-positive and FM PT-negative patients [median age 40.5 (range from 18 years to 69 years) versus median age 37.5 (range from 5 years to 81 years), rank sum test, $P = 0.301$].

Atopic diathesis was found in 7 patients in FM PT-positive cases and 40 in FM PT-negative ones. No significant difference was found between the 2 groups (11.7% versus 12.6%, χ^2 test, $\chi^2 = 0.039$, $P = 0.844$).

Relevant FM PT results and causative fragrance could be identified in 30 patients. Among them, 16 patients were allergic to Chinese traditional medicine, 7 patients were allergic to cosmetics and 6 patients were allergic to both Chinese traditional medicine and cosmetics. 1 patient was allergic to both Chinese traditional medicine and fragrant reagent. Altogether, 23 of 30 patients were allergic to Chinese traditional medicine (76.7%), and 13 patients were allergic to cosmetics (43.3%) (There were overlaps between the 2 groups). Patients allergic to Chinese traditional medicine were more common than those allergic to cosmetics (χ^2 test, $\chi^2 = 6.944$, $P = 0.008$). The ingredients labelled in these Chinese traditional medicines included camphor, pure camphor oil, menthol, eucalyptus oil, cloves oil, cassia oil, wintergreen oil, myrcia oil, cinnamon aldehyde, pine oil, eugenol, honeysuckle flower, dandelion, common cnidium fruit, musk, medicinal evodia fruit, propolis, cypress, crazyweed, radix aconiti, kusnezoff monkshood root, divaricate saposchnikovia root and colophonium.

The colophonium PT-positive rate was significantly higher in FM PT-positive patients than that in negative ones (18.9% versus 3.0%, χ^2 test, $\chi^2 = 15.547$, $P < 0.01$, OR = 7.636, 95% confidence interval 2.633–22.139). No significant difference was found in PT-positive rates of other allergens between FM PT-positive and FM PT-negative patients.

Discussion

FM is an indicator for fragrance contact allergy. The 8 components of FM are a-amyl cinnamal, cinnamic alcohol, cinnamal, eugenol, isoeugenol,

Table 1. Standard patch test series of allergens

Allergen
Benzocaine
Black rubber mix [<i>N</i> -isopropyl- <i>N</i> -phenyl-4-phenylenediamine (IPPD), <i>N</i> -cyclohexyl- <i>N</i> -phenyl-4-phenylenediamine (CPPD), <i>N</i> , <i>N</i> -diphenyl-4-phenylenediamine (DPPD), 2-bromo-2-nitropropane-1,3-diol (Bronopol)]
Carba mix (1,3-diphenylguanidine, ZDC and ZBC)
Colophonium
Epoxy resin
Ethylenediamine dihydrochloride
Formaldehyde
Fragrance mix (cinnamic alcohol, cinnamal, hydroxycitronellal, amylcinnamal, geraniol, eugenol, isoeugenol and oakmoss absolute)
Imidazolidinyl urea
Mercapto mix (<i>N</i> -cyclohexylbenzothiazylsulfonamide, mercaptobenzothiazole, dibenzothiazyldisulfide and morpholinylmercaptobenzothiazole)
<i>N</i> -(Cyclohexylthio) phthalimide
Nickel sulfate
4-Phenylenediamine base (PPD)
Parabens (methyl-4-hydroxybenzoate, ethyl-4-hydroxy benzoate, propyl-4-hydroxy benzoate and butyl-4-hydroxy benzoate)
Potassium dichromate
Sesquiterpene lactone mix (alantolactone, dehydrocostus lactone and costunolide)
Thiuram mix (TMTM, TMTD, TETD and PTD)
Thimerosal (Merthiolate)
Tixocortol-21-pivalate

TETD = tetraethylthiuramdisulfide; TMTD = tetramethylthiuramdisulfide; TMTM = tetramethylthiuram-monosulfide; PTD = dipentamethylenethiuramdisulfide; ZBC = zinc dibutyl dithiocarbamate; ZDC = zinc diethyldithiocarbamate.

geraniol, hydroxycitronellal and oak moss absolute. It is reported that FM could detect 70%–80% of fragrance-sensitive patients (10). The FM PT-positive rate was 15.9% in our study. Previous studies showed that the prevalence of FM reactions in PT clinics worldwide was high and often ranked among the top 3 allergens (11). In dermatitis patients evaluated by patch testing, reactions to FM have ranged from 5.9% in Slovenia to 19.5% in Hong Kong (3, 4).

Table 2. Final diagnoses of the patients and the results of patch test to fragrance mix (FM)

Diagnosis	No.	FM positive no. (%)
Confirmed CACD*	20	6 (30)
Suspected CACD	25	5 (20)
Confirmed NCACD*	46	14 (30.4)
Cosmetic irritant contact dermatitis*	8	0
Non-cosmetic irritant contact dermatitis	10	1 (10)
Atopic dermatitis*	7	0
Asteatotic eczema	6	1 (16.7)
Seasonal facial dermatitis*	16	1 (6.3)
Facial dermatitis*	50	8 (16)
Hand eczema	69	9 (13)
Unclassified eczema	126	16 (12.7)

CACD = cosmetic allergic contact dermatitis; NCACD = non-cosmetic allergic contact dermatitis.

*1 patient with atopic dermatitis and 1 patient with seasonal facial dermatitis were also diagnosed as confirmed CACD. 1 patient with facial dermatitis was also diagnosed as cosmetic irritant contact dermatitis. 2 patients with seasonal facial dermatitis were also diagnosed as NCACD.

The average frequency worldwide of positive FM PT is 11.2% (12). Our result is within this range.

The highest positive rate (30.4%) of FM PT was found in NCACD patients. No significant difference could be found in FM PT-positive rates between NCACD and CACD patients. Fragrance exists not only in cosmetics but also in other products, such as toiletries, foods, clothing, industrial products and pharmaceuticals (1). Aromatic products besides cosmetics are also important causes of fragrance contact allergy.

A 17-year study in Britain found a higher FM PT-positive rate in females, and the authors thought that this was maybe because females were exposed to more cosmetics and toiletries (13). Both similar and conflicting results have also been reported (14–16). No significant differences were found in FM PT-positive rates between males and females in our study.

There were no significant differences between the average ages of FM PT-positive and FM PT-negative patients. Age may have little effect on fragrance contact allergy. In our study, atopic diathesis had no effect on FM PT.

In the 30 patients in whom causative fragrance could be identified, patients allergic to Chinese traditional medicine were the most common. Much of Chinese traditional medicine contains fragrance (17). We have reported that the FM and colophonium PT-positive rate in patients with contact dermatitis caused by Chinese traditional medicine was 55.6%, which was much higher than that of the control group (18).

Patients allergic to fragrance should not use fragrant Chinese traditional medicine. Colophonium is commonly used in Chinese medicine topically for the treatment of furuncle, carbuncle, scabies, fungal skin infection and eczema. It is also commonly included in topical pain-relieving Chinese medicine (19).

Colophonium has been used as an indicator for fragrance allergy. Previous studies found that FM and balsam of Peru PT-positive rates were high in colophonium-positive PT patients (20). It is reported that 45.5% colophonium-allergic patients were FM PT positive (20). A possible reason for this apparent cross-allergy is the same fragrant components being in both FM and colophonium (20). Our study also showed that the positive PT rate to colophonium in the patients with positive FM PT is higher than that in negative ones. The FM PT-positive rate in patients with a positive colophonium reaction was 62.5%. Therefore, colophonium-allergic patients should be careful when using fragrance.

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