

臺大醫院 23 年來甲醛貼膚試驗結果分析

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Evaluation of Formaldehyde Allergy in a Patch-test Population

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Formaldehyde (FA) in industrial, cosmetics and house-hold products is of importance for the induction of allergic contact dermatitis. Among 3,403 patients (1,006 men, 2,397 women) consecutive-ly patch tested at National Taiwan University Hospital in the past 23 years, 128 patients (23 men, 105 women) showed a positive reaction to FA. The overall prevalence rate of FA sensitivity was 3.8%. The women patch-tested presented with eczema primarily involving the head and neck region, followed by the hands and arms, whereas the men more frequently presented as a hand dermatitis. Among them 19.5% (25 women) were suspected due to cosmetics; 24 women presented with a facial dermatitis and, 1 presented with a dermatitis on the scalp. 18% (10 women and 13 men) of the studied population diagnosed an occupational dermatitis, 87% (20 patients) had a dermatitis involving at least the hands. Often the sources of FA sensitivity are occult. Further patch testing with preservative series or industrial biocide tray, as well as chemical analysis for the identification of FA using chromotropic acid method in the cosmetics, hair preparations and chemical products in contact with the patients may facilitate in identifying the source of allergen. (Dermatol Sinica 21 : 119-125, 2003)

Key words: Cosmetics, Occupational Exposure, Facial dermatitis, Formaldehyde

甲醛 (formaldehyde) 是常見於工業用品，化妝品及日常用品中的防腐劑，而且是一種強的過敏原，常造成過敏性接觸皮膚炎。我們報告二十三年來在臺大醫院對於甲醛之貼膚試驗的結果。在 3403 位受試者 (1,006 位男性，2,397 位女性) 當中，有 128 位 (23 男，105 女) 對甲醛呈現過敏反應。甲醛過敏的盛行率為 3.8%。甲醛所造成的皮膚炎，在女性病人最常見的位置為頭頸部 (45.5%) 及手部 (24.4%)；在男性病人最常見的位置為手部 (44.1%) 及頭頸部 (30.3%)。甲醛的來源，19.5% (25) 與化妝品有關，只見於女性，其中 96% (24) 以臉部濕疹，1 位病人以頭部濕疹表現。18% (10 女，13 男) 與職業有關，87% (20) 以至少包含手部的濕疹表現。大部分甲醛的來源難以界定。臨床上往往需要其他輔助的方法來協助找尋甲醛的來源。我們並針對甲醛陽性之貼膚試驗結果及臨床上判讀所面臨的問題作整理回顧。(中華皮誌 21 : 119-125, 2003)

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INTRODUCTION

Formaldehyde (FA) is a frequent allergen known worldwide. It is widely used as a preservative in chemical products, cosmetics, shampoos, textiles and etc. The prevalence of FA sensitization varies greatly, as shown by the results of the patch test series in different countries. The majorities of series report sensitivity prevalence between 2.0% and 6.0%, calculating to an overall incidence of 3.9% in 119,505 patients.¹ The prevalence of sensitization is high in the western countries. For the North American Contact Dermatitis Group in 1984-85 it was 8.4%.² In West Germany, Gollhausen *et al*³ reported a FA sensitivity of 3.5% in 11,962 patients. In Japan, the prevalence dropped from 17.9% in 1977 to 2.8% by 1978 and 1.9% in 1979; corresponding to the government regulations in restricting the levels of FA allowed in underclothes.⁴

Our investigation spanned the 23 years 1978-2000. It was undertaken to determine our prevalence of FA sensitivity and to establish whether there is a significant correlation between FA sensitivity and the clinical relevance.

MATERIALS AND METHODS

We retrospectively reviewed the patch test

records of the Contact Dermatitis Clinic of National Taiwan University Hospital between January 1978 and January 2000. A total of 3,403 patients were referred to the special clinic, all patch-tested with the European standard series and selected materials according to individual clinical suspicion. A thorough review of the patients' present illness, family history, medical history and any history of atopy, namely asthma, allergic rhinitis or atopic dermatitis were recorded in detail, in addition to the sites and appearance of lesions. The relation of the skin lesions and occupational exposure was also questioned. Exposure to formaldehyde was considered to be occupational if a definite relationship between the dermatitis and the work could be established, and the anatomic distribution of the dermatitis was consistent with the workplace exposure.⁵

The standard series of allergens were applied to the upper back of the patients using Finn Chambers for 2 days. This standard series contains FA 1% aq. Readings are performed at 48- and 96-hours, or at 72-hours alone. A positive reaction was defined as an erythema (+) with infiltration (++), or erythema with infiltration, papules and vesicles (+++).

We used Chi-Square test with α value of 0.05 to examine the statistically significant rela-

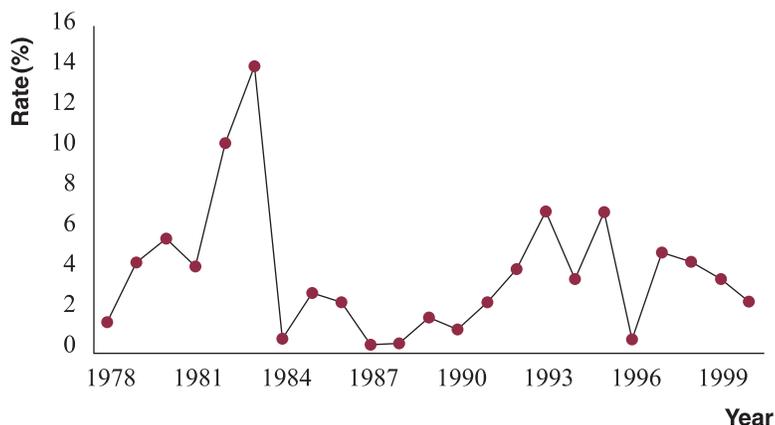


Fig. 1

The rate of positive patch test result to formaldehyde in 1978-2000.

Table I. The basic data of 128 patients with a positive reaction to formaldehyde

	FA positive			
	Men	Women		
Age (mean ± SD, year)	36.4 ± 14.37	31.8 ± 11.99		
Atopy (personal and/or family, %)	17.4	23.9		
Site (%)				
Head and neck	30.3	45.5		
Hands and arms	44.1	24.4		
Trunk	12.1	3.8		
Generalized	6.1	3.8		
Others	9.1	22.7		
Sources of exposure (%)				
Cosmetics	0	23.8*		
Occupation (P<0.001)	56.5	9.5		
(no.)	Construction workers (5)	Electronic (2)		
	Dye-industry (2)	Office work (2)		
	Electronic/engineering (1)	Dentistry (2)		
	Leather (1)	Hairdresser (1)		
	Furs (1)	Metal industry (1)		
	Paper industry (1)	Others (2)		
	Others (2)			
Site in relation to sources of exposure (%)				
Cosmetics (women: N=25)	0	Face	96	
		Scalp	4	
Occupation	Hands	69.2	Hands	70
(men: N=13, 1 missing)	Hands & others	7.7	Hands & others	20
(women: N=10)	Forearm	7.7	Forearm	0
	Face	7.7	Face	10
Total no. of patch tested	1006		2397	
No. of positive reaction	23		105	

*One patient was sensitive to formaldehyde in shampoo

tionship between atopy and allergy to FA; the occupations and the gender difference among the patients with a positive reaction to FA patch test result; the gender difference and the lesion sites of patients with FA sensitivity. All statistical analyses were done by means of SAS (version 6.12).

RESULTS

From 1978-2000, a total of 3,403 patients (1,006 men, 2,397 women) were patch-tested, 128 (23 men, 105 women) were positive to FA, representing 3.8% of the total patch-tested population. The incidence of FA sensitization ranged from 0.4% to 14% during these 23 years (Fig. 1). By using the Wilcoxon rank sum test,

Table II. Concomitant allergens among the 128 patients with formaldehyde sensitivity

Allergen	Men (no.)	Women (no.)
Nickel sulphate	3	21
Ammoniated mercury	3	11
Potassium dichromate	8	6
Cobalt chloride	3	11
Thimerosal	2	10
Fragrance mix	1	8
Skin care cosmetics	0	6
Medicaments	1	2
Para-tertiary butyl phenol	0	3
Total	23	105

a statistically significant decline in the incidence of FA sensitization over the years was shown ($P < 0.001$). Table I. shows the basic data of the total patch-tested population with a positive reaction to FA. There is no association between atopy and allergy to FA. Table I also revealed the relationship between the sites of dermatitis and the gender. In addition, the relationship of the gender and the source of FA sensitization being cosmetics or occupation were also examined.

An analysis of the presence of any concomitant allergen was also performed, with nickel sulphate, potassium dichromate, ammoniated mercury and cobalt chloride being the more frequent concomitant allergens (Table II.). 6 patients, exclusively women, developed concomitant sensitization to skin care cosmetics. 3 patients also showed a positive patch test reaction to para-tertiary-butyl-phenol, which is a phenol-formaldehyde resin. Another 3 patients had an additional positive reaction to medicaments. In overview, the pattern of FA sensitization between men and women was different, especially in the source of exposure, which was statistically significant (Table I.).

Men

Of the 23 men who were sensitized to FA, the sites affected primarily or exclusively were the hands and arms in 44.1%, the head and neck region in 30.3%, and the trunk in 12.1%. In

these 23 men, 13 were believed to be occupational (Table I.). The occupations of these men were construction workers (5), workers in dye industry (2), metal industry (2), others (4). Of the occupational-related cases, 76.9% (10) presented with a dermatitis involving at least the hands.

Women

In the 105 female patients with a positive reaction to FA, the sites affected were the head and neck region in 45.5% of the patients, the hands and arms in 24.4%, and the trunk in 3.8%. 25 patients were sensitized to cosmetic, 10 cases were occupational related. Only one patient of the cosmetic-related group presented as a scalp dermatitis and she showed a positive patch test result to both FA and a hair shampoo. Table I also showed the jobs of the 10 cases being interpreted as occupational sensitization to FA. The occupations involved were electronic manufacture (2), office work (2), dentistry (2), hairdressers (1), metal industry (1), others (2).

DISCUSSION

FA is a ubiquitous chemical which has many important commercial and industrial applications. It is generally found in the environment in one of the three forms: as free FA, as FA donated from a FA-releasing preservatives (FRP), and as FA resins (with varying

potentials in liberating FA). Over the past 20 years, FA has experienced decreasing use in most countries, presumably due to an increased utilization of FA donor preservatives (e.g. imidazolidinyl urea, diazolidinyl urea, and dimethyloldimethylhydantoin), which are generally agreed to be safer. In our series, the incidence of FA sensitization ranged from 0.4% to 14% during these 23 years, except in 1982 and 1983, when the incidence was exceedingly high (>10%). No possible contributing factors could be elicited. Nevertheless, statistical analysis of the trend did suggest a decline in the incidence of the FA sensitization over the years.

The majorities of significant exposures include cosmetic products containing free FA (particularly shampoos and hair-care products); industrial biocides in metalworking fluids (MWF); FA-releasing biocides; FA-resins treated paper products; paper products using inks and dyes which contain FA; textiles, furs and leathers treated with FA; glues and paints containing FA or FA resins encountered by construction workers⁶, as well as direct occupational contact in medical and dental personnel. Domestic exposure occurs from shampoos⁷⁻¹⁰, cosmetics¹, cleaning products¹¹ and fabric softeners.¹²

In this series, among the 23 men with a positive patch test reaction to FA, 56.5% was considered to be occupational. Their principle sources of exposure were most likely glues and paints, MWF, leather, paper product. The primary sites of dermatitis were the hands and arms. The sources of FA exposure in our series were somewhat different from the previous reported cases of occupational sensitization to FA.¹³ Regrettably however, we were unable to perform a product screening test such as chromatographic acid method, for the presence of FA in all the potential chemicals in contact with these patients and thus unable to unravel other potential sources of FA exposure.

The FA in cosmetics appeared to be an important source of sensitization among the 105 women. 25 patients diagnosed as cosmetic-related with their dermatitis on the face. Only

one of these patients developed an allergic contact dermatitis from FA in a hair shampoo. The relative low incidence of FA dermatitis caused by shampoos despite the frequent presence of FA in shampoos may be due to its high dilution and the low contact dermatitis reactivity of the scalp.¹⁴ Unlike men, eczema involving the head and neck region was the principle manifestation in the female population. Since there were more female patients sensitized to cosmetics, this finding was not surprising.

Allergy to FA is rarely suspected clinically or considered prior to patch testing. The incidence of cross-reactivity of FA with other FRPs and the significance of FA allergy on patch testing is less understood. Even if a positive reaction to FA is found, it is often ignored because its source and relevance are unknown. It is generally accepted that sensitization to FA develop mostly from occupational or cosmetic exposure.¹⁵ Non-occupational and non-cosmetic sensitization to FA itself and not due to release from FA resins is rather unusual. However, once sensitization has occurred, threshold responses to FA may vary greatly.¹ Hypersensitivity reaction to as low as 0.02 ppm FA had ever been reported.¹⁶ Most investigators agreed that, topical products containing less than 30 ppm FA may be tolerated by most sensitive patients.¹⁷ The content of FA as a preservative in cosmetic products is regulated in many countries. A survey of FA in shampoos in Denmark revealed a FA content within a range of 10 ppm - 1470 ppm in some hair preparations and skin creams.¹⁸ In Taiwan, the content of free FA allowed in cosmetics is 1000 ppm. However, there seemed to have a lack of FA content labeling in cosmetics or most chemical products in our country. A preliminary high-performance liquid chromatography (HPLC) analysis of the FA content based on random sampling of various shampoo and skin care products on the Taiwan market revealed that the FA content lies within 0.008 ppm-2720 ppm (submitted for publication).

The prognosis of a clinically relevant FA-sensitive patient is generally considered to be

bad because of widespread exposure to FA. The interpretation of a positive patch test reaction to FA remains to be a challenge for dermatologists. Epstein & Maibach¹⁹ interpreted the positive FA reactions as being significant especially when the repeat test also showed positive reactions. Fransway & Schmitz¹⁵ stated that although most reactions to FA in patch tests are only weakly positive, they often have a clinical relevance. We would suggest interpreting the positive reaction as relevant, and would like to emphasize the importance of an additional effort in search of the source of FA. When the relevance of positive patch test reactions to FA was based on information obtained on exposure, a very high rate of current relevance was noted. Chemical analysis for the presence of FA in the products could be performed using various methods, e.g., the chromotropic acid test in which the test substance is added to several drops of H₂SO₄/chromotropic acid solution in a 1:4 mixture ratio, and the amount of FA is proportional to time and to a violet color appearance.²⁰ A color change to violet indicates the presence of free FA 0.25 ppm.²¹ Our government regulated that the free FA content in cosmetics should not exceed 1,000 ppm, whereas the acceptable limit of free FA in textiles is 75 ppm. Thus, the method is sensitive enough for the analysis of the patients' cosmetic products and may serve as a practical screening tool in a clinical setting. Supplier information on the content of preservatives should also be obtained for suspected items. Further patch tests based on preservative series or an industrial biocide tray in the FA-sensitive patients may facilitate in the identification of the source of allergen.²² FA-sensitized patients were advised to use alternatives to those products containing FA or FA releasers.

To conclude, allergic contact dermatitis from FA has posed a diagnostic challenge to most of the clinicians for many reasons: ① The history is often unreliable, ② The clinical presentation is often non-specific, ③ FA is ubiquitous, ④ There is a lack of public awareness towards FA allergy, ⑤ The labeling of FA con-

tent and thus identification of FA on chemical products is not required, ⑥ There is no comprehensive database regarding the FA content in various products. Further patch testing of patients showing an equivocal patch test reaction to FA may be needed to confirm its relevance. Product screening for FA content using a convenient detection method, such as the chromotropic acid method, may be helpful.

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