Acetylator phenotype in Iraqi patients with allergic contact dermatitis

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BACKGROUND: Few studies have been done on acetylator status in ACD. This study determined acetylator status in Iraqi patients with allergic contact dermatitis (ACD) in comparison to a matched control group.

PATIENTS AND METHODS: The study included 35 ACD patients and 67 healthy volunteers. The ACD patients were diagnosed clinically and the diagnosis was confirmed by patch test. A detailed history was taken from the patients. After an overnight fast, each control subject and each patient received a single oral dose of 100 mg of dapsone. A blood sample was collected after 3 hours and plasma was separated for determination of dapsone and monoacetyldapsone by HPLC.

RESULTS: Twenty-six of the 35 ACD patients returned for follow up. The frequency of slow acetylators in healthy individuals was 71.6%, while the frequency of rapid acetylators was 28.4%. The frequency of slow acetylators in ACD patients was 60.0% while the frequency of rapid acetylators was 40.0%. There was no association between the acetylator status, personal history of allergy, patch-test positivity or sites of dermatitis in ACD patients.

CONCLUSION: A rapid acetylator status might predispose to ACD, but does not seem to influence other features of the disease.

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Contact dermatitis is an inflammatory process in the skin caused mainly by external agents. Two types occur: the irritant type, which is provoked by direct cell damage¹ and the allergic type, which is an inflammation of the skin due to an immunological process. The latter is a cell-mediated, delayed hypersensitivity reaction that affects a limited number of individuals after one or a few exposures to an antigenic substance.²

Acetylation is considered a major metabolic pathway in the biotransformation of a number of drugs.³ Acetylation exhibits a genetically controlled bimodal distribution within any given population. Individuals can be phenotyped as either slow or rapid acetylators using a test drug. Slow acetylation is inherited in an autosomal recessive fashion.³ Polymorphic N-acetylation has been linked to variations in drug response, susceptibility to adverse reactions, and an increased incidence of certain spontaneous disorders including cancer.³

Few studies have been done on acetylator status in ACD. However, one study revealed a predominance of rapid acetylators in ACD.⁴ This was confirmed by genotype determination in ACD which revealed a predominance of patients carrying the allele for rapid acetylation.^{4,5} The present paper examined the acetylator phenotype status in Iraqi ACD patients. The Iraqi population, as well as other Middle Eastern populations, are characterized by a predominance of slow acetylators.⁶

Therefore, it is interesting to examine this problem in a predominantly slow acetylator population. In addition, the possible association of the acetylator state on different aspects of the disease was also examined

Patients and Methods

Thirty-five adult patients, 13 males and 22 females, ranging in age from 17 to 43 years (mean $\pm$ SD, 27.4 $\pm$ 0.9) were recruited from the outpatient clinic of the Department of Dermatology of Baghdad Teaching Hospital/Medical City. Specialist dermatologists made an initial diagnosis. A detailed history was taken by questionnaire. Smokers, drinkers and individuals on medication less than one week before the study were excluded.

All patients suspected of having ACD were tested for allergens by a patch test using the closed method technique. If the suspected allergen was a solid (for example, shoe leather, wood, rubber), a portion was cleaned and extracted with alcohol (70%) over a period of 15 minutes.¹ If the suspected allergen was a cosmetic, medicament, or a fume from liquids, a small amount was poured onto a piece of cotton placed in the bottom of a small glass cup. The cup was then inverted and scrapped onto the skin of the upper outer surface of forearm or sometimes to the skin of antecubital fossa and covered with an adhesive bandage.¹ Solids were applied to the skin in the same manner. The bandage was removed after 48 hours to see the reaction. The criteria of the International Contact Dermatitis Research Group (ICDG) was used to categorize the reaction (doubtful reaction, weak reaction [non-vesicular], strong reaction [edematous or vesicular], extreme reaction [markedly bullous or ulcerative], irritant reaction, negative reaction). The control group consisted of 67 healthy adults, 27 males and 40 females. Their ages ranged from 18–48 years (mean 28.3 $\pm$ 2.9 SD). None had a history of serious illness and were normal on physical examination. Excluded from this study were individuals with glucose-6-phosphate dehydrogenase deficiency or allergy to sulfonamides. Approval to conduct this study was granted by the appropriate local ethical committee. The nature of the trial was explained to each subject and consent was obtained.

After an overnight fast, each subject received a single oral 100 mg dose of dapsone (AL-NILE Company for Pharmaceuticals and Chemical Industries, Cairo, Egypt). A blood sample (5 mL) obtained by venipuncture 3 hours after drug intake was added to a 10-mL polyethylene tube containing

50 μ L of heparin (Heparin Leo 5000 IU/mL, Leo Pharmaceutical Products, Denmark). Plasma was separated within one hour after collection by centrifugation at 3000 rpm for 10 minutes. The samples were subsequently stored frozen at -20°C pending analysis. A rapid, simple, one-stage protein precipitation method was used for estimation of plasma dapsone and monoacetyldapsone concentrations by high performance liquid chromatography (HPLC),⁸ as described in a previous study.⁶ Caffeine-containing beverages were not allowed throughout the study period. Individuals were considered slow acetylators if their acetylation ratio was less than 0.30 and rapid acetylators if their acetylation ratio was greater than 0.30. The acetylation ratio was defined as the ratio of monoacetyldapsone to dapsone in the same individual.

Statistical analyses were done using SPSS version.¹⁰ Differences between groups were assessed by the chi-square test. An estimate was considered statistically significant if the *P* value was <0.05 .⁹

Results

Twenty-one of 35 ACD patients (60%) were slow acetylators compared with 48 of 67 control subjects (72%), a statistically significant difference (Table 1) ($P=0.009$). Plasma concentrations of dapsone and monoacetyldapsone in slow and rapid acetylators are shown in Table 2. In the ACD patients, there were no statistically significant differences between slow and rapid acetylators in personal or familial history of allergy (Table 3). Only 26 of 35 suspected ACD patients (10 males and 16 females) returned after 48 hours for follow up of patch test results. There were no statistically significant differences in patch test results between slow and rapid acetylators (Table 4).

In the ACD patients, lesions presented mainly in the limbs but were also found on other sites, such as the mouth and axillae. About three times as many slow acetylator patients had sites of dermatitis situated in the upper part of the body (face, neck and upper limbs) compared with rapid acetylator patients. Other sites of dermatitis (chest, oral region and axillae) were predominantly found in the rapid acetylator patients. However, the differences were not statistically significant.

Discussion

This study demonstrates that there is a predominance of rapid acetylators in ACD patients compared with a control group. The results are in accordance with two previous studies, which showed a predominance

Table 1. Frequency distribution of acetylation phenotype in ACD patients and controls.

	Patients (n=35)	Controls (n=67)	$[\chi^2HI]2$	P value
Slow acetylators				
No. (%)	21 (60.0)	48 (71.6)	8.919	0.009
Female/Male (n)	13/8	31/17		
Age (mean $\pm$ SD)	26.8 $\pm$ 1.18	28.7 $\pm$ 3.9		
Rapid acetylators				
No. (%)	14 (40.0)	19 (28.4)	9.439	0.003
Female/Male	9/5	9/10		
Age (mean $\pm$ SD)	28.2 $\pm$ 0.61	27.1 $\pm$ 2.3		

Slow acetylators defined by acetylation ratio ≤ 0.30 , rapid acetylators by acetylation ratio >0.30 .

Table 2. The mean and range of the concentrations of dapsone (DDS) and monoacetyldapsone (MADDS) in slow and rapid acetylators in ACD patients and controls.

	Slow acetylators		Rapid acetylators	
	Patients (n=21)	Controls (n=19)	Patients (n=14)	Controls (n=48)
DDS	0.91 $\pm$ 0.66 (0.17-2.50)	0.29 $\pm$ 0.24 (0.12-0.61)	1.09 $\pm$ 0.43 (0.75-2.12)	0.57 $\pm$ 0.92 (0.11-2.59)
MADDS	0.28 $\pm$ 0.15 (0.09-0.51)	0.43 $\pm$ 0.37 (0.06-1.03)	0.47 $\pm$ 0.26 (0.38-1.02)	0.78 $\pm$ 0.51 (0.47-1.92)

Data are mean $\pm$ SD and range of plasma concentration

Table 3. Acetylation type and allergy in 35 ACD patients.

	Slow acetylators (n=21)	Rapid acetylators (n=14)	Total (n=35)
Eczema	8 (38.1)	2 (13.3)	10
Hay fever	6 (28.6)	5 (33.3)	11
Asthma	2 (9.5)	0	2
Familial history of allergy	0	0	0
Non-allergic	5 (23.8)	7 (53.3)	12

Data are number and percentage of patients. $P=0.186$, $[\chi^2HI]2=4.81$

Table 4. Acetylation type and patch test results in 26 ACD patients.

	Slow acetylators (n=14)	Rapid acetylators (n=12)	Total (n=26)
Positive patch test	12 (85.7)	11 (91.6)	23 (88.4)
Negative patch test	2 (14.3)	1 (8.4)	3 (11.6)

Data are number and percentage of patients. $P=0.338$, chi-square test.

of ACD patients carrying the allele for rapid acetylation.^{4,5} It confirms that even in a population of predominantly slow acetylators, rapid acetylators are more common among ACD patients.

However, the study failed to show an association between acetylator status and different aspects of allergic disease. No association was found between positive patch test results and acetylator status although it was reported that variations in N-acetylation in human skin could account for variations in positivity in patch testing.¹⁰ In a parallel study of the acetylator status among children with atopic dermatitis, an association was found between the severity and site of the atopic dermatitis and acetylator status.¹¹ However, in this study no such association was found. Thus, although a rapid acetylator status

may predispose to ACD, it does not appear to affect patch test results.

Other studies from the department have shown an association between certain diseases and the acetylator status. Behcet's disease patients had a predominantly slow acetylator status.⁶ Moreover, the severity of the disease was associated with the acetylation ratio. On the other hand, no association was found between systemic lupus erythematosus (SLE) and acetylator status and there was no association between the severity of SLE and acetylator status.¹²

In conclusion, in a population of slow acetylators, it appears that the rapid acetylator phenotype can be considered a genetic trait predisposing to ACD. However, acetylator phenotype does not appear to influence the disease.

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