ACETYLATOR PHENOTYPE IN CHINESE PATIENTS WITH SPONTANEOUS SYSTEMIC LUPUS ERYTHEMATOSUS

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SYNOPSIS

We studied 42 Chinese patients with spontaneous systemic lupus erythematosus but without any renal impairment. Our results, which showed 31% slow acetylators, were no different from previously studied non-SLE Chinese populations. There was also no association between slow acetylation and disease severity.

INTRODUCTION

The rate of metabolism of a number of drugs containing aromatic amino- or hydrazino-groups by N-Acetylation is subject to a genetically determined bimodal distribution in man. In any population, the proportion of slow, as compared to rapid acetylators, varies according to the ethnic composition of that population; being generally higher in Caucasoid than in Mongoloid races (1).

Perry (2,3) first reported the association between slow acetylation and hydrallazine-induced systemic lupus erythematosus (SLE). Other investigators (3) observed a similar association with procainamide-induced SLE and subsequently reports appeared which suggested that the association could be extended to spontaneous SLE (4-7).

We wondered if we might find the same association in Chinese patients with spontaneous SLE. Knowing that the proportion of slow acetylators in Chinese was about half that of whites (3), we would expect, therefore, if slow acetylation was an important aetiological factor in the genesis of SLE, that the prevalence of SLE would be lower in Chinese populations. Instead we were intrigued by Serdula's (8) findings that the age adjusted prevalence rates for SLE was 4-5 times higher in Hawaii Chinese than in Hawaii whites. Furthermore, a recent study from West Malaysia suggested an apparent predisposition of the Chinese to idiopathic SLE (9). It thus appeared to us that the association of slow acetylation to SLE prevalence might not hold in the case of a Chinese population. We were further encouraged by Ishizaki et al (1981) (10) who found that there was no difference in the proportion of slow acetylators in Japanese patients with idiopathic SLE and non SLE controls.

MATERIALS AND METHODS

We studied 42 Chinese patients with spontaneous SLE. Diagnosis was made by criteria suggested by the American Rheumatism Association (11) and by the presence of antinuclear factors, anti-double stranded DNA antibodies and serum complement. None of the patients has been on hydrallazine or procainamide. One patient was, however, on phenytoin at the time of the study. All patients had serum creatinine values of less than 3 mg/100 mls.

Acetylator phenotyping was done by measuring the ratio of the acetylated metabolite (AcSM) to free sulphadimidine (SM) in the 6th hour blood and 5th to 6th hour urine samples (12) following an oral (10 mg/kgm) (13) dose of sulphadimidine. Slow acetylators were defined as those having ratios of less than 0.75 and 2.33 in the blood and urine respectively (14).

RESULTS

The frequency distributions (Fig. 1) of the ratios of AcSM to SM in the blood and urine samples gave clear bimodal distributions with cut off points at 0.75 and 2.33 respectively. The separation was even clearer when both ratios were considered together (Fig. 2). By our method 13/42 (31%) were classified as slow and 29/42 (69%) as fast acetylators. There were no indeterminate values. The proportion of slow acetylators in our Chinese SLE patients was not significantly different ($p > 0.1$) from that in Chinese tuberculosis patients (14) on isoniazid (22%) nor that in normal Chinese subjects (32%) (15).

Fig. 3 shows the proportion of slow acetylators in the SLE patients arbitrarily divided into mild (those with skin and joint disease only) and severe disease (other systemic involvement). There was no significant difference between the two groups.

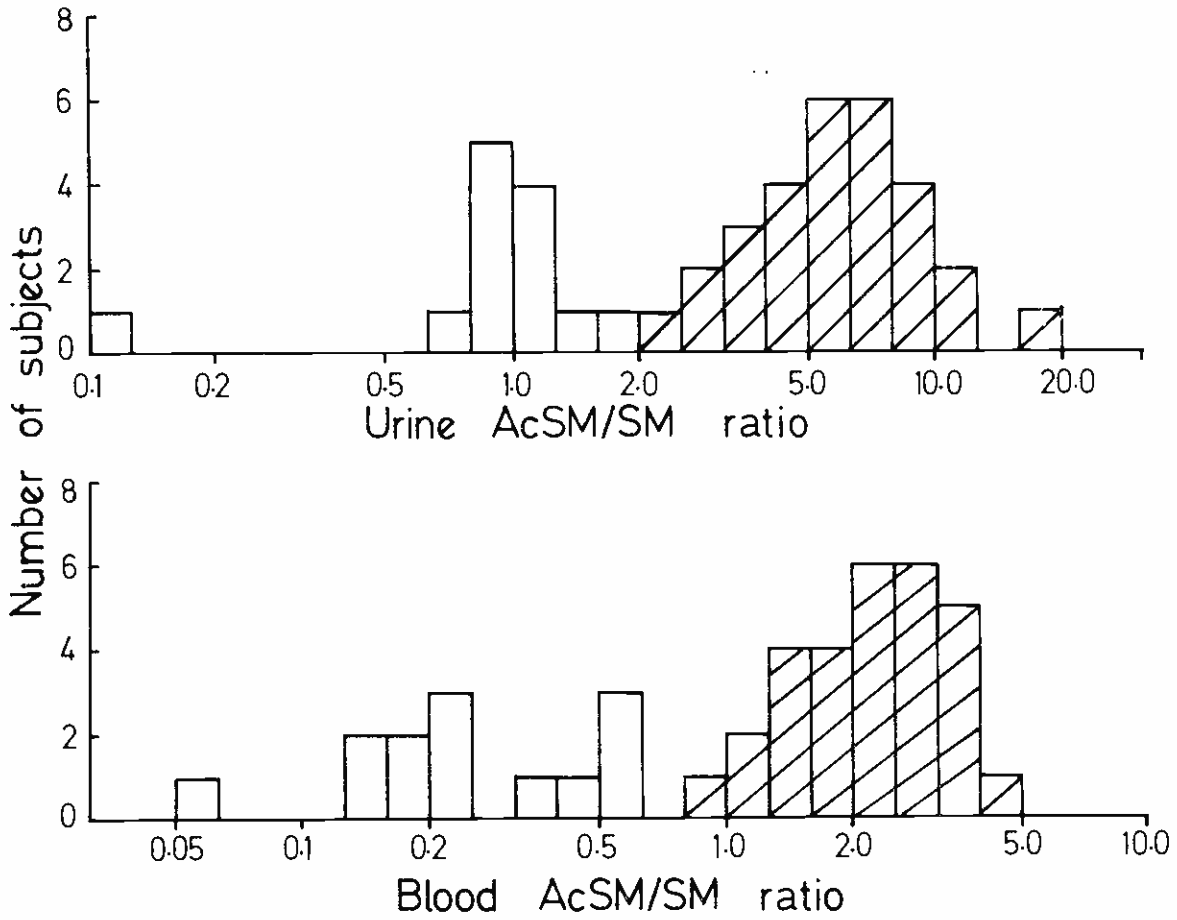

Fig 1: Frequency histogram of AcSM/SM ratios in the 5th-6th hour urine and 6th hour blood samples of 42 Chinese SLE patients. Fast acetylators are shaded.

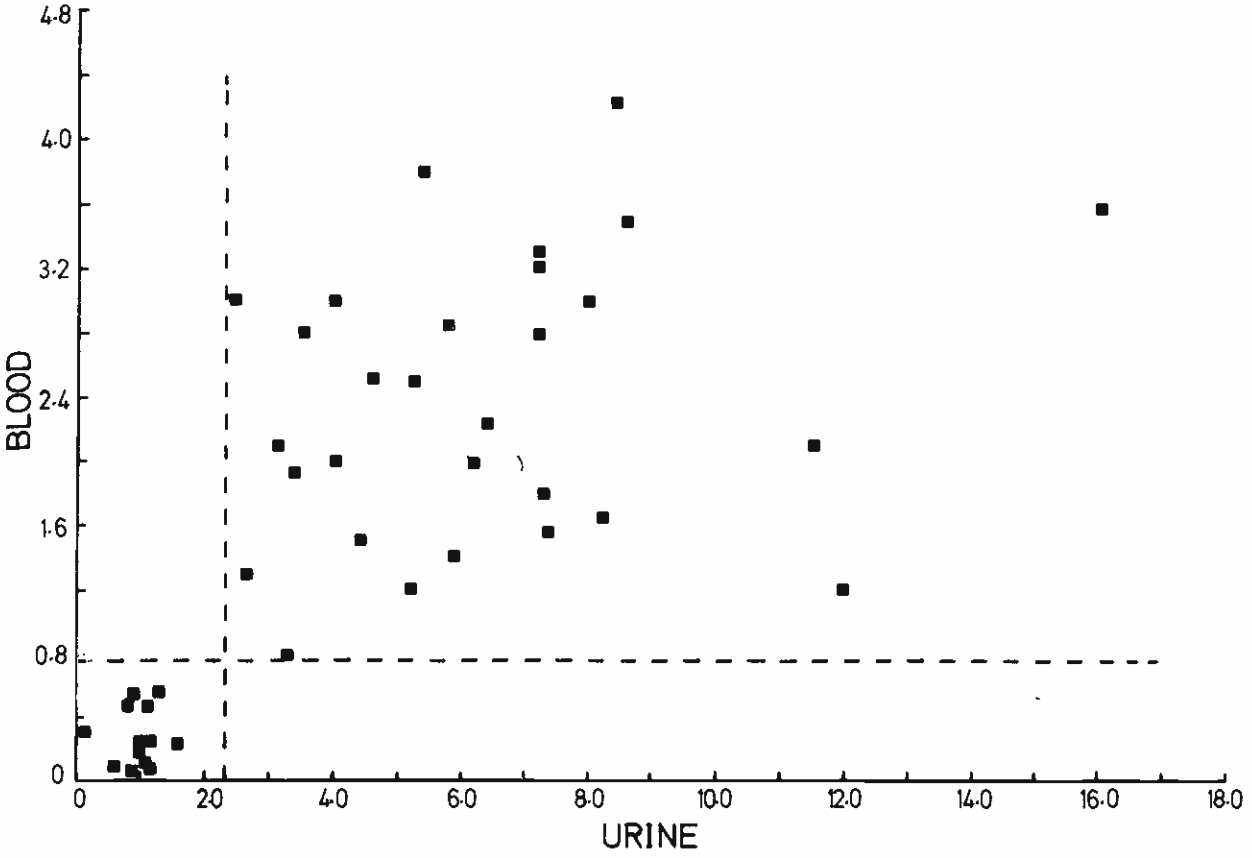

Fig 2: AcSM/SM ratios of urine and blood samples in 42 Chinese SLE patients.

	Mild	Severe
Slow	4 (28.5%)	9 (32.1%)
Fast	10 (71.5%)	19 (67.9%)
Total	14	28

Fig 3: Proportion of slow and fast acetylators according to severity of SLE.

DISCUSSION

Since the initial association of slow acetylation with drug induced SLE by Perry, it has been very tempting to try and similarly link the slow acetylation phenotype to spontaneous SLE. Interest in the area has been sparked off by the observations of Reidenberg and Martin (5) and subsequently others have tried to confirm these findings. It was suggested that the same mechanisms which protect fast acetylators on hydrallazine or procainamide from developing SLE, similarly reduce the risk of fast acetylators developing spontaneous SLE, (4,5) by the acetylation of as yet unidentified chemicals. Recently, however, Vansant, (19) Morris (20) and Lawson (21) have produced evidence against this view. There is therefore, at this time, a controversy over this point.

Looking at the issue in perspective, one can make out a few reasons why reports so far have been conflicting. Firstly, in a disease as heterogenous as SLE and where ethnic considerations are important, identification of the ethnic origins of the population to be studied becomes crucial. This factor becomes doubly important when one realises that the proportion of slow acetylators in any population is similarly dependent on its ethnic makeup (1). Most of the reported studies (5-7, 16-21) have either used a heterogenous population or failed to identify the ethnic origins of its subjects. Identification of the nationality or country of origin of the study is hardly the same as identifying the ethnic composition of the population studied.

Secondly, because studies so far have been with relatively small number, comparisons resulting in statistically significant differences are difficults. In an attempt to overcome this difficulty, Reidenberg et al added the findings of all the reported series together and concluded that "patients with idiopathic SLE have a higher than expected frequency of slow acetylators" (17). However, considering the varied composition of patients in some studies as well as the ethnic differences between studies, one wonders if such a statistical exercise is valid.

An additional factor is the presence of renal impairment in the subjects studied. Renal impairment tends to overestimate the incidence of slow acetylation (16,21,22). Only in the studies of Reidenberg (5) and Lawson (21) were patients with renal impairment excluded from the study.

For the reasons given above we limited our study to Chinese patients with spontaneous SLE without significant azotemia (defined as a serum creatinine of less than 3 mg/100 mls).

Serdula and Rhoads (8) reported from their epidemiological study that the age adjusted prevalance of SLE in Hawaii Chinese was much higher than that in Hawaii whites. In contrast, the prevalence of slow acetylation in Chinese is much lower than that of white populations (1,14,15). Ellard (14) in his study of 386 Chinese tuberculosis patients in Singapore, found 22% to be slow acetylators. Lee (15) found a slightly higher incidence (32%) of slow acetylators in his study of 74 normal Chinese in Singapore. In our study of 42 patients there was a clear separation into 13 (31%) slow and 29 (69%) fast acetylators. These results were not significantly different from those of Ellard and of Lee ($p > 0.1$ Chi square). Our method of acetylator phenotyping was essentially similary to those of Ellard and of Lee.

The same proportions exist when we separate the SLE patients into mild and severe subgroups. We, therefore, have no evidence that the slow acetylator phenotype increases either the risk or severity of spontaneous SLE in Chinese. For, if such an association existed, there should be a much higher proportion of slow acetylators amongst the Chinese. It may be that the slow phenotype is of greater importance in other ethnic groups where insults by environmental chemicals bearing aromatic amino groups may be more prevalent, whereas in Chinese other factors are obviously more important; factors about which we unfortunately, still know very little about.

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