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Drug Acetylation and Expression of Lupus Erythematosus

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Summary. Acetylator phenotype was measured in 58 patients presenting to a skin clinic with discoid lupus erythematosus (DLE) and in 51 normal healthy subjects. Twenty seven of the patients with DLE were found to have evidence of systemic lupus erythematosus (D + SLE). Frequency of slow acetylator phenotype was 58% in all DLE patients, 52% in those with D + SLE and was no different from the 57% in controls. The distribution of acetylator phenotypes within the groups with DLE and those with D + SLE was similar to controls. Severity of DLE was assessed as number of skin lesions and median lesion count was 11.5 in slow acetylators and 10 in fast acetylators but in D + SLE median lesion count was 22 in slow acetylators and 12 in fast acetylators, and there was a significant inverse relationship between lesion count and rate of acetylation; scores for systemic involvement showed no relationship. We conclude that there is no difference in the frequency or distribution of slow acetylator phenotype between normal subjects and patients with DLE with or without SLE but that actual rate of acetylation may determine severity of expression of the disease in slow acetylators.

Key words: lupus erythematosus, acetylation; discoid and systemic lupus, frequency, distribution, severity

Several drugs metabolised by acetylation are associated with the development of systemic lupus erythematosus (SLE) and this is more frequent and happens more quickly in slow acetylators (Strandberg et al. 1976; Woosley et al. 1978). An increased frequency of slow acetylator phenotype has also been reported in idiopathic SLE (Reidenberg and Martin 1974; Reidenberg et al. 1980) although this has been disputed (Morris et al. 1979). The relationship of acetylator phenotype to discoid lupus erythematosus (DLE) is not known, although identical skin changes occur in patients with DLE and SLE, many patients with DLE have features of SLE, and DLE may progress to SLE. We therefore measured acetylator phenotype in patients presenting to skin clinics with DLE and attempted to relate this to severity of the rash and features of SLE.

Method

Fifty-eight patients aged 23–69 years with DLE diagnosed clinically (and with histological confirmation in 53 patients), and 51 normal healthy subjects aged 20–62 years were studied. Extent of skin disease was assessed by counting the number of active and inactive lesions and the extent of systemic involvement was assessed on the basis of the ARA criteria for classifying SLE (Tan et al. 1982). Each criterion (fixed malar rash; discoid rash; photosensitivity; Raynaud's phenomenon; painless oral or nasal ulcers; arthritis; serositis; neurological disorder: fits or psychosis; haemolytic anaemia; leukopenia; lymphopenia; thrombocytopenia; anti ds DNA antibodies; anti nuclear factor) was scored one point to a maximum of 15, a score in excess of 4 being taken as diagnostic of SLE. Severity was also assessed by a second observer in a subgroup of 17 patients by review of their case notes and physical examination and then scoring on a 0–10 analogue scale. These results were then compared with the previously described method. Because renal disease can interfere

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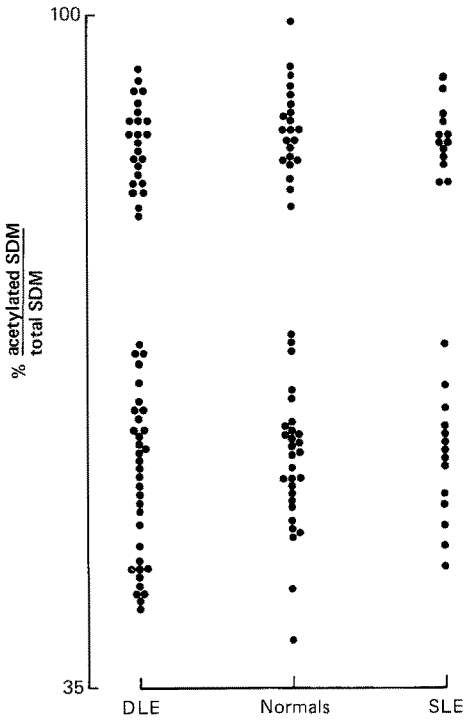

Fig. 1. Percentage of acetylated: total urinary sulphadimidine in 58 patients with DLE, 51 normal subjects, and 27 patients with SLE

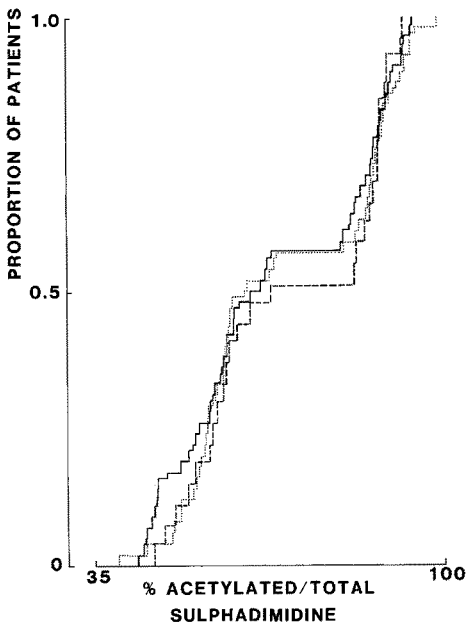

Fig. 2. Cumulative frequency of slow acetylator phenotype in 58 patients with DLE (——), 51 normal subjects (· · · · ·) and 27 patients with SLE (-----)

with the measurement of acetylator phenotype, patients and normal subjects were only included in the study if they had normal serum urea and creatinine concentration. None was taking a drug metabolised by acetylation. Urine was collected for 1 h between 5 and 6 h after 1 g sulphadimidine orally, taken at 8 am after an overnight fast. Urine was stored at −20 °C until acetylated and total sulphadimidine content was measured in duplicate (Evans 1969).

Results

Acetylator phenotype is expressed as % acetylated sulphadimidine/total urinary sulphadimidine. The results show a clear bimodal distribution of acetylator phenotype in both patients with DLE and in normal subjects (Fig. 1), no value lying in the interval 70–80%: values of less than 70% are therefore designated slow acetylator, those greater than 80% are fast acetylator. Of the patients with DLE 34/58 (58%) are slow acetylators and 24/58 (42%) are fast acetylators, which is not different from the 29/51 (57%) and 22/51 (43%) respectively for normals. In the group of 58 patients with DLE there were 27 who fulfilled the diagnostic criteria for SLE. Of these patients 14/27 (52%) were slow acetylators compared with an expected frequency of 57%, and this difference was not

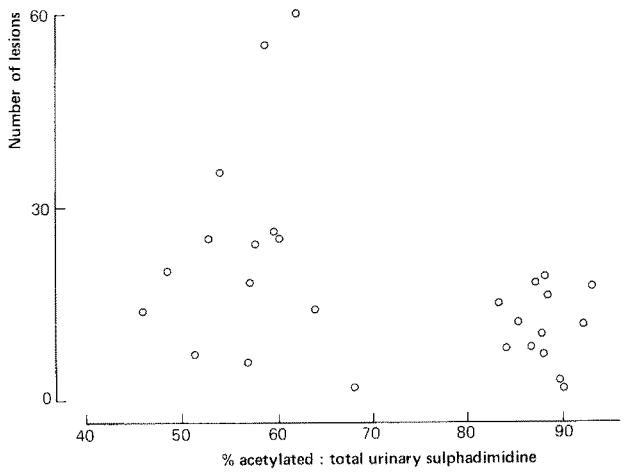

Fig. 3. Number of skin lesions in patients with DLE + SLE compared with rate of acetylation

significant ($\chi^2 = 1.79$, $p > 0.67$). Comparison of cumulative relative frequencies of % acetylated/total urinary sulphadimidine by the Kolmogorov-Smirnov test (Fig. 2) showed no significant difference in the distribution of acetylator phenotype between all 58 DLE patients and normal subjects ($d = 0.12$, $p > 0.20$). Similarly there is no difference in the distribution of SLE acetylator phenotypes from normals ($d = 0.10$, $p > 0.30$). Median number of skin lesions was 11.5 in the 20 slow acetylators with DLE and 10

in the 11 fast acetylators (NS Wilcoxon rank sum test). However in the 14 slow acetylators with D+SLE median number of skin lesions was 22 compared with 12 in the 13 fast acetylators ($p<0.05$ Wilcoxon rank sum test) although these results were not significantly different from those for the 31 patients with DLE alone ($\chi^2=0.82$). Moreover, there was a significant inverse relation between the number of skin lesions in patients with DLE+SLE and the rate of acetylation (Fig. 3, $r_s=-0.67$, $p<0.01$ Spearman rank correlation test) but not for patients with DLE alone ($r_s=-0.166$, $p>0.15$). These differences in disease expression could not be accounted for by difference in duration of disease which was 13.5 years ± 2.1 SEM in the 31 patients with DLE and 14.1 years ± 1.9 SEM in those with D+SLE ($t=0.2$ NS). Comparison of an individual's score for extent of systemic involvement with % acetylated/total urinary sulphadimidine showed that there was no correspondence between these two variables both in all 58 patients with DLE ($r_s=0.01$, Spearman rank correlation test) and in the 27 patients who also had features of SLE ($r_s=0.01$). Comparison between the scores of 17 patients using both methods for assessing severity showed a significant correlation between the two ($r_s=0.70$, $p<.01$).

Discussion

Our results show that there is no difference in frequency of slow acetylator phenotype in patients with DLE, patients with DLE who also have features of SLE and normal subjects. Likewise the distribution curves of the % of acetylated/total sulphadimidine of these three populations are similar. Thus neither the development of DLE nor its transition to SLE is related to acetylator status. However, our findings show that the number of skin lesions is significantly greater in D+SLE patients who are slow acetylators compared with D+SLE fast acetylators, with an overall inverse correlation between number of lesion counts and rates of acetylation, although this relationship was not found in patients with DLE alone. There was no relationship between the extent of systemic involvement and the rate of acetylation either in the whole group or in the subgroup of 27 patients with DLE who also had features of SLE.

The previous findings of an increased frequency of slow acetylators in idiopathic SLE (Godeau et al. 1973; Reidenberg and Martin 1974) have been confirmed (Johannson et al. 1976; Foad et al. 1977; Fishbein and Alarcon-Segovia 1979; Lawson et al. 1979) and refuted (Vansant et al. 1978; Morris et al. 1979). Overall however, published studies (Reidenberg et al. 1980) show a prevalence of slow acetylator phenotype in SLE of 150/227 patients (66%) compared with the expected number of 122/227 (54%; $p<0.001$). Our present findings do not confirm these observations. It seems likely that the small numbers of patients and controls in these previous studies including one of our own (Marsden et al. 1983) may explain the differences in the apparent prevalence of slow acetylator phenotype since the numbers in the present study are large enough to confirm a difference of the order suggested by previous findings. Moreover, many of these studies use historical controls some of whom had other diseases (Reidenberg et al. 1980) whereas our control group was studied at the same time as the patients and the numbers of controls and patients were similar. Also several different methods for determining acetylator phenotype have been used e.g. isoniazid (Fishbein and Alarcon-Segovia 1979) dapsone (Vansant et al. 1978), sometimes within a single study (Reidenberg et al. 1980). Furthermore, national differences in prevalence of slow acetylator phenotype (Uetrecht and Woosley 1981) make comparisons between these studies difficult and simple summations of different findings unreliable. Impaired renal function decreases the ratio of acetylated/total sulphadimidine in the urine and hence causes a spurious predominance of slow acetylator phenotype (Molin et al. 1977); in the present study patients with abnormal renal function were excluded. We conclude that these factors, particularly small sample size, may explain the previous contradictory findings, and that the prevalence of slow and fast acetylator phenotype is no different from normal in patients with LE.

Although acetylator phenotype appears to have little or no effect on the development of LE it is possible that rate of acetylation might affect expression of LE, just as procainamide will induce SLE more rapidly in slow acetylators (Woosley et al. 1978). Although we found no evidence of a relationship between acetylator phenotype and severity of systemic disease graded by a scoring system, we have reservations about this method of quantifying severity, because it summates independent variables which are arbitrarily graded as equal. When severity of an individual feature was measured, as we did for extent of skin involvement in patients with DLE and evidence of SLE, then an inverse relationship was found between severity and absolute rate of acetylation. The numbers of patients studied were small and the finding requires confirmation and application to other features of the disease; nevertheless, the inverse correlation between extent of rash and rate of acetylation suggests that acetylator status may indeed modify disease expression. This raises the general

principle of use of actual rate of acetylation rather than the current exclusive analysis by fast and slow phenotype: in situations where the acetylator gene is unrelated to the gene for the disease under study, absolute rate of acetylation may be more relevant to its expression.

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