



Acetylation genotype and phenotype in patients with systemic lupus erythematosus

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Abstract:

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease affecting various tissues and organs. In the studies on SLE etiopathogenesis, a potential role of genetically determined impairment of xenobiotic metabolism has been emphasized. *N*-acetyltransferase 2 enzyme (NAT2) exhibits gene polymorphism and the acetylation rate with NAT2 involvement varies from person to person.

The study on acetylation phenotype was carried out using isonicotinic acid hydrazide (isoniazid) as a model drug, while *NAT2* alleles were determined by the polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) assays. Among patients with SLE, *NAT2**4/*NAT2**6 and *NAT2**5/*NAT2**5 genotypes occurred most frequently, while *NAT2**4/*NAT2**6 and *NAT2**5/*NAT2**6 prevailed in the control group. The concordance of 96.8% was achieved between acetylation phenotype and *NAT2* genotype in the group of SLE patients studied.

Conclusion: Acetylation polymorphism appears not to be an important risk factor in SLE.

Key words:

N-acetyltransferase 2, polymorphism, systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by enhanced production of autoantibodies against various antigens. Contemporary medicine is capable of soothing patients' ailments only to a limited extent and apparently there are no methods of SLE treatment due to insufficient knowledge on its etiopathogenesis. However, besides evidence favoring envi-

ronmental agents and factors modulating the immune system, genetic predisposition has been reported to play a crucial role in SLE etiology [6, 31, 36, 37].

Some researchers suggest that acetylation rate, genetic predisposition and involvement of the immune system may be the SLE determinants [12, 17, 19, 29].

N-acetyltransferase 2 (NAT2) exhibiting diverse metabolic activity is responsible for *N*-acetylation of drugs and carcinogens bearing aromatic amine, sul-

fonamide and aliphatic amine structures which are comprised in such commonly used drugs as caffeine, dihydralazine, isonicotinic acid hydrazide (isoniazid), sulfamethazine, clonazepam, nitrazepam, procainamide, dapsone, acebutolol and others [11].

Acetylation polymorphism with NAT2 involvement is caused by point mutations responsible for various phenotypic effects. Fast acetylation is coded by wild-type *NAT2*4* allele, while impaired acetylation is caused by several mutated alleles (e.g., *NAT2*5*, *NAT2*6*, *NAT2*7*) [4, 5]. *NAT2* gene mutations were induced by the replacement of a wild-type allele nucleotide sequence at positions 192, 282, 341, 434, 481, 590, 813, 845, 857 [2, 7]. In the Caucasian population the most frequent polymorphism occurs at positions 341 (TC; Ile114–Thr), 481 (CT; Leu161), 803 (AG; Lys268–Arg), 590 (GA; Arg197–Gln), 857 (GA; Gly286–Glu) [21]. Identification of mutations at positions 481, 590, 803, 857 will be sufficient to determine mutated alleles as the remaining mutations accompany the above-mentioned alleles in 98% [7].

The aim of the study was to estimate whether the *NAT2* genotype may be considered a predisposing factor in SLE induction, to assess the frequency of *NAT2* gene polymorphism in patients with SLE and to determine correlation between acetylation phenotype and *NAT2* genotype in the group of SLE patients.

Materials and Methods

The study was carried out in 63 patients who met at least four SLE classification criteria according to the American Rheumatism Association (ARA). The group of SLE patients comprised 60 women and 3 men aged 15–76 years (mean 39.5 ± 13.3). The patients were hospitalized at the Medical University of Łódź, Dermatology Department and Nephrology Department, Poland, all subjects coming from Poland. The *NAT2* phenotype was estimated in a control group consisting of 100 subjects (52 women, 48 men) aged 20–89 years (mean age 54.5 ± 18.8), whereas, the *NAT2* genotype was determined in another control group of 100 volunteers (59 women, 41 men) aged 18–90 years (mean age 52.4 ± 18.7). All controls had no acute or chronic autoimmune disease.

During examinations, the patients and volunteers did not take any drugs that undergo acetylation. The

study was approved by the local ethics committee on human research, and informed consent was obtained from all patients.

At the beginning of the study, all subjects underwent and their detailed history was taken physical examination. With regard to the disease, each patient was examined for joint, muscle and organ involvement. Laboratory tests, such as erythrocyte sedimentation reaction, blood cell count, urine test and protein fraction pattern, were performed. The antinuclear antibody was detected using indirect immunofluorescence on Hep-2 cells, and by means of double immunodiffusion with calf thymus extract. The duration of SLE was from 1 year to 10 years (mean 4.7 years).

The investigation of acetylation phenotype was performed according to the Eidus method using isoniazid as a model drug [10]. Isoniazid was administered orally at a single dose of 10 mg/kg of body weight; urine samples were collected 6–8 h after the drug administration. Acetylisoniazid concentration was determined before and after acetylation by spectrophotometric analysis at 550 nm wavelength. To determine acetylation phenotype the acetylation index, i.e. the ratio of extracted acetylisoniazid to a total amount of the extracted isoniazid in urine was calculated.

The inactivation index (proportion of acetylisoniazid and free isoniazid expressed as milligrams per liter) was calculated according to the following formula:

$$I_i = A/(B-A) \times 0.761$$

Where, I_i – inactivation index, acetylation index; A – optical density of aliquot containing only acetylisoniazid; B – optical density of an aliquot containing acetylisoniazid and isoniazid artificially converted to acetylisoniazid; multiplication by 0.761 compensates for the molecular weight of acetylisoniazid and free isoniazid.

The value below 3 was considered to characterize a slow acetylator phenotype and that above 5 – fast acetylator phenotype, while the value between 3 and 5 – intermediate acetylator phenotype.

NAT2 alleles were identified by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assays [34].

If at least 1 wild-type *NAT2*4* allele has been identified in the genotype of the examined subject, he/she is considered to be a fast acetylator (FA), whereas, if both alleles are mutated and the *NAT2* metabolic activity decreases, then an individual is a slow acetylator (SA) [14]. Mutations at positions 481 and 801 can

Tab 1. Distribution of acetylation phenotype in patients suffering from systemic lupus erythematosus and in control subjects

Acetylation phenotype	Patients with SLE (n = 63)		Control subjects (n = 100)		χ^2	P
	No.	%	No.	%		
Slow Acetylation index (0–3)	35	55.6	48	48	0.8829	0.3474
		C.I. 0.43–0.68		C.I. 0.38–0.58		
Fast Acetylation index (>5)	16	25.4	34	34	1.6597	0.1979
		C.I. 0.15–0.36		C.I. 0.25–0.43		
Intermediate Acetylation index (3–5)	12	19	18	18	0.1108	0.7392
		C.I. 0.9–0.29		C.I. 0.10–0.26		

P < 0.05, 95% confidence interval (C.I.), test χ^2 comparison between 2 groups of patients with SLE and control subjects

Tab 2. Distribution of *NAT2* genotypes in patients with SLE and control subjects

Classes of <i>NAT2</i>	Patients with SLE (n = 63)		Control subjects (n = 100)		P
	No.	%	No.	%	
Homozygous fast acetylators					
<i>NAT2*4/NAT2*4</i>	7	11.1	4	4	0.1494
Heterozygous fast acetylators					
<i>NAT2*4/NAT2*5</i>	9	14.3	12	12	0.6724
<i>NAT2*4/NAT2*6</i>	14	22.2	30	30	0.2761
<i>NAT2*4/NAT2*7</i>	–	–	1	1	0.8151
Total	23	36.5	43	43	0.4110
Homozygous slow acetylators					
<i>NAT2*5/NAT2*5</i>	14	22.2	14	14	0.1754
<i>NAT2*5/NAT2*6</i>	12	19.1	25	25	0.3770
<i>NAT2*5/NAT2*7</i>	1	1.6	1	1	0.6900
<i>NAT2*6/NAT2*6</i>	5	7.9	12	12	0.5732
<i>NAT2*6/NAT2*7</i>	–	–	1	1	0.8151
<i>NAT2*7/NAT2*7</i>	1	1.6	–	–	0.8151
Total	33	52.4	53	53	0.9386

p < 0.05

be identified using restriction enzymes Kpn1 (481 C → T – loss of etching locus in the mutated allele) and Dde1 (803 A → G – occurrence of additional restriction method in the mutated allele). G → A transition at 590 is detectable by using restrictase Taq1 (loss of etching locus), while G → A transition at position 857 was recognized by the restriction enzyme BamH1 (loss of restriction locus in the mutated allele).

The frequency distribution of *NAT2* genotypes and acetylation phenotypes in SLE patients was compared with healthy subjects and analyzed statistically using the χ^2 test alone and with the Yates modification for small groups.

In order to assess frequency of *NAT2* genotypes, *NAT2* gene pointed mutations, wild and mutated alleles in the examined population, 95% confidence intervals were established (C.I.)

Tab. 3. Frequency of point mutations in the NAT2 gene in patients with SLE (n = 63) and in control subjects (n = 100)

Position	Mutation frequency				χ^2	P
	Patients with SLE		Control subjects			
	n1	%	n2	%		
481 (C → T)	29	23 C.I. 0.16–0.30	42	21 C.I. 0.15–0.27	0.18	0.6676
590 (G → A)	31	24.6 C.I. 0.17–0.32	68	34 C.I. 0.27–0.41	3.23	0.0724
803 (AG)	29	23 C.I. 0.16–0.30	48	24 C.I. 0.18–0.30	0.04	0.8386
857 (G → A)	2	1.6 C.I. 0.0–0.04	3	1.5 C.I. 0.0–0.03	0.00	0.9502

n1 frequency referring to 126 alleles, n2 frequency referring to 200 alleles, test χ^2 comparison between 2 group patients with SLE and control subjects

Results

The frequency distribution of acetylation phenotypes determining slow, intermediate and fast acetylation in the patients suffering from systemic lupus erythematosus (SLE) and in controls is shown in Table 1.

In the whole group of SLE patients, 35 subjects (55.6%) had the phenotype of slow, 12 (19%) intermediate and 16 (25.4%) fast acetylation, whereas in

the control population 48 subjects (48%) were slow, 18 (18%) intermediate and 34 (34%) fast acetylators. The subjects with the intermediate acetylation phenotype possessed 1 *NAT2*4* allele in their genotype, which, in compliance with the generally accepted rules, allowed us to classify them as fast acetylators. As it is seen in Table 1, a slight preponderance of slow acetylators in the SLE patients over healthy volunteers was observed, however, the differences were not statistically significant ($p = 0.3474$).

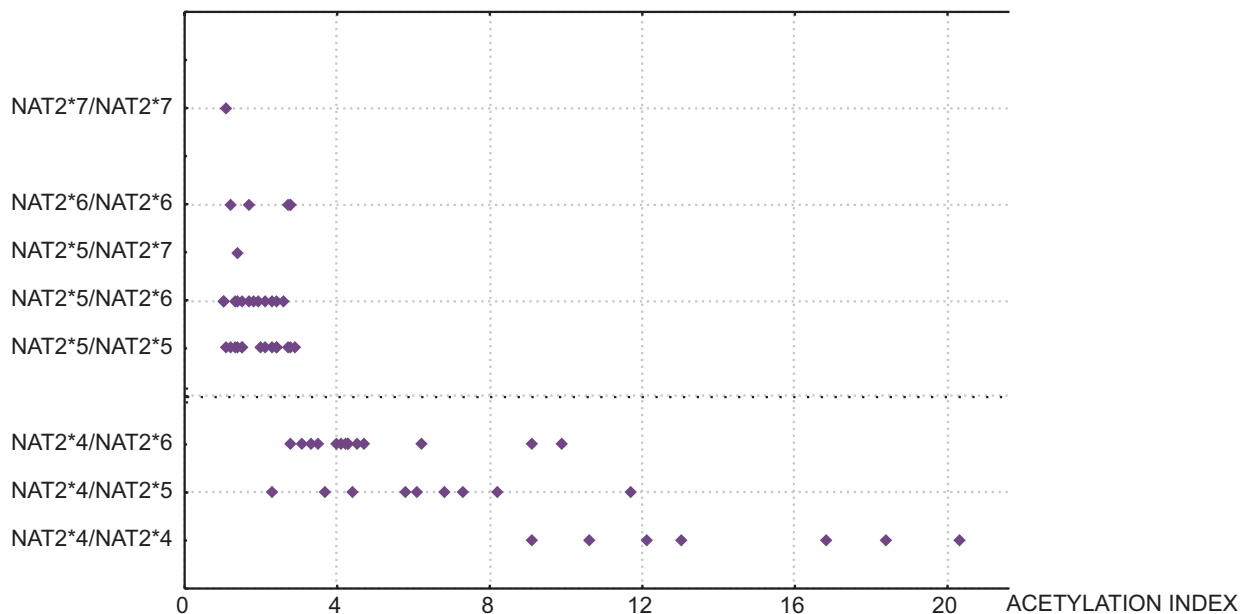


Fig. 1. Relations between NAT2 genotype and phenotype in patients with SLE

The frequency distribution of slow and fast acetylator genotypes in the SLE patients and controls is presented in Table 2. Genotypes *NAT2*4/NAT2*6* and *NAT2*5/NAT2*5* phenotypes were found the most frequently in SLE patients, while *NAT2*4/NAT2*6* and *NAT2*5/NAT2*6* predominated in the control group.

The frequency of the tested point mutations in the *NAT2* gene among SLE patients and controls is demonstrated in Table 3. Of all point mutations in the gene coding for *N*-acetyltransferase enzyme, the mutation at the position 590 (change of guanine into adenine) appeared most often in SLE patients and controls. The percentage of mutations at the position 590 in SLE patients constituted 24.6% of 126 alleles tested, whereas in the control group – 34% of 200 alleles tested. In both groups the rarest mutation was at position 857 (change of guanine into adenine). In SLE patients the percentage of mutations at 857 constituted 1.6% and in healthy volunteers – 1.5%.

NAT2 genotypes were compared with acetylation phenotypes in 63 patients with SLE. Figure 1 depicts phenotypic activity of particular *NAT2* alleles. There was a good correlation between *NAT2* genotype and acetylation phenotype (96.8%).

Discussion

Numerous authors have suggested that acetylation rate and genetic traits associated with the immune system may be considered to be the SLE indicators [12, 17, 19, 29]. In the present study, we have tried to find out whether there is any relationship between genetically determined *NAT2* activity, i.e. one of the isoenzymes of phase II metabolism, and SLE incidence. The assessment of genetically determined polymorphism of *N*-acetyltransferase 2 (*NAT2*) in patients suffering from systemic lupus erythematosus was carried out and the results were compared with the data obtained in the control group.

Polymorphism of xenobiotic acetylation plays an essential role in etiopathogenesis of various diseases including those induced by environmental factors. Greater prevalence of liver and larynx neoplasms has been found in slow acetylators [1, 9, 15]. However, there are also some reports showing that slow acetylators are at smaller risk of colorectal cancer, while fast acetylators are more prone to this disease, especially

when they eat much heat-processed meat (long frying or baking) [13, 16]. In patients with stomach cancer, more frequent occurrence of *NAT2*4* allele associated with high concentration of *N*-acetyltransferase has been observed recently. Moreover, patients with lung cancer more frequently appear to be homozygous for *NAT2*4* [3, 18].

Furthermore, a higher risk of breast cancer has been reported in women with fast acetylation phenotype [27, 32]. Patients with hemopoietic neoplasms (Hodgkin's disease, lymphomas and acute leukemia) have been found to be more frequently fast acetylators [40]. The investigations of patients with neurological and psychiatric disorders demonstrated an association between fast acetylation genotype and multiple sclerosis, while epilepsy and Parkinson's disease were more often evident in slow acetylators [22, 23, 24].

The first reports of a relationship between acetylation phenotype and SLE were published in the 1970s. The studies conducted by many authors on American, Scandinavian, Mexican and Polish populations revealed preponderance of slow acetylation phenotype in SLE patients over controls. The results of these reports were predominantly based on small samples (14–32 SLE patients) [12, 17, 19, 25, 28, 29, 38]. However, in our study carried out on 63 SLE patients, no statistically significant difference in the frequency of slow acetylation phenotype in SLE patients (55.6%) was observed, as compared to the control group (48%) ($p = 0.3474$).

The publications dealing with frequency of acetylation phenotype in patients with systemic lupus erythematosus have not provided an unequivocal evidence whether a slow acetylation phenotype predisposes a subject to appearance of disease signs and symptoms. Therefore, we have incorporated determinations of *NAT2* genotype into our study.

In our study *NAT2*5/NAT2*5* (42.4%) was the most frequent genotype coding for slow acetylation in SLE patients compared with *NAT2*5/NAT2*6* (47.2%) in controls, while *NAT2*4/NAT2*6* dominated among fast acetylation – coding genotypes in SLE patients and controls, constituting 46.7% and 63.8%, respectively. The differences were not statistically significant ($p = 0.1378$). Furthermore, the frequency of homozygous subjects with fast D/D ($p = 0.0780$) and slow Mut/Mut ($p = 0.9386$) acetylation in comparison with heterozygous fast acetylators D/Mut ($p = 0.4110$) in both groups did not differ significantly, either. The considerable preponderance of mutated alleles over wild

forms ($p < 0.0001$) was found in SLE patients and controls. In SLE patients, mutated alleles constituted 70.6% of all alleles studied, whereas in the control group – 74.5%.

Our study did not reveal any differences in the frequency of point mutations in both groups. Mutation at position 590 was most often found in the NAT2-coding gene among SLE patients and healthy subjects, constituting 24.6% and 34%, respectively ($p = 0.0724$).

The results of the study indicate that acetylation polymorphism is not a risk factor for SLE. Probability of SLE is similar in both slow and fast acetylators. However, determination of NAT2 genotype or phenotype in patients with systemic lupus erythematosus is of clinical importance and thus phenotyping performed prior to chemotherapy seems to be beneficial for them. SLE usually involves many organs and sometimes application of drugs metabolized by acetylation is required. The results of such therapy are less satisfactory in fast acetylators as compared to slow acetylators. Relapses are more often observed and remissions are rarely achieved. In slow acetylators the efficacy of therapy is higher but the therapy appears to be more frequently accompanied by noxious side effects appearing after administration of standard doses of drugs [26].

It has been reported that patients with a slow acetylation phenotype more often develop systemic lupus erythematosus and produce antinuclear antigens following the exposure to hydralazine and procainamide [33, 35]. They are at a higher risk of SLE and peripheral neuropathy after administration of isoniazide [26], and are more prone to hematological complications (methemoglobinemia, anemia), especially in the presence of a coexisting deficiency in glucose-6-phosphate dehydrogenase, and allergic reactions after the use of dapsone [39].

N-acetyltransferase 2 also participates in sulfonamide metabolism [30]. Outcomes of some studies prove that over 90% of subjects hypersensitive to sulfonamides are characterized by a slow acetylation phenotype [8, 20, 41].

More frequent dysrhythmia, thrombocytopenia and dyspepsia have been reported after using amrinone in the treatment of acute circulatory failure in individuals with slow acetylation phenotype. Also, exposure to clonazepam and nitrazepam in slow acetylators can result in more frequent dizziness, somnolence and malaise in comparison to patients with fast acetylation status [4].

In the present study, no predominance of slow acetylator genotype among our SLE patients has been identified. However, it should be emphasized that slow acetylators constitute a considerable percentage in the Caucasian population (50%) and, therefore, the studies on acetylation polymorphism and prevention of adverse reactions seem to be fully justified. Investigation of acetylation genotype or phenotype allows us to individualize pharmacotherapy. The knowledge of acetylation polymorphism in the course of SLE may be helpful in choosing more efficient and safer therapy, particularly in case of a disease involving various organs and treated with drugs belonging to diverse therapeutic groups.

Conclusions

1. Acetylation polymorphism is not an important risk factor in SLE.
2. The frequency of the mutations in NAT2 gene in SLE is similar to the control group.
3. Both methods are equally useful in estimation of N-acetyltransferase activity.

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