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## Systemic lupus erythaematosus in a multiethnic US cohort (LUMINA) LIII: disease expression and outcome in acute onset lupus

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### Abstract

**Objective**—To determine the features associated with acute onset systemic lupus erythaematosus (SLE).

**Methods**—A total of 631 SLE patients from LUMINA (for “lupus in minority populations: nature vs nurture”), a multiethnic (Hispanics, African–Americans and Caucasians) cohort, were studied. Acute disease onset was defined as the accrual of  $\geq 4$  American College of Rheumatology (ACR) criteria for the classification of SLE in  $\leq 4$  weeks. Socioeconomic demographic features, clinical manifestations, disease activity, damage accrual, mortality, autoantibodies. *HLA* class II and *FCGR* alleles, behavioural/psychological variables were compared between patients with acute and insidious disease onset by univariable ( $\chi^2$  and Student t test) and multivariable (stepwise logistic regression) analyses.

**Results**—A total of 94 (15%) patients had acute disease onset. In the multivariable analysis, patients with acute onset lupus had more renal involvement (odds ratio (OR) = 1.845, 95% CI 1.076–3.162;  $p = 0.026$ ) and higher disease activity (OR = 1.057, 95% CI 1.005–1.112;  $p = 0.030$ ). By contrast, age (OR = 0.976, 95% CI 0.956–0.997;  $p = 0.025$ ), education (OR = 0.901, 95% CI 0.827–0.983,  $p = 0.019$ ), health insurance (OR = 0.423, 95% CI 0.249–0.718;  $p = 0.001$ ) and skin involvement (OR = 0.346, 95% CI 0.142–0.843;  $p = 0.019$ ) were negatively associated with acute onset lupus. No differences were found regarding the serological, genetic and behavioural/psychological features; this was also the case for damage accrual and mortality.

**Conclusions**—Patients with acute onset lupus seem to be younger, have a lower socio-economic status and display more severe disease in terms of clinical manifestations and disease activity. However, intermediate (damage) and long-term (mortality) outcomes appear not to be influenced by the type of disease onset in SLE.

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As a chronic disease, systemic lupus erythaematosus (SLE) results in higher morbidity and mortality rates when compared to the general population.<sup>1–5</sup> During the past few decades, the

factors influencing the expression and outcome of this disease have been examined by different investigators. Several factors ranging from genetics<sup>6–9</sup> to the socioeconomic demographic and background of the patient<sup>10 11</sup> are now commonly recognised features influencing the disease course and its long-term outcome. However, not all patients display a disease pattern according to these factors, which suggests that other variables yet to be elucidated are also important disease modulators.

Acute onset lupus is generally thought to constitute a more severe subset of SLE; however, no study has addressed this in a systematic manner to date. We have previously determined that time to the accrual of the American College of Rheumatology (ACR) criteria for the classification of SLE is variable, ranging from a few months to several years, and that ethnicity, age, marital status and genetic variables may influence the time elapsed between the first and the fourth criteria required for classifying a patient as having SLE.<sup>12</sup> Hispanic ethnicity (from Texas) and the presence of *HLA-DRB1\*0301* were found to be predictors of a shorter time to criteria accrual, whereas older age and being married/living together were associated with a longer time. However, in that study, the impact of accrual time in the course of the disease and its outcome were not examined.

We have now examined the factors associated with acute disease onset and also addressed the question of whether type of disease onset is associated with a different disease pattern. We hypothesised that type of disease onset has a modifying effect in the clinical expression of SLE; ie, those patients with acute disease onset will have more severe clinical manifestations, a higher degree of disease activity, accrue more damage over time and display higher mortality rates when compared to those with insidious disease onset.

## PATIENTS AND METHODS

As previously described,<sup>13 14</sup> LUMINA (for “lupus in minorities: nature vs nurture”) is a longitudinal study of outcome in lupus established in 1994. To be eligible for enrolment (T0), patients must meet the American College of Rheumatology (ACR) criteria for the classification of SLE,<sup>15 16</sup> have disease duration  $\leq 5$  years, be  $\geq 16$  years of age, be of a defined ethnicity (self-stated and the same for the four grandparents: African–American, Hispanic (from Texas and from the island of Puerto Rico) and Caucasian), and live in the geographical recruitment area of the participating centres (University of Alabama at Birmingham (UAB), The University of Texas Health Science Center at Houston (UTH) and The University of Puerto Rico Medical Sciences Campus (UPR)). Over 90% of patients eligible for the study agreed to participate. The Institutional Review Board of each participating centre approved the LUMINA study, and written informed consent was obtained from each participating subject according to the declaration of Helsinki. At the time these analyses were conducted, 631 patients constituted the cohort.

Prior to T0, all medical records were reviewed to confirm the patient’s eligibility and to gather socioeconomic demographic and relevant clinical data from the time of diagnosis (TD) to T0. Each patient has a baseline visit at T0; follow-up visits are conducted every 6 months for the first year (T0.5 and T1, respectively), and yearly thereafter (T2, Tn). A LUMINA study visit consists of an interview, a physical examination and laboratory tests. Data for missed study visits are obtained, whenever possible, by review of all available medical records. TD is defined as the time at which patients meet four ACR criteria for the classification of SLE. Follow-up time is defined as the interval between T0 and the last study visit (TL).

### Variables

As previously described,<sup>17</sup> the LUMINA database includes variables from the following domains: socioeconomic demographic, clinical, immunological, genetic, behavioural and

psychological. These variables are ascertained at T0 and at every subsequent visit. For the purpose of this study, variables recorded at T0 and during the follow-up time were examined. Only the variables included in these analyses will be described. Acute onset lupus, our variable of interest, was defined as the accrual of four ACR criteria for the classification of SLE in 4 or fewer weeks; otherwise the patient was considered as having an insidious disease onset.

Variables included from the socioeconomic demographic domain were age, gender, ethnicity, education, poverty (as defined by US government guidelines and adjusted for the number of subjects in the household),<sup>18</sup> marital status, health-related behaviours (smoking, drinking, not exercising, and using recreational drugs), and health insurance. The total number of hospitalisations and the weighted average of non-study out-patient visits were also analysed.

Clinical variables included the number of ACR criteria at diagnosis, total disease duration (from TD to TL), cumulative clinical manifestations attributable to lupus, disease activity, damage accrual and mortality.

Disease activity was assessed using the Systemic Lupus Activity Measure – Revised (SLAM-R).<sup>19</sup> The SLAM-R was examined at TD, T0 and all other visits; since the interval between visits tends to fluctuate with some intervals being longer than others, a weighted average SLAM-R was used for the TD–TL interval. Damage was measured with the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage index (SDI).<sup>20</sup>

The presence of autoantibodies including ANA (by immunofluorescence using Hep-2 cell line), anti-double stranded DNA (anti-dsDNA, by immunofluorescence against *Crithidia luciliae* (abnormal  $\geq 1:10$ )),<sup>21</sup> anti-Smith and anti-Ro (by counter immunoelectrophoresis against human spleen and calf thymus extract),<sup>22</sup> and IgG and IgM antiphospholipid ((aPL, abnormal  $>13$  GPL U/ml and/or  $>13$  MPL U/ml respectively) by ELISA) antibodies<sup>23</sup> were analysed at T0.

From the genetic domain, *HLA-DRB1* (*HLA-DRB1\*1503*, *HLA-DRB1\*0301*, *HLA-DRB1\*08*), *HLA-DQB1* (*HLA-DQB1\*0201*, *HLA-DQB1\*0602*), *HLA-DQA1* (*HLA-DQA1\*0501*) and *FCCR3A* alleles were included. Genomic DNA was extracted using the PureGene kit (Gentra Systems, Minneapolis, Minnesota, USA) following the manufacturers recommendations. *HLA-DRB1*, *HLA-DQB1* and *HLA-DQA1* were genotyped as previously described.<sup>24</sup> *FCGR* alleles were genotyped by pyrosequencing (Biotage, Charlottesville, Virginia, USA) using gene specific primers.<sup>25</sup>

Behavioural and psychological variables included social support, ascertained with the Interpersonal Support Evaluation List (ISEL) where higher scores indicate better social support;<sup>26</sup> learned helplessness, ascertained with the Rheumatology Attitude Index (RAI) where higher scores indicate higher levels of helplessness<sup>27</sup> and abnormal illness-related behaviours, ascertained with the Illness Behaviour Questionnaire (IBQ) where higher scores indicate more abnormal illness-related behaviours.<sup>28</sup> Finally, self-reported health-related quality of life physical and mental functioning was ascertained with the Short Form-36 (SF-36) physical and mental components summary measures (PCS and MCS, respectively) where higher scores indicate better function.

## Statistical analyses

Features from the different domains for patients with acute vs insidious onset lupus were compared by univariable analyses using the  $\chi^2$  and Student t tests for categorical and continuous variables, respectively. Then, a multivariable analysis, with acute onset lupus as the dependent variable, using conditional logistic regression with a backward selection method was examined.

All variables with a p value  $\leq 0.10$  as per the univariable analyses were entered in the model; gender, a possible confounder, was entered in the model. All statistical analyses were performed using SPSS software, V.11.0 (SPSS, Chicago, Illinois, USA).

## RESULTS

A total of 631 patients were included in these analyses; 94 (15%) of them had acute onset disease. Patients were predominantly women (89.1%) and middle age (mean (SD) 36.5 (12.6) years). All ethnic groups were represented, 117 (18.5%) were Hispanics from Texas, 102 (16.3%) were Hispanics from Puerto Rico, 234 (37.1%) were African-American, and 178 (28.1%) were Caucasians. The total disease duration was 5.5 (3.6) years.

### Univariable analyses

Table 1 shows selected baseline socioeconomic demographic and healthcare utilisation features. Patients with acute onset lupus were more likely to be younger, of Hispanic (from Texas) ethnicity, less educated and less likely to have health insurance. Hospitalisations were also more frequent among them.

Patients with acute onset lupus were more likely to have accrued more ACR classification criteria at diagnosis and to exhibit renal, cardiopulmonary and haematological involvement over time more frequently. The weighted average SLAM-R and SDI at last visit were also higher among patients with acute disease onset. By contrast, this patient group was less likely to have skin and musculoskeletal involvement over the duration of the disease. The proportions of deceased patients were comparable in both groups. These data are depicted in table 2.

Anti-dsDNA antibodies were more frequently found among patients with acute disease onset (69.1% vs 51.6%;  $p = 0.002$ ). No differences were found for other autoantibodies or in the genetic profile between patients with acute vs insidious onset (data not shown). Likewise, no differences were found in the behavioural and psychological variables examined (data not shown).

### Multivariable analysis

Table 3 shows the results of the multivariable analysis with acute onset lupus as the dependent variable. Variables associated with acute onset lupus were renal involvement (odds ratio (OR) = 1.845, 95% CI 1.076–3.162;  $p = 0.026$ ) and disease activity (OR = 1.057, 95% CI 1.005–1.112;  $p = 0.030$ ). By contrast, age (OR = 0.976, 95% CI 0.956–0.997;  $p = 0.025$ ), education (OR = 0.901, 95% CI 0.827–0.983,  $p = 0.019$ ), health insurance (OR = 0.423, 95% CI 0.249–0.718;  $p = 0.001$ ) and skin involvement (OR = 0.346, 95% CI 0.142–0.843;  $p = 0.019$ ) were negatively associated with acute onset lupus. Damage accrual was not retained in the model.

## DISCUSSION

SLE is a heterogeneous disease in terms of its presentation, course and outcome. According to its presentation, SLE can evolve in a relatively short time period, the so-called acute onset lupus, or, in contraposition, it can be insidious, which implies that certain time elapses from the first manifestation until the diagnosis can be made. Although generally believed to represent a more severe disease, the short- and long-term prognosis of acute onset lupus has not yet been elucidated. In this study, we found that patients with acute onset lupus were younger, from a more disadvantage socioeconomic background, and more likely to develop renal involvement and display higher degree of disease activity when compared with those patients with an insidious disease onset. However, these patients did not accrue more irreversible damage or

have a less favourable survival experience when compared to those with an insidious disease onset.

Some of our findings are not surprising; as previously described, the clinical presentation and course of SLE may be influenced by age at disease diagnosis and socioeconomic factors. Younger patients show a poorer prognosis in terms of major organ involvement<sup>29–31</sup> as well as higher disease activity when compared with older patients.<sup>32</sup> Moreover, the socioeconomic status of the patient has been consistently found to influence the prognosis of the disease,<sup>10</sup> this is particularly the case for lack of health insurance.<sup>33–35</sup> However, we do not have a clear explanation for the association between the variables from the socioeconomic domain and type of disease onset; it is possible that these variables are acting as surrogates of a much broader construct, such as of ethnicity.

As we hypothesised, patients with acute disease onset have more severe clinical manifestations (renal involvement) and showed a higher degree of disease activity. These findings are of utmost importance as they have clinical and therapeutic implications. Lupus nephritis is one of the most frequent clinical manifestations (52% of the patients in this cohort have had lupus nephritis at some point in time since diagnosis) and it also represents a significant source of morbidity, health-related expenditure and mortality among SLE patients.<sup>36–40</sup> Patients with acute onset disease should, therefore, be closely followed-up with particular attention paid to checking for the occurrence of renal disease so that adequate treatment is provided without delay.

By contrast, acute onset lupus does not seem to impact the long-term prognosis of the disease as we failed to find any association between the type of disease onset, damage accrual and mortality. It is reasonable to assume that type of disease onset could exert its effects early in the course of the disease decreasing its influence over time, and, therefore, ameliorating the impact on long-term outcome variables such as damage accrual and mortality. Another possibility is that a longer time may need to elapse for these long-term outcomes to be impacted by type of disease onset. In this sense, LUMINA is a relatively young cohort<sup>14</sup> with a mean total disease duration of only 5 years. Thus, the impact of the type of disease onset on damage accrual and mortality might not yet have become evident.

Unexpectedly, neither ethnicity nor the genetic variables were found to be associated with acute onset lupus. Although Hispanic (From Texas) ethnicity was significantly associated with acute onset disease in the univariable analyses, it was not so in the multivariable model. This is in contrast with our previous study on the natural history of the accrual of the ACR criteria,<sup>41</sup> in which we found Hispanic (from Texas) ethnicity and the presence of HLA-*DRB1*\*0301 to be associated with a shorter time to criteria accrual. In those analyses, however, the variable of interest (time to accrual of four ACR criteria) was continuous rather than the dichotomous variable (acute vs insidious disease onset), which, at least in part, could explain these discrepancies.

This study is not without some limitations. It is possible that misclassification of type of disease onset may have occurred, especially for those non-incident cases included in the cohort. Furthermore, the ACR classification criteria, although quite specific, still shows some drawbacks for the correct classification of patients; for example, some criteria, arthritis and photosensitivity among them, are less specific than others and these manifestations may be either overlooked or wrongly attributed to SLE. By contrast, some clinical and laboratory features quite suggestive of SLE such as hypocomplementemia are not included. Both scenarios can, consequently, modify the time to the accrual of four criteria required for the diagnosis of SLE.

In conclusion, a relatively small number of patients (15%) in this cohort showed an acute disease onset. However, these patients seem to conform quite a defined subset with important clinical and therapeutic implications. Patients with acute onset lupus are younger and more likely to develop renal involvement as well as show higher degrees of disease activity over time. Close monitoring and education, especially for those patients from a more disadvantage socioeconomic background, is therefore warranted in order to detect major organ involvement early and to provide prompt treatment accordingly.

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**Table 1**

Baseline socioeconomic demographic and healthcare utilisation features of LUMINA patients according to type of disease onset

Variable	Acute onset lupus		p Value
	Yes (n = 94)	No (n = 537)	
Age, mean (SD)	32.1 (12.1)	37.4 (12.6)	<0.001
Female gender, %	92.6	88.9	0.311
Ethnicity, %			<0.001
Hispanic (Texas)	35.1	15.8	
Hispanic (Puerto Rico)	5.3	18.2	
African-American	42.6	36.0	
Caucasian	17.0	30.0	
Marital status, married, %	41.3	49.8	0.136
Education, years, mean (SD)	11.8 (3.1)	13.2 (3.0)	<0.001
Poverty <sup>*</sup> , %	37.2	32.6	0.403
Health insurance, %	60.9	83.2	<0.001
Yearly outpatient visits, weighted average (SD)	2.7 (3.6)	2.6 (3.2)	0.404
Total hospitalisations, mean (SD)	0.9 (1.2)	0.5 (0.8)	0.003
Exercising, %	38.5	41.4	0.603
Smoking, %	12.0	14.0	0.596
Drinking, %	6.5	10.6	0.228
Using recreational drugs, %	3.3	1.1	0.113

\* As per US Federal government guidelines.

LUMINA, lupus in minorities, nature vs nurture.

**Table 2**

Selected clinical features of LUMINA patients according to type of disease onset

Variable	Acute onset lupus		p Value
	Yes, n = 94	No, n = 537	
Total disease duration (TD–TL), mean (SD)	5.7 (4.0)	5.4 (3.6)	0.521
ACR criteria number at diagnosis, mean (SD)	6.0 (1.3)	5.4 (1.3)	<0.001
SLAM-R at T0, mean (SD)	11.5 (6.5)	9.1 (5.6)	0.001
SLAM-R, weighted average (SD)	9.8 (5.9)	7.6 (4.4)	0.001
SDI at T0, mean (SD)	0.9 (1.3)	0.7 (1.6)	0.252
SDI at TL, mean (SD)	2.2 (2.2)	1.7 (2.2)	0.039
Clinical manifestations:			
Skin involvement, %	90.4	95.1	0.067
Musculoskeletal, %	94.7	98.1	0.044
Cardiopulmonary involvement, %	76.6	56.1	<0.001
Neurological involvement, %	81.9	80.5	0.747
Renal involvement, %	71.3	48.8	<0.001
Haematological involvement, %	91.5	78.6	0.004
Deceased, %	17.0	11.1	0.101

ACR, American College of Rheumatology; LUMINA, lupus in minorities, nature vs nurture; SLAM-R, Systemic Lupus Activity Measure – Revised; SLI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; Tn, timepoint n (D, time of diagnosis; L, last follow-up).

**Table 3**

Variables independently associated with acute onset lupus by multivariable conditional logistic regression analysis

Variable*	Odds ratio (95% CI)	p Value
Age	0.976 (0.956–0.997)	0.025
Education (years)	0.901 (0.827–0.983)	0.019
Health insurance	0.423 (0.249–0.718)	0.001
Clinical manifestations:		
Skin involvement	0.346 (0.142–0.843)	0.019
Renal involvement	1.845 (1.076–3.162)	0.026
SLAM-R (weighted average)	1.057 (1.005–1.112)	0.030

\* Variable included in the model are those noted in the table plus: Hispanic ethnicity (from Texas), gender, number of ACR criteria at diagnosis, anti-dsDNA antibodies, musculoskeletal involvement, cardiovascular involvement, haematological involvement, damage at last visit and total number of hospitalisations. As this regression was examined with a backward selection procedure, these variable were removed from the model in earlier steps of the analysis.

ACR, American College of Rheumatology; SLAM-R, Systemic Lupus Activity Measure – Revised.