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Organ Damage in High Risk Patients with Systemic and Incomplete Lupus Syndromes

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Abstract

The objective of this study was to characterize organ damage in lupus patients enrolled in the Dallas Regional Autoimmune Disease Registry (DRADR). Retrospective chart review was carried out on 99 patients with 4 or more diagnostic criteria for systemic lupus erythematosus (SLE) and 15 with less than 4 of these criteria, who were designated as having incomplete lupus (ILE). The majority of patients (84%) were African American or Hispanic/Latino; mean disease duration was 9.5 years. The mean damage score was 1.57 (range 0 to 8) and a damage score greater than 0 was present in 64% of the patients. The ILE group had lower mean damage scores (0.67) than the SLE group (1.67; $P=0.04$), explained in part by the shorter disease duration in the ILE patients (4.33 years vs. 10.24 years; $P=0.003$). The most prevalent damage category was renal, present in 24% of patients. Malignancies occurred in individuals who were significantly older than those who had renal or peripheral vascular damage ($P=0.0007$). The findings confirm clinical impressions that the DRADR includes a high-risk lupus population. The ILE patients have less damage but also shorter disease duration, suggesting that this might represent an earlier disease stage. These results are consistent with the hypothesis that ILE patients include a subset that is likely to experience progressive organ damage. Longitudinal study of these patients has significant likelihood of tracking the changes that are correlated with disease progression to SLE.

Keywords

Systemic lupus erythematosus; Incomplete lupus

Systemic lupus erythematosus (SLE) is a multisystem disorder that can lead to significant and permanent dysfunction in major organ systems. It has a major peak of onset in young adults and is one of the few chronic diseases that has a declining risk with age. This means that the devastation caused by the disease has a long-lasting impact on young patients.

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Previous studies have demonstrated that organ damage in lupus is more likely to occur in African-Americans and Hispanic/Latinos [1, 2], racial and ethnic subgroups that make up the majority of SLE patients in the Dallas Regional Autoimmune Disease Registry (DRADR). In this high-risk population, individuals with fewer than 4 of the SLE diagnostic criteria [3] are labeled as having incomplete lupus (ILE) and are likely at high risk for development of complete SLE [4]. Identification of the factors in ILE that correlate with disease progression may provide insights into approaches to development of disease prevention strategies.

To characterize the DRADR patients, and to confirm that these assumptions are valid, we measured SLE criteria and the Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology Damage Index (SDI) [5, 6] in DRADR patients with SLE and ILE. The findings confirm that this registry includes a high prevalence of organ damage and suggests that the ILE patients are likely to be accumulating lupus features at a rate that can be detected with regular followup.

Patients and Methods

Patients

The DRADR enrolls individuals with autoimmune disease, first-degree relatives of autoimmune disease patients and healthy control subjects with the purpose of facilitating clinical, immunologic and genetic studies in autoimmune diseases including systemic lupus erythematosus. Individuals enrolled in DRADR have been recruited from the University of Texas Southwestern Medical School clinics at Parkland Hospital and the Aston Ambulatory Care Center as well as from local practitioners in North Texas. Standard disease criteria are used to classify patients using data obtained from patient interview and medical record review. Although the DRADR was not designed to collect drug safety data, the design of this registry does incorporate the major elements that have been recommended by a EULAR task force, including a defined purpose, collection of components of composite scores and compliance with guidelines for security of patient identifiers [7]. The present study utilized 124 individuals enrolled in DRADR between 2003 and 2009, including 99 with SLE defined as satisfying 4 or more of the diagnostic criteria for this disease [3] and 15 with ILE, defined as having less than 4 of the diagnostic criteria (Table 1). Since extensive medical record review was needed to determine disease features, only individuals who had complete records available for review were included. There were no other selection criteria. Disease duration was recorded as the time from physician diagnosis of lupus or in the case of ILE from the time that the symptoms or lab findings were first noted, to the time of record review. Race and ethnicity were self-declared. All subjects gave written informed consent for entry into the Dallas Regional Autoimmune Disease Registry. Research carried out under the auspices of this registry has been approved by the UT Southwestern Institutional Review Board.

Determination of SLE criteria

Each individual was evaluated at the time of enrollment for the number of SLE criteria that had been present at any time in the disease course up to that point. Information was obtained

from chart review and patient interviews. Clinical symptoms reported by patients were verified with the medical records.

Determination of SLE damage

The SLICC/ACR Damage Index (SDI) (<http://www.rheumatology.org/practice/clinical/indexes/slicc.asp>) was used to classify damage features. All medical record reviews were carried out during 2009-2010.

Autoantibody measurements

Routine autoantibody measurements obtained in the clinical laboratories were obtained by chart review. In addition, the anti-nuclear antibody (ANA) value was measured at the time of enrollment by enzyme-linked immunosorbent assay (ELISA). Anti-extractable nuclear antibody (ENA) values were measured in a subset of 30 individuals with positive ANA levels using a multiplex Luminex assay as described previously [8].

Statistical analyses

Data are presented as the mean and standard deviation or SEM; for some variable, 95% confidence intervals are also shown. Groups of continuous variables were compared using Student's t-test or one-way analysis of variance for more than two groups with Tukey's posthoc analysis for pairwise comparisons. Dichotomized variables were compared using Fisher's exact test. Correlations were determined using Pearson's coefficient. P values less than 0.05 were considered significant. Graph Pad Prism Version 6.0 (Graph Pad Software, Inc., San Diego CA) was used for data analyses.

Results

Demographic and clinical features

The majority of the SLE/ILE patients were female (88%) and 84% were either African American or Hispanic/Latino. The average age was 41 years and 43% were older than 40 years. The average number of SLE criteria that were satisfied was 5.9 and mean disease duration was 9.5 years (Table 1). The most prevalent clinical category satisfied was arthritis, in 75% of subjects, followed by hematological (68.5%), malar rash (58.9%) and renal (53.2%). The prevalence of criteria in DRADR fell within ranges reported from other cohorts (Table 2)[9-12]. Antibodies to dsDNA were present in 67% of the patients, and were significantly correlated with renal manifestations ($P=0.0007$). Antibodies to the Sm antigen were less common, with positivity in 23% of the patients, and association with renal manifestations was only marginally significant ($P=0.05$).

Damage features

The mean SDI score in the 124 patients was 1.57 ± 0.15 , with a range of 0-8. Males and females had similar scores (1.75 ± 0.35 vs 1.53 ± 0.15 ; $P=0.5$). A damage score of 0 was present in 45 patients (36%), with a somewhat higher prevalence of this score in non-Hispanic Caucasians (53%) than in African-Americans (32%) or Hispanic/Latinos (38%), but this difference was not statistically significant. SDI score was correlated with disease

duration ($P<0.0001$) and the subgroup with scores >0 had a longer mean duration of disease (11.1 ± 0.9 years) than those with scores equal to 0 (6.7 ± 0.73 years; $P=0.001$). Since other studies have evaluated damage scores in the first 5 years of SLE, the subgroup of 31 SLE patients with duration of 5 years or less was evaluated separately to allow comparison. Thirteen of these 31 patients (42%) had damage scores of 0, which is similar to other reports [13].

Patients with ILE had a significantly lower mean damage score (0.67 ± 0.32) than patients with SLE (1.67 ± 0.17 ; $P=0.036$). Ten of the 15 ILE patients (67%) had damage scores of 0, which compared to 35 of the 99 SLE patients (35%; $P=0.026$). However the ILE patients also had significantly shorter disease duration (4.33 ± 0.94 years) than the SLE patients (10.24 ± 0.75 years; $P=0.003$) and this difference was likely a contributing factor to the lower ILE damage scores.

The most common category of damage was renal, which was present in 24% of the patients, all of whom were in the SLE group (Table 3). All of the Hispanic/Latino patients with renal damage ($N=12$) had disease durations of less than 15 years, compared to the non-Hispanic patients, for which 5 of 18 individuals had had disease longer than 15 years ($P=0.06$). This suggests that renal damage in Hispanic/Latino patients occurs earlier in the disease course or is associated with decreased survival. Within the renal damage category, nine patients (7% of total) had end-stage renal disease. All of these patients were either African-American or Hispanic/Latino with the exception of one patient who was Asian; none were non-Hispanic Caucasians.

Other highly prevalent damage categories or conditions were: diabetes mellitus (18%), musculoskeletal (16%), neuropsychiatric (14%) and cardiovascular (12%; Table 3). Only one patient had a score for damage in the skin domain. The musculoskeletal system included 6 patients with avascular necrosis (AVN), all of whom were either African-American or Hispanic/Latino. In the peripheral vascular domain, 11 of the 12 patients scored were females; all had venous thrombosis and 7 had positivity for antiphospholipid antibodies. Seven patients had malignancies, the most common of which was breast, in 3 patients, one of whom had two primary breast cancers. Other malignancies were renal cell carcinoma, chronic lymphocytic leukemia, endometrial and cervical cancer. The various domains did not show significant differences in disease duration ($P=0.5$), but the average age was significantly longer in patients who had malignancies than those who had renal or peripheral vascular disease ($P=0.0007$; Figure 1).

Autoantibodies

ANA positivity measured in the clinical laboratory was present in more than 97% of the patients (Table 2). ANA values measured by ELISA were compared in DI score subgroups. Patients with SDI scores of 3 or less had a lower average ANA than those with 4 or more damage points (116 EU vs 228 EU; $P=0.037$). Positivity for dsDNA, as measured in the routine clinical laboratory, was present in 62% of individuals with SDI scores of 0-3 and in 73% of those with SDI scores of 4 or greater ($P=0.08$). Antibodies to Sm measured in the clinical laboratory were not correlated with SDI scores (data not shown). In the subgroup of 30 patients in whom the anti-ENA panel was measured in the research lab, mean values for

anti-RNP and anti-Sm were significantly lower in patients with SDI scores of 4 or greater than in those with scores of 0-3 (P values 0.0025 and 0.0096, respectively; Figure 2).

Discussion

Profiling of damage in lupus patients enrolled in the DRADR was carried out to address two objectives. The first was to provide documentation to confirm the clinical impression that this population includes individuals at high risk for organ damage, as would be predicted from the ethnic and racial composition represented in this registry. The second was to use these data to develop insights into the relative risks of SLE for those individuals in the registry who have ILE. Other reports have documented that ILE patients generally show lower SDI scores [4, 14], and we verified that finding in our patients. This was somewhat confounded by the finding that the ILE patients had significantly shorter disease duration, which is one of the major determinants of the cumulative damage score. However, the precise definition of disease duration in ILE is somewhat problematic, since in fact this is not recognized as a distinct clinical entity. Furthermore, the presence of serologic criteria may in fact be present for many years before it is detected through medical evaluation. Whether in fact the ILE patients had longer duration of at least some of the criteria elements than what was recorded is a distinct possibility.

One of the main objectives of the ILE cohort is to view disease progression, and this would best be done in a high risk population where time to disease might be shorter and where the disease risks are greater. The damage analysis results suggest that the ILE population under study in the DRADR most likely has a high risk of developing organ-damaging forms of SLE. It is reasonable also to hypothesize that this may occur more rapidly in DRADR than in other populations where the ILE to SLE transition has been studied. In a study carried out in Sweden, a mean followup period of 5 years (range 1 – 10 years) was required to observe development of 4 or more lupus criteria in 16 of 28 ILE patients [4]. In a more recent Swedish study of patients with cutaneous lupus (CLE), transition to SLE was observed in 18% over a 2-year period, a higher rate of conversion than expected [15]. A report from Denmark, another low-incidence lupus country with predominantly Caucasian patients, identified SLE transformation in about one-fifth of 37 ILE patients over a period of 8 years [16]. Based on the current study results, it is reasonable to hypothesize that transitions will be more prevalent and more rapid in DRADR than in these other reported cohorts.

The high damage scores in our population are not unexpected, as previous studies have suggested that damage, especially in the renal domain, is greater in African-American and Hispanic patients, groups that taken together constituted a majority of our patients [12]. The prevalence of DRADR SLE damage scores greater than 0 (65%) was very similar to the value of 60% reported in the Hopkins Lupus Cohort, which is approximately 50% African American; the mean damage score of 1.67 in the DRADR SLE patients is also similar to the mean score of 1.51 in the Hopkins cohort [13]. By comparison, a predominantly Caucasian SLE cohort in the United Kingdom was reported to have a prevalence of DI scores greater than 0 of only 33% after 5 years of disease and the corresponding mean damage score was 0.42 [17]. Damage scores in Asian populations are somewhat more variable. A southern Chinese cohort was reported to have a damage prevalence of 38% [18] and in Koreans

damage was reported in 41.5% of SLE patients [11]. By contrast, a South Asian population in Pakistan showed a damage prevalence of 76% at 10 years of followup [19].

Renal damage is especially important as this has been shown to be a predictor of poor outcomes and increased mortality [19, 20]. Significantly, in the DRADR cohort, renal was the most prevalent damage category, present in 24% of the entire study group and in 30% of the SLE patients. By comparison, renal damage was present in 20% of the LUMINA cohort [20], 14.5% in Southern Chinese at year 3 [18] and 12.9% of U.K. patients at year 10 [17].

Limitations of the present study include the retrospective design, which did not permit an accurate assessment of the rate of change in damage scores. Full details of medications and disease activity scores also were not available on all patients. This is a limitation of the analysis, as other studies have shown that use of cyclophosphamide is an independent predictor of damage accrual [18, 21]. High dose glucocorticoid treatments may also mediate damage, and even though that has not been shown in all studies [11] and may be confounded by the indications for the treatment [13], minimizing steroid doses is an urgent therapeutic goal [22]. Other recent reports suggest that hypertension is a very important predictor of damage accrual, and that variable was not collected in our cohort [23]. The sample size was small and though there were trends to suggest that damage was more prevalent in African-Americans and Hispanics, these were not statistically significant. However, the findings do suggest that patients with ILE in the DRADR are at high risk of developing SLE and that longitudinal studies to quantitate and characterize these changes are likely to provide insights into mechanisms of disease pathogenesis. The long-term goals of these studies are to develop biomarkers of progression and identify targets for therapeutic intervention that would possibly halt or reverse changes that lead to irreversible organ damage.

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Figure 1.

Mean (and S.E.M.) values for age and disease duration in each of the damage categories. P values analyzed by 1-way ANOVA. Posthoc analyses confirmed that patients with malignancies were significantly older than those with renal or peripheral vascular manifestations. NP = neuropsychiatric; CV = cardiovascular; PV = peripheral vascular; GI = gastrointestinal; MS = musculoskeletal.

Figure 2.

Immunoassay measurements (Inova) for RNP (left) and Sm (right) autoantibodies. The Low DI group (N=26) had scores of 3 or less; HI DI (N=4) included individuals with scores of 4 or greater. Values represent mean and S.E.M.; P values calculated using t-test.

* P=0.0025; ** P=0.0096.

Table 1

Demographic and clinical features of 124 ILE and SLE patients from the Dallas Regional Autoimmune Disease Registry

Female	108 (87)
Ethnicity and race	
Non-Hispanic Caucasian	15 (12)
Asian	4 (3)
African-American	65 (52)
Hispanic/Latino	40 (32)
Age (years)	41 ± 13
> 40 years old	53 (43)
SLE with 4 or more criteria	99 (80)
ILE with < 4 criteria	15 (20)
SLE Criteria satisfied	5.9 ± 2.1
Disease Duration (years)	9.5 ± 7.3
Damage Index Score	1.57 ± 1.6

Values represent number of patients in each category (with percent of total) or mean and SD.

Table 2

SLE criteria in DRADR Compared to Other Lupus Cohorts

Criterion	DRADR (N=124)	Vila et al [*] (N=553)	Kamen et al (N=184)	Sung et al (N=588)	Alarcon et al (N=78)
Malar rash	58.9**	49.5	56.0	41.8	64.1
Discoid rash	30.6	12.1	34.2	9.0	6.4
Photosensitivity	50.8	51.6	60.9	30.1	59.0
Mucocutaneous	31.5	42.9	43.5	35.54	57.7
Arthritis	75.0	76.8	89.1	61.05	91.0
Serositis	36.3	42.0	45.1	29.08	11.5
Renal	53.2	30.8	55.4	44.22	59.0
Neurological	14.5	9.1	21.2	7.82	11.5
Hematological	68.5	67.2	54.3	83.33	84.6
ANA	97.6	96.8	98.9	100	97.4
Immunological	69.4	67.8	71.7	87.24	83.3

* Ethnicities: Vila, 72% AA or H; Kamen 100% AA Gullah; Sung 100% Korean, Alarcon 100% H

** Values represent percent in each category.

Table 3

Damage features in DRADR patients with ILE or SLE

Category	Number (% of total=124)	Female (% of category)	African- American (% of category)	Hispanic (% of category)	Age - Years Mean ± SD	Duration - Years Mean ± SD
Musculoskeletal	20 (16) (10-24)*	17 (85) (62-97)	12 (60) (36-81)	3 (15) (3-38)	46.0 ± 13.3 (39.8- 52.2)	13.0 ± 9.1 (8.6- 17.4)
Neuropsychiatric	17 (14) (8-21)	16 (94) (71-100)	11 (65) (38-86)	4 (24) (7-50)	43.7 ± 9.7 (38.7- 48.7)	11.2 ± 6.0 (8.2- 14.3)
Renal	31 (25) (18-34)	23 (77) (55-88)	15 (48) (30-67)	13 (42) (25-61)	36.2 ± 12.1 (31.7- 41.0)	10.3 ± 6.5 (7.9- 12.7)
Ocular	7 (6) (2-11)	5 (71) (29-96)	3 (43) (10-82)	3 (43) (10-82)	47.7 ± 17.6 (31.5- 64.0)	16.7 ± 16.2 (1.7- 31.8)
Cardiovascular	15 (12) (7-19)	15 (100) (78-100)	10 (67) (38-88)	2 (13) (2-41)	46.6 ± 11.4 (40.3- 52.9)	13.0 ± 8.0 (8.8- 17.3)
Pulmonary	10 (8) (4-14)	10 (100) (69-100)	7(70) (35-93)	3 (30) (7-65)	41.5 ± 13.1 (32.1- 40.7)	13.4 ± 7.1 (8.3- 18.5)
Skin	1 (1)	1 (100)	1 (100)	0	29	10
Peripheral vascular	12 (10) (5-16)	11 (100) (62-100)	4 (33) (10-65)	8 (58) (35-90)	34.1 ± 10.8 (27.3- 40.9)	11.4 ± 8.3 (6.2- 16.7)
Diabetes Mellitus	22 (18) (12-26)	17 (77) (55-92)	13 (59) (36-79)	5 (23) (8-45)	45.5 ± 15.0 (38.6- 51.8)	11.5 ± 9.5 (7.3- 15.7)
Gastrointestinal	10 (8) (4-14)	10 (100) (69-100)	6 (55) (26-88)	2 (18) (3-56)	43.5 ± 13.3 (36.0- 50.9)	12.3 ± 7.1 (7.5- 17.0)
Malignancy	7 (6) (2-11)	7 (100) (59-100)	2 (29) (4-71)	3 (43) (10-82)	58.1 ± 5.0 (45.9- 70.4)	17.9 ± 12.7 (6.1- 29.6)

* 95% confidence intervals (CI) are shown and were calculated for percents or mean values.