Concise Report

Clinical and immunological characteristics of 56 patients with systemic lupus erythematosus in Uganda

Felix Bongomin 1,2, Maria Sekimpi1 and Mark Kaddumukasa1

Abstract

Objectives The prevalence and burden of SLE in Africa are poorly understood. This health-facility-based retrospective study aimed to describe the frequency and the clinical and immunological characteristics of SLE in Uganda.

Methods We reviewed clinical notes of patients presenting with rheumatological complaints in two large rheumatology outpatient clinics in Uganda between January 2014 and December 2019.

Results Of the 1019 charts reviewed, 5.5% (56) of the patients had confirmed SLE, with a median age of 29 (range: 14–65) years. The male-to-female ratio was 1:10, and 19.6% (11/56) of the patients had SLE and RA overlap syndrome. Patients presented with joint pains or swellings (n = 39, 69.6%), typical photosensitive malar rash (n = 34, 60.7%), oral ulceration (n = 23, 41.1%), anaemia (n = 14, 25.0%), hair loss and polyserositis (n = 12, 21.4% each), constitutional symptoms (n = 10, 17.9%), RP (n = 4, 7.1%) or LN (n = 3, 5.4%). ANA and anti-dsDNA autoantibodies were both positive in 25 (75.8%) of the 33 patients with available results. ANA titres were ≥1:160, with a median titre of 1:160 (range: 1:160 to 1:3200). Six patients had titres ≥1:320. The median dsDNA level was 80 (range: 40–283) IU. Ten patients had results of C3 and C4 complement protein levels and, of these, 4 patients had low C3 levels and 3 had low C4 levels.

Conclusion SLE is uncommon among patients presenting with rheumatological complains in Uganda. SLE overlaps with RA in our setting, and a majority of patients present to care with complications.

Key words: systemic lupus erythematosus, epidemiology, Uganda, ANA, dsDNA

Introduction

SLE is a heterogeneous, chronic autoimmune disease of unknown cause, with a wide range of clinical and serological manifestations that can affect virtually any organ of the body [1]. The clinical presentation, course and prognosis of SLE are highly variable [1]. Irrespective of age or ethnicity, SLE predominantly affects women of childbearing age rather than men, with a ratio of 10:1 [1, 2]. The clinical
heterogeneity of SLE and the lack of pathognomonic features or tests pose a diagnostic challenge for the clinician, and often, patients may present with only a few clinical features of SLE, which can resemble other autoimmune, infectious or haematological diseases [3].

Globally, the incidence and prevalence of SLE vary remarkably with sex, age, ethnicity and time [2, 4]. North America is reported to have the highest incidence (23.4–24.0/100 000 person-years) and prevalence (130–352/100 000) of SLE, compared with an incidence rate of 0.3/100 000 person-years in Africa [2]. However, a recent survey of physicians in Africa suggests that a significant number of African patients are presenting with SLE [5].

Information regarding the burden of SLE in sub-Saharan Africa is lacking. In general, the incidence and prevalence of SLE in Africa are largely undetermined for several reasons, including poor access to health care, low disease recognition within primary health-care settings, poor health record keeping, limited access to the required diagnostic tools and inadequate numbers of specialist physicians, including rheumatologists, within sub-Saharan Africa [5]. Establishing the epidemiology of SLE would allow us to identify and explore changes in potential risk factors for the disease and enable planning of health services in response to the overall disease burden [3].

Mulago National Referral Hospital Rheumatology Clinic serves as the main outpatient clinic in Uganda for rheumatological cases. The clinic runs once a week, reviews rheumatological referrals and handles attendant problems, drug refills, disease monitoring and drug toxicity monitoring. These patients are referred from various clinics and hospitals all over the country. The patients are followed up at scheduled visits for disease activity monitoring, response to therapy and toxicity monitoring monthly to quarterly. Most of the DMARDs are procured out of pocket by the patients, and this impacts their drug compliance. Hence, most of them usually present with frequent flares and disease complications. The purpose of this study, therefore, was to describe the frequency of occurrence and the clinical and immunological characteristics of Ugandans with SLE to guide policy-makers and health-care providers.

Methods

Study design

We conducted a health facility-based retrospective chart review of patients diagnosed with SLE over a 5-year period (from January 2014 to December 2019).

Study sites and population

The study was conducted in two large specialist rheumatology outpatient clinics, that is, Mulago National Referral Hospital, a public hospital located in Kampala, Uganda, and Lincoln Medical, a private medical centre located in Mukono, Uganda. Patients with rheumatological complaints constituted our study population.

Inclusion criteria

All patients were assessed against the ACR criteria (1997), the SLICC criteria (2012) or the ACR/EULAR criteria (2019) to confirm the diagnosis of SLE [6, 7]. Immunological assays were performed on patients who had clinical signs suggestive of SLE to help confirm the diagnosis. The ANA test uses an indirect fluorescent assay technique with HEp-2 cells. ANA titres >1:160 were considered positive and low titres negative.

Exclusion criteria

Files with missing data and those with other rheumatological diagnoses were excluded from further evaluation.

Data collection

We carefully reviewed all archived clinical notes of patients in the two clinics. We set aside the files of patients with a diagnosis of SLE for thorough review. A standardized data-collection tool was used to extract data on sociodemographics (age, sex and region of origin of the patient), clinical data (symptoms, signs and clinical diagnoses), immunological data (autoantibodies and titres) and other laboratory data.

Data analysis

Microsoft Excel 2010 and GraphPad Prism v.8.3 were used for data entry, cleaning and for generation of summary statistics.

Ethical statement

Data were collected as part of a routine quality-improvement scheme and, being a retrospective chart review, was exempt from patients’ informed consent and ethical review. All data were anonymized before analysis.

Results

We reviewed a total of 1019 (769 from Mulago National Referral Hospital and 250 from Lincoln Medical) clinical case notes. Overall, SLE was diagnosed in 5.5% (n = 56) of the patients; 4.7% (36/1019) in Mulago National Referral Hospital and 8.0% (20/250) in Lincoln Medical. The male-to-female ratio was 5:51 (21.4%).

The median age at the time of SLE diagnosis was 29 (range: 14–65) years. Twelve (21.4%) patients were ≥45 years of age. Thirty-nine (69.6%), 11 (19.6%), 4 (7.1%) and 2 (3.6%) patients were from the Central, Eastern, Western and Northern region of Uganda, respectively. The median duration of symptoms was 6 (range: 2–24) months.

Overall, 42 (75%) patients had isolated SLE, and 14 (25%) had SLE overlapping with RA (n = 11, 19.6%), SSc (n = 2, 3.6%) or DM (n = 1, 1.8%). The 11 cases of RA were confirmed clinically and serologically with RF...
Table 1 Frequency of signs and symptoms of SLE at presentation

| Presentation                        | Frequency (%) |
|-------------------------------------|---------------|
| Non-erosive arthritis/synovitis     | 39 (69.6)     |
| Malar/discoid rash                  | 34 (60.7)     |
| Oral sores                          | 23 (41.1)     |
| Anaemia                             | 14 (25.0)     |
| Non-scarring alopecia               | 12 (21.4)     |
| Polyserositis                       | 12 (21.4)     |
| Systemic symptoms                   | 10 (17.9)     |
| RP                                  | 4 (7.1)       |
| LN                                  | 3 (5.4)       |
| Sicca symptoms                      | 1 (1.8)       |
| Visual disturbance                  | 1 (1.8)       |
| Hepatitis                           | 1 (1.8)       |

Discussion

The burden of SLE is thought to be more common in the African population than previously assumed [2, 5, 8], but to our knowledge, the burden of such disease in Uganda has not been assessed previously. This is the first report of SLE in our settings. Over a 5-year period, we were able to diagnose and manage 56 patients in the two centres. Overall, these data suggest that SLE is an uncommon condition in our communities but a rather common condition among patients presenting to our rheumatology outpatient clinics. The reason for the low number registered over the study period could also be explained in the following ways. First there is a low index of suspicion and inexperience among clinicians, leading to underdiagnosis and misdiagnosis of SLE in our settings. Second, SLE patients die young from complications of SLE, such as LN. Third, there is no national registry for SLE in our country to collect data on this disease systematically from centres across the country. It is interesting to note that most of the patients presented with complications of the diseases, notably oral ulceration and alopecia. We also reveal that RA and SLE overlap in ≤20% of our patients. In this setting therefore, it may be advisable to undertake serological investigation for both disorders to optimize management.

SLE commonly presents with a mixture of constitutional complaints, with skin, musculoskeletal, mild haematological and serological involvement [9]. About one in five of our patients had constitutional symptoms, whereas arthralgia, photosensitive malar rash and oral ulceration were the most common complaints at presentation. Serological findings are important in suggesting the possibility of SLE, with some antibodies [e.g. dsDNA and anti-Smith (Sm)] being highly associated with this condition [7, 10]. In the present study, dsDNA was demonstrated in ≤24% of the patients with ANA-negative SLE.

Although we routinely order these tests for all patients with suspected SLE, in the present study, only 33 (~60%) patients had both ANA and dsDNA autoantibody tests done. This is because most centres (including both centres included in this study) do not have the laboratory capacity to carry out these serological tests. Patients are often referred to private laboratories or outside the country for these tests. Thus, the accessibility, affordability and availability of these autoantibody tests remain a major challenge in our practice. ANA is an extremely important serological test required for the fulfillment of the SLE diagnostic criteria. The recent ACR/EULAR classification criteria require an ANA titre of ≥1:80 on human epithelial-2-positive cells for SLE diagnosis [7]. In the ACR/EULAR (2019) criteria, the addition of the autoantibodies in the immunological criteria greatly improved the sensitivity and specificity of the tool compared with the past criteria. This has significantly led to an improved diagnosis and classification of SLE. All our patients had ANA titres of ≥1:160 (thus meeting the 2019 criteria), with ~18% of the patients

and ACPA. Both patients with SSc had suggestive clinical features, with positive anti-Scl-70 and anti-ribonucleoprotein 1 (anti-nRNP-1) autoantibodies. The patient with DM had features of proximal myopathy, skin lesions (Gottron’s papules and heliotrope rash) and positive anti-nRNP-1 autoantibodies.

Most patients presented with two or more clinical features of SLE. The most common clinical features at presentation were joint pains or swellings, typical photosensitive malar rash, oral ulceration, anaemia, hair loss and polyserositis occurring in one-fifth to two-third of the patients (Table 1). Accordingly, more than one-third of the patients were diagnosed using the ACR criteria (n = 22, 39.3%), 20 (35.7%) patients using the SLICC criteria and 14 (25%) using the ACR/EULAR criteria, as shown in Table 2.

One patient had poorly controlled HIV infection and was being managed on second-line anti-retroviral agents. Both ANA and anti-dsDNA autoantibodies were available for 33 (58.9%) patients. ANA and dsDNA were each positive in 25 (75.8%) patients. Eight (24.4%) patients with a negative ANA had a positive anti-dsDNA (Table 2). All the 33 patients had ANA titres ≥1:160, with a median titre of 1:160 (range: 1:160 to 1:3200). Six patients had titres ≥1:320. The median dsDNA level was 80 (range: 40–283) IU. Ten patients had results of C3 and C4 complement protein levels; of these, 4 patients had low C3 levels and 3 had low C4 levels.

All patients had raised ESR. The median ESR was 100 (range: 45–140) mm/h. The median total white cell count was 4 (range: 2–12)×10⁹/μl. The median haemoglobin concentration was 11 (range: 6–15) g/dl, and the median platelet count was 263 (range: 129–543)×10⁹/μl.

All patients were initiated on standard dosages (5 mg/kg of ideal body weight/day) of HCQ with or without an additional DMARD, including CsA and AZA. Adjunctive treatment included the use of systemic CS, NSAIDs and vitamin supplementation. Patients with SLE and RA overlap syndrome were commenced on both HCQ and a weekly MTX regimen.
**Table 2** Classification of SLE based on published criteria

| Criteria | ACR, 1997 | SLICC, 2012 | ACR/EULAR, 2019 |
|----------|-----------|-------------|------------------|
| Clinical Criteria | Satisfy 4 of 11 criteria | Satisfy four of the criteria with at least one clinical criterion and one immunological or biopsy-proven LN with positive ANA or anti-dsDNA antibodies | Score ≥ 10 points with ANA of ≥ 1:80 on HEp-2 cells or equivalent |
| SLE classification criteria | | |
| | n = 22 | n = 20 | n = 14 |
| Joints | | | |
| 1. Malar rash | 6 | | |
| 2. Photosensitivity | | | |
| 3. Discoid rash | 4 | | |
| 4. Oral/nasopharyngeal ulceration | 9 | | |
| 5. Non-erosive arthritis | 15 | | |
| 6A. Pleuritis or | | | |
| 6B. Pericarditis | 2 | | |
| Serositis | | | |
| 7A. Persistent proteinuria > 0.5 mg/24 h or ≥3+ dipstick or | | | |
| 7B. Cellular casts | 1 | | |
| Renal | | | |
| 7B. Red blood cell casts | 1 | | |
| 8A. Seizures or | 0 | | |
| 8B. Psychosis or | 0 | | |
| Neurological | | | |
| 8A. Seizures | | | |
| 8C. Psychosis | | | |
| Haematological | | | |
| 8D. Myelitis | | | |
| 8E. Peripheral/cranial neuropathy or | | | |
| 8F. Acute confusional state | | | |
| 9A. Haemolytic anaemia or | | | |
| 9B. Leucopenia (<4000/mm³) | | | |
| 9C. Lymphopenia (<1500/mm³) | | | |
| 9D. Thrombocytopenia (<100,000/mm³) | | | |
| Constitutional | | | |
| | | | |
van titres >1:320. Given that most of our patients had missing ANA/dsDNA and complement levels, the 2019 criteria would misclassify them, or they would not be eligible for SLE diagnosis.

SLE and HIV co-morbidity is associated with a reduction in SLE disease activity [11]. Our patient with concomitant SLE and HIV infection had poor HIV control despite a switch to second-line anti-retroviral agents. We do not know whether this is attributable to the SLE or other underlying resistance to her HIV drugs.

Understanding the disease burden of SLE might help us to understand the socioeconomic impact and the impact on quality of life associated with the condition and facilitate resource allocation to improve the quality of life of people with SLE. It might also provide clinicians and policy-makers with valuable information for prioritization of services and estimation of the impacts of policy and practice decisions [12].

**Recommendation**

SLE is a somewhat uncommon rather than a rare presentation in our settings and frequently occurs with and mimics RA. Most of our patients presented to care in late stages of the disease, with complications. Increased awareness among clinicians would hasten early disease identification and facilitate commencement of appropriate management and, possibly, provide a better overall prognosis. We recommend a heightened index of suspicion among clinicians for patients with compatible clinical features of SLE. We also recommend installation of regional registers for SLE in sentinel clinics across the different regions of country to define better the local and regional burden of SLE in Uganda.

**Limitation of the study**

The main limitation of our study lies in its retrospective design. We were unable to assess the outcomes of treatment. Another limitation relates to the serological testing, because both ANA and dsDNA are not performed routinely within the public health-care services and are procured privately with out-of-pocket costs for patients. Some of our patients were unable to have these tests performed and were managed based on the clinical symptoms, and some of these patients had their diagnoses much earlier, before the serological tests were available in Uganda, and the attending
rheumatologists thought that there would be no benefit of retesting these patients. Most of the patients were from the central part of the country, which is the main catchment area of the two clinics, thus we must have missed some of the diagnosed and undiagnosed cases in other parts of the country. However, this is the largest and the first study to describe the burden and characteristics of SLE in Uganda. Our data will inform clinical practice and guide future studies pertaining to the epidemiological trends, quality-of-life outcomes, treatment and treatment outcomes of SLE patients in Uganda.

Acknowledgements

We thank our study participants and the records offices of Mulago National Referral Hospital and Lincoln Medical. F.B. and M.K.: conceptualization. F.B., M.S. and M.K.: data collection and entry. All authors contributed to the drafting, review and final approval of the manuscript.

Availability of data and material: All data related to this study are available upon request.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

References

1 Fanouriakis A, Kostopoulou M, Alunno A et al. 2019 Update of the EULAR recommendations for the management of systemic lupus erythematosus. Ann Rheum Dis 2019;78:736–45.

2 Rees F, Doherty M, Grainge MJ, Lanyon P, Zhang W. The worldwide incidence and prevalence of systemic lupus erythematosus: a systematic review of epidemiological studies. Rheumatology 2017;56:1945–61. doi: 10.1093/rheumatology/kex260.

3 Banchereau J, Pascual V. Type I interferon in systemic lupus erythematosus and other autoimmune diseases. Immunity 2006;25:383–92. doi: 10.1016/j.immuni.2006.08.010.

4 Danchenko N, Satia JA, Anthony MS. Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden. Lupus 2006;15:308–18. doi: 10.1191/0961203306lu2305xx.

5 Tiffin N, Hodkinson B, Okpechi I. Lupus in Africa: can we dispel the myths and face the challenges? Lupus 2014; 23:102–11. doi: 10.1177/0961203313509296.

6 Fang K, Orr-Skirvin JA. Systemic lupus erythematosus, its treatment, and future directions. US Pharm 2019;44: 3–7.

7 Aringer M, Costenbader K, Daikh D et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis 2019;78:1151–9. doi: 10.1136/annrheumdis-2018-214819.

8 Dessein PH, Gledhill RF, Rossouw DS. Systemic lupus erythematosus in black South Africans. S Afr Med J 1988;74:387–9.

9 Ghosh A. Cutaneous manifestations of systemic lupus erythematosus. Indian J Rheumatol 2007;2:156–64. doi: 10.1016/S0973-3698(10)60060-X.

10 Kaul A, Gordon C, Crow MK et al. Systemic lupus erythematosus. Nat Rev Dis Primers 2016;2:16039. doi: 10.1038/nrdp.2016.39.

11 Mody GM, Patel N, Budhoo A, Dubula T. Concomitant systemic lupus erythematosus and HIV: case series and literature review. Semin Arthritis Rheum 2014;44:186–94. doi: 10.1016/j.semarthrit.2014.05.009.

12 Fatoye F, Gebraye T, Svenson LW. Real-world incidence and prevalence of systemic lupus erythematosus in Alberta, Canada. Rheumatol Int 2018;38:1721–6.