

Systemic lupus erythematosus: disease manifestations in patients from Central Punjab (Pakistan)

Systemic lupus erythematosus has variable systemic manifestations and severity across ethnic groups and geographical locations. Disease behavior recognition in the multiethnic and environmentally varied Indo-Pak subcontinent is hampered by a relative lack of organized census and health services. There are reports of severe systemic disease in the immigrant Western Pakistani population. We studied disease manifestations in 65 consecutively presenting patients with systemic lupus erythematosus at two tertiary care centers. Renal (65% of patients), pulmonary (61%) and cardiovascular (55%) involvement was much higher than data from most countries. Although variability in renal involvement has been best studied across different ethnic populations, we believe that the frequency of not only renal, but also other systemic involvement is higher and more severe in patients from Punjab (Pakistan).

KEYWORDS: Asia • prevalence • pulmonary • severity • systemic

Systemic lupus erythematosus (SLE) is an autoimmune disease with many manifestations, and each person's profile or list of symptoms is different. SLE can mimic other diseases, such as multiple sclerosis and rheumatoid arthritis, making it difficult to diagnose [101]. Although the most common patient is a young woman of child-bearing age, the illness affects patients of all ages, ethnic backgrounds, both sexes and all geographical locations. In total, 20% of all cases of lupus are diagnosed during the first two decades of life [1].

Although the generalization of body system involvement in SLE keeps evolving, the incidence and severity of systemic involvement vary not only from person to person, but also according to ethnic origin and geographical locations [2]. There are also other factors that likely influence the manifestation of disease, for example, family history, concurrent autoimmune diseases, sun-exposure, age of patient, education status and treatment-seeking behavior, background radiation exposure in local environment, hormonal status, emotional stress, drug intake and infections prevalent in the community (tuberculosis, infectious gastroenteritis and so on) [3,4]. Many developed countries maintain national registries of these relatively less common diseases [102]. Geographical and ethnic factors have such a strong influence on SLE manifestation that in the USA alone more than 50 papers on SLE from various geographically, environmentally and ethnically different states can be found on the Lupus Foundation of America website [103]. The incidence is reported to be one per 1000

in Caucasian individuals compared with four per 1000 in African–American individuals [101]. Similarly, a study of eight cases of large pericardial effusions due to SLE seen at Tygerberg Hospital (Cape Town, South Africa) reported that concurrent Raynaud's phenomenon, arthralgia and nephritis were the most common clinical features [5]. In a study of 36 cases of childhood SLE treated in the nephrology units of two large hospitals at Johannesburg (South Africa), rashes, polyarthritides and renal pathology were the most common clinical features seen at diagnosis [6]. In the same way prognosis of SLE remains highly variable and poor survival of SLE is still reported in certain ethnic groups such as Indian [7], black Caribbean and Hispanic populations [8].

In Pakistan, two excellent papers on SLE were published recently noting various aspects of disease manifestation from Rawalpindi and Karachi (Pakistan) [9,10]. In brief, the papers document a relatively high incidence of internal, life-threatening body system involvement than is documented in literature [9]. In addition, the projected survival curves show much lower chances of survival than is otherwise reported [10].

This prospective study on patients with SLE planned to concentrate on manifestations of the disease in various organ systems on the premise that ethnic, cultural and environmental conditions in midland Punjab are sufficiently different from the rest of this multiethnic environmentally varied country to warrant such a series. Midland or central Punjab is a plane with ample sunshine throughout the year

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and one of the hottest areas in the country. Compared with other parts of the country most of the village women work outdoors in fields, especially in crop seasons. Punjabi individuals are different in their ethnic origin from the Pothohari and Sindhi population, on which the abovementioned studies were conducted.

Methodology

This was a prospective descriptive study, conducted from June 2008 to June 2011 in the departments of medicine of Jinnah Hospital and General Hospital (Lahore, Pakistan). It included all SLE patients attending the outpatient departments of specialties or admitted through emergency. Written and verbal informed consent was obtained after an explanation of the study purpose and informing the patients that it is observational, in no way going to either interfere or modify treatment and that data will remain confidential. SLE diagnosis was established according to the American College of Rheumatology classification criteria [104]. Patients with discoid lesions only were not included.

Data were collected by taking a detailed history, physical examination and sorting out previous patient notes, laboratory reports and other information, and laboratory data gathered during patient admissions or outpatient visits. Assessment of organ system involvement was divided into specific and nonspecific involvement and was made using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology index [105]. Involvement of organs, clinically or on laboratory investigations, not covered by the damage index, for example, pleural effusions and anemia among others, were taken as nonspecific involvement and reported as such.

All the data were examined in detail by one of the authors who was also the consultant physician evaluating the patient. The data obtained was also seen anonymously by another consultant physician working in a different institution and a consensus was reached. Patients were informed that data collection ensures anonymity of their personal identity (i.e., name) and any photographic material disclosing such identity will not be included. In some cases, the treatment plan was changed after information was exchanged by the two physicians, although this was not the purpose of the study.

Antinuclear antibodies (ANA) were tested by an indirect immunofluorescence technique using HEp-2 cells (Euroimmun, Lübeck, Germany)

as the substrate. Anti-dsDNA antibodies were quantified by radioimmunoassay (Trinity Biotech Plc, Bray, Ireland) or enzyme-linked immunosorbent assay (EliA dsDNA, Pharmacia, Freiburg, Germany). The presence of anti-Ro/SSA, anti-La/SSB, anti-RNP or anti-Sm antibodies was detected by quantitative enzyme-linked immunosorbent assay screening (ORGENTEC, Mainz, Germany) and positive samples were analyzed by immunoblotting (INNO-LIA™, Innogenetics, Ghent, Belgium) or specific enzyme-linked immunosorbent assay (Orgentec). IgG or IgM anticardiolipin antibodies were quantified by specific anti-IgG or IgM enzyme-linked immunosorbent assay (Corgenix, CO, USA).

Statistics

All the data reported were descriptive and nominal and reported as percentages. Our target population was 'hospital presenting or admitted' patients with SLE and we intended to note their frequency of clinical manifestations. This population of hospital patients has ranged from 50 to a maximum of 1000 patients (in the Europa Lupus Project) in previous studies and averages at approximately 150–200 patients. Keeping this average sample size from previous studies, a sample size of 76 for our study was likely to reveal any differences in system involvement from previous studies, keeping a margin of error of 7%, CI at 95% and variability (proportions) of 50%. The sample size required is less if the variability (frequency of organ involvement) is on either side of 50% – that is, approximately 20 or 80%. We compared the frequency of our findings with other studies by Pearson's χ^2 test. Where our number of observations was small we corroborated our findings with Fisher's exact test. A p-value of <0.05 was taken as statistically significant.

Results

A total of 65 consecutively presenting patients with SLE comprised the study. There were four male patients (6.15%, with an approximate female to male ratio of 16:1). Patients' age ranged from 14 to 46 years, with a mean age of 28.45 ± 8.5 years. In total, 50% of the patients presented were between 19 and 35 years of age. The mean time to diagnosis from onset of disease-related complaints was 4.35 ± 2.3 years. We did not find a later age peak of SLE (after 55 years) in our patients.

FIGURE 1 shows the frequency of organ system involvement at presentation in percentages. Patients most frequently had musculoskeletal (89%), hematological (85%), muco-cutaneous

(72%), renal (68%) or cardiovascular (55%) problems.

TABLE 1 provides details of cumulative frequency of organ system involvement divided into specific and nonspecific involvement, as discussed in the 'Methodology' section. We adopted this method to reduce personal bias and selective reporting.

TABLE 2 draws comparison of systemic involvement between this study and a study from Karachi [10] and another large multicenter European study with a predominantly Caucasian population [11]. A comparison of the frequencies of organ system involvement by χ^2 test with the two studies shows a rather high rate of renal, pulmonary and neurological involvement in this study. Of note is the pulmonary involvement, which remains under-reported in most of the studies.

Discussion

SLE shows differences in its incidence, preferential organ system involvement and its severity according to geographical location, ethnicity, environmental factors and multiple other known and unknown factors. This series of patients shows that patients with SLE from midland Punjab may be sufficiently different from western patients and even from patients from other areas of the same country in presentation and severity of internal organ involvement, including renal disease.

SLE is a disease typically found in young women during their reproductive years. Mean age at presentation in this study was 28 years, while another small study comprising 50 patients from Pakistan report a mean age of presentation of 22 years, and another study from the same country comprising 198 patients presenting to a tertiary care center reported it to be 31 years [9,10]. A Euro Lupus Project with data from 1000 patients presenting to European hospitals reported age at diagnosis to be 31 years [11]. The same project reports a mean delay in diagnosis from presenting symptoms to be 2 years, which in this study was found to be more than 4 years. This seems understandable when considering the relative illiteracy of the community and the lack of access to specialized healthcare, which is further compounded by the problem of a lack of specialized rheumatological services even in tertiary care health centers.

The most striking external manifestations of SLE are skin rashes, in particular, malar and discoid rash, photosensitivity, and their point prevalence has been found to be too low (30%) to be always diagnostically helpful in southeast Asian populations [12]. Even in European

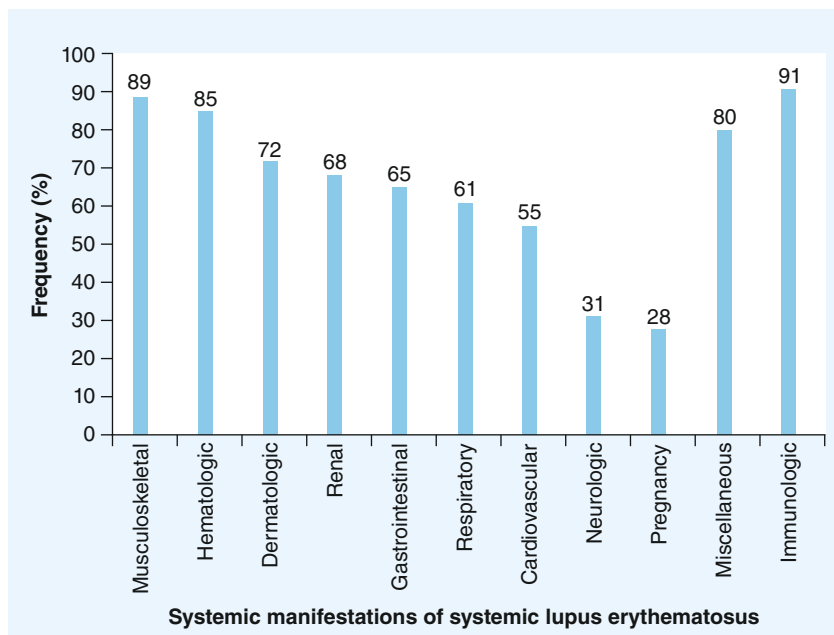


Figure 1. Frequencies (in percentages) of systemic manifestations of systemic lupus erythematosus in this series.

populations with relatively fair complexions, where such rashes appear more striking, a typical SLE rash was a presenting feature of no more than 50% of patients [11]. Most of the studies, however, report the cumulative prevalence of rash during disease duration, which in this study was found to be 70%; relatively lower than the standard cumulative prevalence of 80–90%. It is important that rash should not be taken as *sine qua non* for SLE and its absence should not in any case rule out SLE.

Major morbidity and mortality from SLE arises from internal organ involvement primarily renal, cardiopulmonary and CNS, in that order. Southeast Asian individuals have been found to have a higher prevalence of SLE than Caucasian individuals. For example, Asian individuals of Indian, Pakistani and Bangladeshi origin who resided in Leicester (UK), were three-times more likely to develop SLE than Caucasian individuals [13]. This was confirmed by another study conducted in Birmingham (UK), where Asian individuals of the same origins, irrespective of their birth place, were found to experience over twice the lupus prevalence rate of Caucasians (Asian populations 46.7 per 100,000 persons vs Caucasian individuals 20.7 per 100,000 persons) [14]. In addition, Asian individuals have been noted to have severe disease with higher morbidity and mortality compared with Caucasian individuals [15]. The LUMINA study group showed a higher cumulative frequency of renal disease in African-American (68.9%) and Hispanic (60.6%)

Table 1. Cumulative frequencies of involvement of various organ systems in systemic lupus erythematosus patients in this series.

System involved	Type of involvement	Clinical features	Frequency (%)
Musculoskeletal	Nonspecific [†]	Arthralgias	85
		Arthritis	28
		Muscle atrophy/weakness	80
	Specific [‡]	Deforming arthritis	10
		Osteoporotic fractures	8
		Avascular necrosis	8
Hematologic	Nonspecific	Anemia	85
		Hemolytic anemia	20
		Thrombocytopenia	40
		Lymphocytopenia	45
Dermatologic	Nonspecific	Malar rash	35
		Photosensitivity	20
		Discoid rash	15
		Alopecia	60
			72
Renal	Specific	GFR <50 ml/min	50
		Nephrotic proteinuria	20
		ESRD ^{†,‡}	35
			68
Gastrointestinal	Nonspecific	Ascites	30
		Hepatosplenomegaly	25
		Diarrhea	40
		Vomiting	40
	Specific	Bowel infarction	5
		Strictures	3
		Upper gastrointestinal surgery	3
			65
Pulmonary	Nonspecific	Pleural effusion	30
		SLE pneumonitis	10
		Pulmonary tuberculosis	8
	Specific	Pulmonary hypertension	20
		Pulmonary fibrosis	20
		Shrinking lung	5
		Pleural fibrosis	5
		Pulmonary infarction	18
			61
Cardiovascular	Specific	Pericarditis	20
		Angina/CABG	5
		Myocardial infarction	5
		Cardiomyopathy	30
		Valvular disease	10
			55
Neurologic	Specific	Cognitive impairment	8
		Seizures	24
		CVA	8
		Neuropathy	12
		Transverse myelitis	3
			31

[†]Organ system affected by SLE-related disease process not otherwise defined in damage index of SLE [14].

[‡]Specific involvement of organ system in the form of damage defined according to damage index of SLE [14].

[§]Anticardiolipin antibodies were checked in 40% of patients only on clinical suspicion. Percentage given is for total number of SLE patients.

ANA: Antinuclear antibodies; CABG: Coronary artery bypass graft; CVA: Cerebrovascular accident; ESRD: End-stage renal disease; GFR: Glomerular filtration rate; SLE: Systemic lupus erythematosus.

Table 1. Cumulative frequencies of involvement of various organ systems in systemic lupus erythematosus patients in this series (cont.).

System involved	Type of involvement	Clinical features	Frequency (%)
Miscellaneous	Nonspecific	Severe weight loss	80
		Fever	74
		58	
	Specific	Premature gonadal failure	20
		Skin ulcerations	5
		Diabetes	8
		Malignancy	0
Ocular	Specific	Cataract	15
		Optic atrophy/retinal changes	7
Immunological tests	Specific	ANA	88
		dsDNA	58
		Anti-Sm	46
		Anticardiolipin antibodies [§]	20
		Rheumatoid factor	8

[†]Organ system affected by SLE-related disease process not otherwise defined in damage index of SLE [14].

[‡]Specific involvement of organ system in the form of damage defined according to damage index of SLE [14].

[§]Anticardiolipin antibodies were checked in 40% of patients only on clinical suspicion. Percentage given is for total number of SLE patients.

ANA: Antinuclear antibodies; CABG: Coronary artery bypass graft; CVA: Cerebrovascular accident; ESRD: End-stage renal disease; GFR: Glomerular filtration rate; SLE: Systemic lupus erythematosus.

individuals than Caucasian (29.1%) individuals after a mean follow-up of 5.5 years [16]. Renal disease is also more commonly reported in Asians. It was diagnosed in 64 and 69.3% in the series of Boey *et al.* [17] and Lee *et al.* [18], respectively, in patients presenting to two tertiary care hospitals. It should be noted, however, that it has been suggested that differences in access to medical care could account for the variation in organ damage prevalence and mortality observed among SLE patients of different ethnicities [19]. This is clearly reflected in the Euro-lupus project, which showed a lower frequency of most SLE manifestations during the last 5 years of this prospective study (1995–2000) [20], compared with the cumulative clinical manifestations during the initial 5 years of the study (1990–1995) [21]. For instance, the frequency of active lupus nephropathy during the last 5 years was 6.8% [20], whereas a cumulative prevalence of 22.2% during the initial 5 years of the study was found [21]. These lower frequencies in the last 5 years probably reflect the effect of therapy and of medical care during the study, but could also be owing to a less severe activity of the disease after a long time of evolution.

Environmental triggers, such as infections and ultraviolet light, constitute another important group of factors determining the burden of SLE. Infectious agents may initiate SLE onset by disturbing immunoregulation, causing damage to tissue, which leads to the release of antigens [22]. Varying levels of sunlight exposure may also contribute to disparities in SLE burden in different parts of the world and different areas of the same

countries. Both the above factors are present and may be operative in our patients' population.

Apart from prevalence, the study from Leicester also compared the systemic involvement of SLE in Asian (Indo-Pak) and Caucasian populations. The Asian subset had less frequent photosensitivity and oral ulcers, but the incidence of renal (80 vs 52%), neuropsychiatric (40 vs 17%) and myalgic (37 vs 8%) disease in SLE was found to be significantly higher [13]. Two studies from Pakistan, however, found the incidence of renal involvement to be 38 and 33% [9,10]. In this study, we have found renal involvement rates to be close to the Leicester study. Moreover, 50% of our patients had mild-to-moderate renal failure rather than renal involvement only (proteinuria and casts, among others).

Neuropsychiatric SLE incidence is also reported to be higher in the Pakistani Asian population compared with both western and other Asian populations [10,13]. The figures of neuropsychiatric involvement in our study match that of Rabbani *et al.* from the same country [10].

Pulmonary involvement in SLE is a relatively neglected area in studies reporting on the frequencies of systemic involvement in SLE. It is either not reported at all or if it is reported, no further breakup into individual pulmonary diseases is given. Most of the research reports serosal involvement in SLE [10,11,15]. The study by Rabbani *et al.*, which included 198 patients, surprisingly could not find evidence of pulmonary damage in their cohort of patients who were retrospectively evaluated, except for serositis [10]. A retrospective

study from Saudi Arabia comprising 624 patients presenting to a university hospital reported a frequency of 36% pulmonary involvement, including mostly serositis (27.4%), but it reported other defined pulmonary involvement at a low rate (all below 5%) [23]. We have found a relatively high cumulative rate of pulmonary involvement at presentation (61%). Half of the involvement was accounted for by pleural effusions, followed by pulmonary infarction, pulmonary fibrosis, pleural fibrosis and shrinking lung. It is possible that part of the reason for these varied manifestations were due to the delay in diagnosis (average: 4.35 years).

The frequency of pericardial involvement (20%) was mostly on par or slightly higher than those noted in other series. However, we found a rather high prevalence of incipient or overt cardiac failure (30%), which to our knowledge has not been reported elsewhere. We believe that severe organ involvement, later presentation, low socioeconomic status, repeated pregnancies and childbirths, and high prevalence of anemia may be some of the contributory factors towards cardiomyopathy. It is worth noting that 28% of our patients presented during pregnancy.

Positivity for ANA with modern indirect immunofluorescence testing generally approaches above 95% using the HEp-2 cell line as is suggested by the position statement of the ACR [106]. While using the recommended technique, we found

ANA positivity in no more than 87% of our patients. The study in Rawalpindi by Ahmed *et al.* found ANA positivity in all of their 50 patients using rodent liver as a substrate [9]. Rabbani *et al.* in their study in Karachi had a rather similar ANA positivity (86%) to our study, although the antigenic substrate was not detailed. Instead of attributing low ANA positivity to patient characteristics we think, similar to Rabbani *et al.*, that an antigenically inadequate substrate could partly account for this. Some of our patients were already on immunosuppressive treatment at presentation to our facilities, which could also partly explain it.

We found anemia to be a universal finding in our cohort of patients (85%). Iron deficiency (due to dietary factors, economic status, anorexia, diarrhea or blood loss from liberal NSAID use), anemia of chronic disease and hemolysis were some of the contributory factors. The incidence of thrombocytopenia and lymphocytopenia was mostly on par with other studies [10,23]. Although nonspecific abdominal manifestations were rather frequent (ascites, hepatosplenomegaly and diarrhea among others), SLE-specific definable gut involvement was about 10%. Severe weight loss was very common (74%) and 58% of patients had fever as one of the prominent presenting features.

Our study included prospective data collection compared with the retrospective nature of most

Table 2. Comparison of the clinical features of systemic lupus erythematosus found in this study with that found in Karachi (Pakistan) and in a western population.

Clinical feature	Central Punjab (Pakistan) study n = 65 (%)	Karachi study n = 198 (%)	p-value	European study n = 1000 (%)	p-value
Arthritis	23 (35.38)	76 (38)	0.665	481 (48.1)	0.046
Malar rash	26 (40)	60 (30)	0.148	311 (31.1)	0.134
Discoid rash	13 (20)	30 (15)	0.359	78 (0.78)	0.0007
Photosensitivity	15 (23)	12 (6)	0.0001	229 (22.9)	0.946
Serositis	23 (35.38)	44 (22)	0.034	160 (16.0)	0.0001
Pericardial effusion	12 (18.46)	18 (9)	0.039	NA	–
Pleural effusion	15 (23)	33 (17)	0.245	NA	–
Renal involvement	44 (67.69)	89 (45)	0.001	279 (27.9)	0.0001
Neurologic involvement	13 (20.00)	52 (26)	0.309	194 (19.4)	0.905
Thrombocytopenia	23 (35.38)	56 (28)	0.698	134 (13.4)	0.0001
Lymphocytopenia	39 (60.00)	107 (54)	0.401	NA	–
Fever	39 (60.00)	105 (53)	0.327	166 (16.6)	0.0001
Lung parenchymal involvement	31 (47.69)	NA	–	NA	–

NA: Not available.
Data taken with permission from [10,11].

studies. It does, however, suffer from limitations. A cohort of 65 patients is rather small and some findings with lower incidence can possibly be attributed to chance. Although we included all SLE patients presenting to hospital without selection bias, the possible existence of referral bias of severer cases towards a tertiary care hospital cannot be excluded, possibly leading to an over-representation of severity and the extent of organ involvement in this hospital-based study compared to that prevalent at the community level.

In conclusion, midland Punjabi patients with SLE are very likely to be different in their organ system involvement from European or Asian patients, or even other patients from different regions of the country. While the differences in SLE renal involvement have been extensively covered, other life- and organ-threatening diseases in the lungs, heart and GI tract possibly remains less well explored in Asian and Pakistani populations.

Future perspective

Organ system involvement in SLE is highly variable across ethnic groups and geographical locations. While literature abounds with variability of renal manifestations, other organ

manifestations, for example, respiratory, cardiovascular and gastrointestinal, although less commonly sought for and reported, nevertheless, are of equal importance. Their elaboration, with regards to severity and incidence in different ethnic groups, such as that for renal involvement, awaits researchers attention and may be the focus of future research.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

Background

- Systemic lupus erythematosus (SLE) is variable in organ system involvement and the severity of involvement in different ethnic groups and geographical locations.
- Even within a single country with variable sun exposure and environmental conditions, and variable ethnic populations (such as in Pakistan), disease manifestations may be widely different.
- Socioeconomic status, general literacy, health education and cultural patterns strongly affect disease-seeking behavior and treatment compliance, but these parameters are difficult to standardize and evaluate across diverse communities.

Methodology

- Consecutive patients of SLE presenting to all the departments of two large tertiary care hospitals were evaluated for involvement of various organs by disease over a 2-year period.
- Involvement of organs was labeled as specific (if damaged by SLE according to Systemic Lupus International Collaborating Clinics/ American College of Rheumatology criteria) or nonspecific if otherwise involved by SLE.

Statistics

- Frequency of organ involvement in our patients was compared by Pearson's χ^2 test with other studies on hospitalized patients.

Results

- Frequency of renal, pulmonary and neurological involvement was higher in this study than other Asian or Western studies on hospitalized patients. Prevalence of fever, thrombocytopenia and serosal involvement was also higher compared with a western study (the Europa Lupus Project). All above differences were statistically significant.

Discussion

- Renal involvement is a frequent organ- and life-threatening manifestation of SLE that has been seen to have widely different incidence and severity amongst different ethnic groups. Descendants of Africans are the most severely affected.
- Although respiratory, cardiovascular, CNS and other organ involvement have a lower incidence than renal involvement, they are nevertheless important as far as morbidity and mortality are concerned.
- Incidence of extra-renal manifestations of SLE is less well reported in research literature.
- In the Pakistani population of Central Punjab origin, a high incidence of extra-renal manifestations of SLE is seen in hospitalized patients, which may be of equal importance, but less commonly noted and documented.

References

Papers of special note have been highlighted as:

▪ of interest

▪▪ of considerable interest

- 1 Klein-Gitelman M, Reiff A, Silverman ED. Systemic lupus erythematosus in childhood. *Rheum. Dis. Clin. North Am.* 28(3), 561–577, vi–vii (2002).
- 2 Lau CS, Yin G, Mok MY. Ethnic and geographical differences in systemic lupus erythematosus: an overview. *Lupus* 15(11), 715–719 (2006).
- **Very good review giving, as the name suggests, a summary of ethnic differences in systemic lupus erythematosus manifestations, although many of the studies quoted give data from Asian immigrants in the western hemisphere and the USA instead of natives.**
- 3 Conti G, Coppo R, Amore A. Pathogenesis of systemic lupus erythematosus. *G. Ital. Nefrol.* 29(Suppl. 54), S84–S90 (2012).
- 4 Mok CC, Lau CS. Pathogenesis of systemic lupus erythematosus. *J. Clin. Pathol.* 56(7), 481–490 (2003).
- 5 Weich HS, Burgess LJ, Reuter H, Brice EA, Doubell AF. Large pericardial effusions due to systemic lupus erythematosus: a report of eight cases. *Lupus* 14(6), 450–457 (2005).
- 6 Faller G, Thomson PD, Kala UK, Hahn D. Demographics and presenting clinical features of childhood systemic lupus erythematosus. *South Afr. Med. J.* 95(6), 424–427 (2005).
- 7 Murali R, Jeyaseelan L, Rajaratnam S, John L, Ganesh A. Systemic lupus erythematosus in Indian patients: prognosis, survival and life expectancy. *Natl Med. J. India* 10, 159–164 (1997).
- **A research article of disease manifestations in Indian patients. The study is, however, retrospective and hospital patient based.**
- 8 Contreras G, Lenz O, Pardo V *et al.* Outcomes in African Americans and Hispanics with lupus nephritis. *Kidney Int.* 69, 1846–1851 (2006).
- 9 Ahmed TA, Ikram N, Hussain T *et al.* Clinical and laboratory features of systemic lupus erythematosus (SLE) in Pakistani patients. *J. Pak. Med. Assoc.* 52(1), 12–15 (2002).
- 10 Rabbani MA, Habib HB, Islam M *et al.* Survival analysis and prognostic indicators of systemic lupus erythematosus in Pakistani patients. *Lupus* 18(9), 848–855 (2009).
- **One of the best and largest series of articles on systemic lupus erythematosus from Pakistan. Its drawbacks are that it is hospital based rather than community based and is retrospective in nature.**
- 11 Cervera R, Khamashta MA, Hughes GR. The Euro-lupus project: epidemiology of systemic lupus erythematosus in Europe. *Lupus* 18(10), 869–874 (2009).
- **A large series of disease manifestations from European hospitals. We used data from this article to compare disease manifestations in our cohort of patients.**
- 12 Kole AK, Ghosh A. Cutaneous manifestations of systemic lupus erythematosus in a tertiary referral center. *Indian J. Dermatol.* 54(2), 132–136 (2009).
- 13 Samanta A, Roy S, Feehally J, Symmons DP. The prevalence of diagnosed systemic lupus erythematosus in whites and Indian Asian immigrants in Leicester city, UK. *Br. J. Rheumatol.* 31, 679–682 (1992).
- **An older research article that gives good insight into how Indian individuals differ in systemic lupus erythematosus manifestations to the immigrant population of the UK. A community-based survey.**
- 14 Johnson AE, Gordon C, Palmer RG, Bacon PA. The prevalence and incidence of systemic lupus erythematosus in Birmingham, England. *Arthritis Rheum.* 38, 551–558 (1995).
- 15 Samanta A, Feehally J, Roy S, Nichol FE, Sheldon PJ, Walls J. High prevalence of systemic disease and mortality in Asian subjects with systemic lupus erythematosus. *Ann. Rheum. Dis.* 50, 490–492 (1991).
- 16 Bastian HM, Roseman JM, McGwin G Jr *et al.* For the LUMINA Study Group. Systemic lupus erythematosus in three ethnic groups. XII. Risk factors for lupus nephritis after diagnosis. *Lupus* 11, 152–160 (2002).
- **Differences in lupus nephritis is the best studied differential organ involvement across geographically and ethnically different populations.**
- 17 Boey ML, Peebles CL, Tsay G, Feng PH, Tan EM. Clinical and autoantibody correlations in Orientals with systemic lupus erythematosus. *Ann. Rheum. Dis.* 47, 918–923 (1988).
- 18 Lee SS, Li CS, Li PCK. Clinical profile of Chinese patients with systemic lupus erythematosus. *Lupus* 2, 105–109 (1993).
- 19 Maskarinec G, Katz AR. Prevalence of systemic lupus erythematosus in Hawaii: is there a difference between ethnic groups? *Hawaii Med. J.* 54, 406–409 (1995).
- 20 Cervera R, Khamashta MA, Font J *et al.* Morbidity and mortality in systemic lupus erythematosus during a 10-year period. A comparison of early and late manifestations in a cohort of 1,000 patients. *Medicine (Balt.)* 82, 299–308 (2003).
- 21 Cervera R, Khamashta MA, Font J *et al.* Morbidity and mortality in systemic lupus erythematosus. A multicenter prospective study of 1,000 patients. *Medicine (Balt.)* 78, 167–175 (1999).
- 22 Ramsey-Goldman R, Manzi S. Systemic lupus erythematosus. Women and Health. *Acad. Press* 704 (2000).
- 23 Al Arfaj AS, Khalil N. Clinical and immunological manifestations in 624 SLE patients in Saudi Arabia. *Lupus* 18(5), 465–473 (2009).
- **Websites**
- 101 Lupus UK. Romford Essex © 2011 LUPUS UK. www.uklupus.co.uk (Accessed 30 March 2004)
- 102 CDC: current projects: lupus registries. www.cdc.gov/arthritis/funded_science/current/lupus_registries.htm (Accessed 12 April 2012)
- 103 Lupus Foundation of America© 2012, Washington, DC 20036. www.lupus.org/newsite/index.html (Accessed 29 October 2012)
- 104 ACR. 1997 Update of the 1982 ACR revised criteria for classification of systemic lupus erythematosus. www.rheumatology.org/practice/clinical/classification/SLE/1997_update_of_the_1982_acr_revised_criteria_for_classification_of_sle.pdf#toolbar=1 (Accessed 12 April 2012)
- 105 ACR. System lupus international collaborating clinics/american college of rheumatology damage index for systemic lupus erythematosus. www.rheumatology.org/practice/clinical/indexes/slicc.pdf (Accessed 12 April 2012)
- 106 ACR. Position statement: methodology of testing for antinuclear antibodies. approved by the committee on rheumatologic care. www.rheumatology.org/practice/clinical/position/ana_position_stmt.pdf#search=%22ana%20testing%20position%20statement%22 (Accessed 12 April 2012)