CLINICO-SEROLOGICAL PROFILE AND DISEASE SEVERITY IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) ATTENDING A TERTIARY CARE CENTRE IN CENTRAL KERALA

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ABSTRACT

BACKGROUND

Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disease characterised by the production of multiple autoantibodies. There is limited available data regarding the presentation patterns of SLE in central Kerala and this is important in generating epidemiological data and also to plan further genetic and serological studies in this population. The study primarily involved the presentation patterns of SLE admitted at a medical college, Kerala, from June 2011 to June 2012.

MATERIALS AND METHODS

An observational cross-sectional and invasive biopsy study was carried out on 40 SLE patients aged 13-50, fulfilling the ACR criterion. The data were analysed using the EPI-INFO statistical package, Chi-square test and p-value.

RESULTS

The commonest presentation found was fever followed by polyarthritis and Lupus Nephritis (LN). In patients with LN, class IV was common followed by class III, class II and class V. Most of the patients had high SLEDAI at presentation with a mean SLEDAI of 17. Autoimmune haemolytic anaemia was present in 22.5%, secondary antiphospholipid antibody syndrome in 20% and neuropsychiatric lupus in 15%. Anti-dsDNA positivity was documented in 97.5% of the patients in this study.

CONCLUSION

In our study, SLE was found more common in females in their third decade. The commonest pattern of the presentation was fever followed by polyarthritis and renal involvement. The incidence of oral ulcers, haematological abnormalities and proteinuria manifestations was high in this region compared to rest of India and western data.

KEYWORDS

Systemic Lupus Erythematosus, Antinuclear Antibody, Lupus Nephritis (LN).

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BACKGROUND

Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disease characterised by the production of multiple autoantibodies. Prevalence of clinical and immunologic manifestations is about 40 per 1,00,000 populations and 14 to 60 per 1,00,000 in western and northern populations, respectively.[1,2] There is limited available data regarding the presentation patterns of SLE in central Kerala and this is important in generating epidemiological data and also to plan further genetic and serological studies in this population.

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Aims and Objectives- This study attempts to find out the presentation patterns of SLE in patients from central Kerala, and also to assess the disease activity at presentation and to study the clinical and serological profile among the enrolled patients.

MATERIALS AND METHODS

We carried out an observational cross-sectional study on the presentation patterns of SLE patients. The study was conducted on patients who reported to the Government Medical College, Thrissur, Kerala, from June 2011 to June 2012. Total 40 patients aged >13 years with a confirmed diagnosis of SLE were considered for the study as per American College of Rheumatology (ACR). Consecutive patients were enrolled into the study from both Inpatient Department (IPD) and Outpatient Department (OPD) of this centre. Informed consents were taken from the patients or close relatives. The study group was evaluated with a clinical history, clinical examination and relevant investigations. Invasive procedures like renal biopsy were done as per the discretion of the treating physician in indicated cases. The

data were analysed using the EPI-INFO statistical package and a SLEDAI scoring were also performed. Categorical variables were analysed using Chi-square test and p-value.

RESULTS

Age and Sex Wise Distribution of Cases- The study group involved 40 patients between the age of 13-50 years with a mean age of 28.1 ± 9.3 (27.8 ± 9.2 years for female and 31.7 ± 10.6 years). The study consisted of 37 females and 3 males with a ratio of 12:1. Therefore, the study involved the maximum number of females from a third decade of life. Among 37 females, 20 were married and 7 were unmarried. Among the 20 married females, 4 (20%) had a history of stillbirth/abortion. Among 4 patients with a history of abortion, 3 were positive for Antiphospholipid antibodies (APLA).

ARA Criteria- All the patients satisfied the study as per American Rheumatism Association (ARA) criteria for the classification of the SLE (Figure 1). Immunological and Antinuclear Antibody (ANA) criteria were found in 39 out of 40. The other such as oral ulcers, arthritis, haematological and renal manifestation was more than 50% and satisfied the required criteria. Least satisfied criteria were discoid lupus (5%) followed by serositis (7.5%).

Presentation Pattern Distributions- Fever was the commonest among all the presentation and found in 34 cases. The other presentations primarily included polyarthritis, LN and skin lesions. Out of 11 patients, 10 presented with a malar rash, 2 had discoid lupus erythematosus and one had lichen planus. There were 3 patients with thrombotic manifestations of which deep vein thrombosis of the leg was found in 2 and arterial thrombosis of leg vessels in 1 patient. Total 5 patients came with bleeding manifestations of which 4 patients had skin and gum bleeding, while 1 had Upper Gastrointestinal Bleeding (UGIB) (haematemesis and melena). Out of 6 patients with neuropsychiatric illness, 4 presented with seizures and 3 with psychosis. Rare patterns of manifestations included protein losing enteropathy, pandysautonomia, lupus pneumonitis with shrinking lung syndrome and lupus hepatitis (Table 1).

Renal Involvement- The renal involvement was observed in 47 patients. Renal involvement, which chiefly included common abnormality like proteinuria was detected in the 50% patients. Microscopic haematuria, pyuria and cast were observed in 27.5%, 27.5% and 15% patients, respectively, (Table 2). LN was significantly related to anaemia with p=0.0008 and hypoalbuminaemia with p=0.003. Among the 20 study patients with LN who underwent renal biopsy, 3 patients were classified to have WHO class II LN (15%), 7 had class III (35%), 8 were with class IV (40%) and 2 were with class V (10%) (Table 3). Out of the 8 patients with hypertension, 7 presented with LN. The association was statistically significant with p=0.012. Out of 7 LN with hypertension, 6 cases had a renal biopsy finding of WHO class IV nephritis and 1 had class V. 20 patients did not have proteinuria quantifiable unto the mark of LN, in the remaining 20 cases, the majority (12) had proteinuria of 1000-3000 mg/day and 5 patients had proteinuria 3000 mg/day or above.

Haematological Involvement- Haematological abnormalities were detected in 62.5% patients. The abnormalities included anaemia, leucopenia, lymphopaenia, thrombocytopaenia, pancytopenia, Direct Coomb's Test (DCT) positivity and detection of antiphospholipid antibodies (including the APLA syndrome). Anaemia was the most common haematological abnormality detected and was seen in 60% patients. Severe anaemia Hb <5 was seen in 1 patient. The mean Hb was 9.53 g/dL ± 2.38. Lowest Hb was 3.0 and highest was 14 g/dL.

Autoimmune Haemolytic Anaemia (AIHA) was observed in 22.5% patients. The mean Hb in these patients at presentation was 7.19 g/dL. Iron Deficiency Anaemia (IDA) as evidenced by a microcytic hypochromic blood picture was present in 20.0% patients. The mean haemoglobin among IDA patients was 8.61 g/dL. The presence of anaemia was associated with LN with a statistically significant p=0.0008. The mean WBC count was 6300 ± 3882/mm^3 at presentation. Lowest count was 1100/mm^3 and highest was 22,500/mm^3. Leucopenia was observed in 17.5% patients. Lymphocytopenia was the most common white blood cell abnormality detected being present in 32.5% patients. The mean lymphocyte count was 1877 ± 1392. Lowest is 264 and highest is 7268.

The presence of lymphopaenia was significantly associated with renal involvement (p=0.002), but not with arthritis (p=0.06). Thrombocytopenia was present in 22.5% patients; out of which, lowest was 23,000/mm^3. A correlation between the presence of APLA and thrombocytopaenia was found (odds ratio=7.54). However, the association was not statistically significant (p=0.06). Association of thrombocytopaenia to bleeding manifestation was also not statistically significant (p=0.188). Pancytopenia was found only in 3 patients.

Mean Erythrocyte Sedimentation Rate (ESR) of patients was 97.5 mm/hour. Lowest was 26 and highest 150 mm/hour. Total 57.5% out of 40 had an ESR of 100 mm/hour or more. A positive direct Coombs test was found in 22.5% patients. Anti-dsDNA positivity was documented in 97.5% of the patients in this study. Low C3 and C4 levels were present in 55% and 37.5% patients, respectively. Low C3/C4 is significantly associated with LN (p=0.007). It is also strongly related with lymphopaenia (p=0.012). Most of the patients had a high total SLEDAI indicating high disease activity at presentation. 52.50% had a score between 11 and 20. The mean SLEDAI at presentation was 17.25, lowest being 4 and highest 54.

Neurological Features- Out of the 40 patients, 15% had neuropsychiatric symptoms. Depression was seen in 12.5%, seizures in 10%, psychosis in 7.5% and lupus headache in 4%.

Gastrointestinal Features

Gastrointestinal manifestations were presented in with bleeding signs like skin and gum bleed and GI bleeding in total 5 patients. One patient had gangrene of fingers of both hands, while other had a vasculitic ulcer of duodenum and colon leading to GI bleed.

Sl. No.	Patterns of Presentation	Number of Cases
1.	Fever	34 (85.0%)
2.	Polyarthritis	27 (67.5%)
3.	Lupus nephritis	20 (50.0%)
4.	Skin lesions	11 (27.5%)
5.	Bleeding	5 (12.5%)
6.	Fatigue	5 (12.5%)
7.	Seizures	4 (10.0%)
8.	Psychosis	3 (7.50%)
9.	Arterial/venous thrombosis	3 (7.50%)
10.	Lupus pneumonitis	2 (5.00%)
11.	Lupus hepatitis	1 (2.50%)
12.	Protein losing enteropathy	1 (2.50%)
13.	Pandysautonomia	1 (2.50%)

Table 1. Distribution of the Patterns of Presentations of SLE in Study Cohort

Urinary Abnormality	Number of Cases	Percentage
Proteinuria	20	50%
Haematuria	11	27.5%
Pyuria	11	27.5%
Cast	6	15%

Table 2. Urinary Abnormalities in Lupus Nephritis Patients

Renal Biopsy	Number of Cases	Percentage
Class I	0	-
Class II	3	15%
Class III	7	35%
Class IV	8	40%
Class V	2	10%
Class VI	0	-

Table 3. Class of Lupus Nephritis in Renal Biopsy

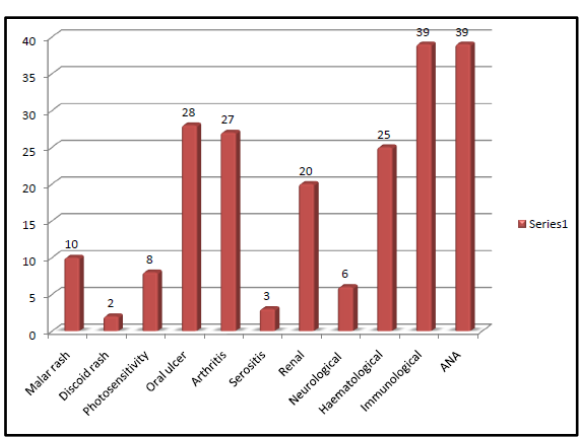

Figure 1. Frequency of Patients who Satisfied Each Diagnostic Criterion

DISCUSSION

In the present study, the mean age of the patients was 28.1 years (males- 31.7, females- 27.8). In similar studies conducted by Malaviya A.N. and Wallace et al reported the median age of onset in SLE is 24.5 and 40.4, respectively.[3,4] In these studies, the age of onset in males was later than that in females. In the present study, female (37) were in majority compared to male (3) in the ratio of 12:1. The similar expected result was observed by Cameron S.J. et al (8:1, M:F) and Malaviya A.N. (11:1, M:F).[3,5] Adverse pregnancy outcomes attributed to the presence of antiphospholipid antibody included late foetal death and recurrent pregnancy loss, which was well established in various studies including that was done by Parke A.L. et al.[6]

Fever was the commonest pattern of presentation of SLE in our study (85%). Wallace D.J. has described an incidence of 84% in their series.[4] The second common clinical feature was arthritis presented in 67.5% of patients. Wallace D.J. studied 520 cases and observed 83-92% of patients had arthritis. Kumar A. described the incidence of arthritis to be 57%, 68% and 75% analysing different series of patients from North, South and Eastern India, respectively.[7] Total 3 patients (7.5%) had definite evidence of myositis with raised CPK and muscle tenderness. This is in concordance with the description by Wallace who stated myositis is relatively uncommon (7 to 15%).[4]

The LN symptom was seen in 50% of patients. According to Seligman V.A., clinically evident renal disease occurs in approximately 50% of the patients with SLE.[8] In another report of 1378 patients with SLE in the United States, renal disease was present in 32% within one year of diagnosis.[9] Malar rash was present in 25% of our patients. The observation in a series described by Wallace D.J. with an incidence of 40-60% occurrence of classic malar rash is not seen in our patients probably due to darker skin texture.[4] Oral ulcers were present in 70% of our patients. Malaviya reported a 50% incidence of oral ulcers in his patients from Eastern India.[3] In a series of studies described by Wallace DJ, oral ulcers were present in 7-36% of the cases.[10] Alopecia occurs in a majority of patients with SLE during their illness.[11] In this study, 45% of patients had a history of hair loss.

Out of 40 patients, 6 (15%) had neuropsychiatric symptoms, out of which, depression was seen in 5 patients (12.5%), seizures in 4 (10%), psychosis in 3 (7.5%) and lupus headache in 1 (4%). One of the South Indian studies by N. K. Thulaseedharan et al found headache (55.6%), seizures (20.51%) and psychosis (16.2%).[12] In our study, 5 patients (12.5%) had bleeding manifestations, 4 had skin and gum bleeding, while 1 had gastrointestinal bleeding. The bleeding was associated with thrombocytopaenia in 2 of them. The patient with GI bleed had a vasculitic ulcer of duodenum and colon. There are no much comparative studies available on bleeding manifestations in SLE patients. Rare patterns of the presentation included protein losing enteropathy, pandysautonomia, lupus pneumonitis with shrinking lung syndrome and lupus hepatitis. There are only rare case reports of lupus patients presenting with shrinking lung syndrome.

Hypertension was the most common past medical illness found in 20% of our patients. In an analysis of 9 published series of SLE patients, a prevalence rate of 12-49% has been described.[13] One study showed a frequent association between hypertension and renal disease in SLE

suggesting the correlation between them.[13] Out of the 8 patients with hypertension, 7 had LN. The association was statistically significant with p=0.012. Our study had 4 patients with a past history of diabetes mellitus, 2 with hypothyroidism and 1 with thyrotoxicosis. SLE is associated with autoimmune disorders like thyroiditis and type 1 diabetes mellitus.[4] Conversely, the numbers in our study were too small to bring out any such associations.

The diagnosis of SLE was based on the ARA criteria. All the patients fulfilled at least 4 standards needed for the diagnosis of SLE as per ARA. The commonest criterion satisfied was ANA and anti-dsDNA positivity and was seen in 39 out of 40 patients. ANA positivity is an expected finding as ANA negative lupus is a rare clinical entity in our setting. ANA positivity is reported to be positive in about 90-95% of cases. Anti-dsDNA antibodies are specific for the diagnosis of SLE.[14] Anti-dsDNA positivity was documented in 97.5% of the patients in this study. Studies from North and South India revealed anti-dsDNA positivity in 55% and 60.5% of the patients, respectively.[3,7] The high prevalence of dsDNA in this study probably maybe because the patients belong to a referral centre where they usually land up with a high disease burden. Oral ulcers (70%), arthritis (67.5%), haematological (62.5%) and renal (50%) were satisfied in descending order of frequency. Least satisfied criteria were discoid lupus (5%) followed by serositis (7.5%).

Haematological abnormalities were detected in 62.5% of patients in our study. In a study done in China by Xu XM et al, haematological abnormalities were detected in 86.2% of the patients.[15] The most common haematological abnormality detected was anaemia (60%). In a series of studies reviewed by Budman R revealed 57-78% of anaemic patients with SLE. AIHA, IDA and ACD were present in 22.5%, 20% and 17.5%, respectively. Anaemia was found to be significantly associated with the presence of LN (p=0.008). Previous studies have shown an association of moderate anaemia with LN and a poor survival among patients with anaemia and associated LN.[5,16]

Lymphopaenia was the most common white cell abnormality detected (32.5%) in the present study. In a study by Nossent J.C. has shown a 20% incidence of lymphopaenia.[17] Even the Indian studies from North India and South India have shown an incidence of 20 and 7.5%, respectively.[18] The presence of lymphopaenia was significantly associated with renal involvement (p=0.002), but not with arthritis (p=0.06). An association between arthritis and nephritis with lymphopaenia has been described by de Barre et al. Leucopenia was present in 17.5% of our patients. Antolin J et al reported a 20% incidence of leucopenia.[19] The presence of leucopenia as such was not associated with any of the major system involvement or outcome parameters.

Thrombocytopaenia was detected in 22.5% of our patients. Budman R described an incidence of 14-26% thrombocytopaenia in different series. The incidence in our patients is similar to that documented in these studies. A correlation between the presence of APLA and thrombocytopaenia was found (odds ratio=7.54). However, the association was not statistically significant (p=0.06). Association of thrombocytopenia to bleeding manifestation was also not statistically significant (p=0.188). Low platelet counts are described to be associated with renal involvement, APLA and neurological involvement in different studies.[19]

Various autoantibodies like SS-A, SS-B, anti-RNP, anti-Jo-1, anti-Histone, etc. were found to be positive in the study group. Low C3 was present in 22 (55%) patients. 15 (37.5%) patients had low C4 levels. Both C3 and C4 were low in 15 (37.5%) patients. Low C3/C4 is significantly associated with LN (p=0.007). It is also strongly related with lymphopaenia (p=0.012). Gladman et al group found low C3 was significantly more common among patients with nephritis.[20]

Proteinuria was the most common urinary abnormality detected in 20 (50%) patients. Microscopic haematuria was present in 11 (27.5%) patients, pyuria in 11 (27.5%) patients and casts in 6 (15%) patients. The most common renal abnormality described in the literature is also proteinuria.[21] LN was significantly related to anaemia with p=0.0008 and hypoalbuminaemia with p=0.003. Austin et al noted anaemia was found to be associated with an increased probability of renal insufficiency. In the study by Esdaile et al, 31 out of 38 patients had shown hypertension and were associated with negative impact on the outcome.

CONCLUSION

Among the 20 study patients with LN who underwent renal biopsy, 3 patients were classified to have WHO class II LN (15%), 7 had class III (35%), 8 were with class IV (40%) and 2 were with class V (10%). None of the patients belonged to WHO class I and class VI LN. According to a study by Schwartz, class IV LN is the most common form of LN and we observed the similar findings in our study.[22] Hypertension was most common in class IV group, which was statistically significant with p=0.008. This is similar to a study by Woo et al who described the similar association between hypertension and class IV. Most of the patients had a high SLEDAI score indicating high disease activity at presentation. A score between 11 and 20 was seen in 52.5%. The mean SLEDAI at presentation was 17.25, lowest being 4 and highest 54. High score at a presentation in the majority of patients maybe because the sample was studied at a tertiary care centre.

We conclude that in our study, SLE was found more common in females in their third decade. The commonest pattern of the presentation was fever (85%) followed by polyarthritis (67.5%) and renal involvement (50%). The incidence of oral ulcers, haematological abnormalities and proteinuria manifestations was high in this region compared to rest of India and western data. Anti-dsDNA positivity was also higher in this study population. Most of the patients had high disease activity at presentation.

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