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Malik Anas Rabbani  
*Aga Khan University*

Bilal Karim Siddiqui  
*Aga Khan University*

Muhammad Hammad Tahir  
*Aga Khan University*

Bushra Ahmad  
*Aga Khan University*, bushra.ahmad@aku.edu

A Shamim  
*Aga Khan University*

*See next page for additional authors*

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## Recommended Citation

Rabbani, M. A., Siddiqui, B. K., Tahir, M. H., Ahmad, B., Shamim, A., Majid, S., Ali, S. S., Shah, S. M., Ahmad, A. (2006). Do clinical manifestations of Systemic Lupus Erythematosus in Pakistan correlate with rest of Asia?. *Journal of Pakistan Medical Association*, 56(5), 222-227.

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**Authors**

Malik Anas Rabbani, Bilal Karim Siddiqui, Muhammad Hammad Tahir, Bushra Ahmad, A Shamim, Shahid Majid, Syed Sohail Ali, Syed Mansoor Ahmed Shah, and Aasim Ahmad

## **Do Clinical Manifestations of Systemic Lupus Erythematosus in Pakistan correlate with rest of Asia?**

Malik Anas Rabbani<sup>2</sup>, Bilal Karim Siddiqui<sup>1</sup>, Muhammad Hammad Tahir<sup>1</sup>, Bushra Ahmad<sup>1</sup>, A Shamim<sup>1</sup>, Shahid Majid<sup>1</sup>, Syed Sohail Ali<sup>1</sup>, Syed Mansoor Ahmed Shah<sup>1</sup>, Aasim Ahmad<sup>2</sup>.

Department of Medicine, the Aga Khan University Hospital<sup>1</sup>, Department of Nephrology, the Kidney Center, Post Graduate Training Institute<sup>2</sup>, Karachi.

### **Abstract**

**Objective:** Systemic Lupus Erythematosus (SLE) is known to be different among people with different racial, geographical and socio-economic back grounds. Asia has diverse ethnic groups broadly, Orientals in the East and Southeast Asia, Indians in South Asia and Arabs in the Middle East. These regions differ significantly from the Caucasians with reference to SLE. The purpose of this study was, therefore, to delineate the clinical pattern and disease course in Pakistani patients with SLE and compare it with Asian data.

**Methods:** Patients with SLE fulfilling the clinical and laboratory criteria of the American Rheumatism Association admitted at the Aga Khan University Hospital between 1986 and 2001 were studied by means of a retrospective review of their records. The results were compared with various studies in different regions of Asia.

**Results:** Demographically, it was seen that SLE is a disease predominantly of females in their third decade, which is generally consistent with Asian data. There was less cutaneous manifestations, arthritis, serositis, haematological and renal involvement compared to various regions in Asia. The neurological manifestations of SLE, however, place Pakistani patients in the middle of a spectrum between South Asians and other Asian races.

**Conclusion:** This study has shown that the clinical characteristics of SLE patients in our country may be different to those of other Asian races. Although our population is similar to South Asians, but clinical manifestations of our SLE patients are considerably different, suggesting some unknown etiology. Further studies are required to confirm the above results and to find statistically sounder associations (JPMA 56:222;2006).

## Introduction

The trend of survival over the past few decades of Systemic Lupus Erythematosus (SLE) has improved but, at the same time the incidence has increased three fold.<sup>1</sup> The exact underlying mechanisms behind clinical findings and etiologic events preceding and causing disease onset remain largely unclear; however, there is substantial circumstantial evidence that the development of SLE is dependent on environmental and genetic factors.<sup>2</sup>

Being the largest continent, both by area and population, Asia encompasses people of different socio-cultural background with diverse ethnic groups broadly Orientals in East and Southeast Asia, Indians in South Asia and Arabs in the middle east. Race has been shown to be a major predictor of clinical manifestations of SLE, laboratory and serologic tests, and disease related morbidity.<sup>3,4</sup> Comparative studies have shown that SLE has a higher prevalence, morbidity and mortality in the Oriental population in comparison to the Caucasians.<sup>5,6</sup> Although there were no major differences in outcomes of SLE among various Arab countries<sup>7</sup>, Arabs as a whole have different clinical characteristics when compared to others.<sup>8,9</sup> The prevalence of SLE in India is low; however, it is not uncommon in South East Asian region.<sup>6,10</sup> Also, studies have shown that clinical manifestations of SLE in India<sup>4</sup> are similar to those in other South Asian countries.<sup>11</sup> Moreover, the data on the characteristics of SLE in Pakistan is scarce with very few citations in the international literature. The purpose of this study was, therefore, to delineate the clinical pattern and disease course in Pakistani patients with SLE and to compare it with other Asian populations.

## Patients and Methods

Medical charts of patients with SLE fulfilling the clinical and laboratory criteria of the American Rheumatism Association (ARA) admitted to the Aga Khan University Hospital, Karachi, Pakistan between 1986 and 2001 were reviewed retrospectively.

Clinical and laboratory manifestations meeting the ARA criteria recorded were: malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis including pleuritis (history of pleuritic pain or rub, or pleural effusion) or pericarditis (documented by ECG or pericardial rub or evidence of pericardial effusion on echocardiography), renal disorder (elevated serum creatinine or persistent proteinuria >0.5 g/day or active cellular casts),

neurological disorder (seizures or psychosis in the absence of other causes), haematological disorder (haemolytic anaemia with reticulocytosis or leucopenia defined as white cell count <4000/3mm on two or more occasions or lymphopenia defined as lymphocyte count <1500/3mm on two or more occasions, or thrombocytopenia defined as platelet count <100000/3mm not due to drugs or infection, immunologic disorder (presence of anti-double-stranded DNA antibody or antibody to Smith nuclear antigen), or antinuclear antibody or antiphospholipid antibodies. A patient was diagnosed with SLE if four of the above criteria were met.

Clinical and laboratory data were collected according to an established protocol, which included a standard haematological and immunologic profile (complete blood count, erythrocyte sedimentation rate, serum electrolytes, serum creatinine, 24 hours urinary protein and creatinine clearance and various immunological tests including ANA, antibodies to double-stranded DNA [dsDNA], anti-Smith antibodies, rheumatoid factor [RF], antineutrophilic cytoplasmic antibodies [ANCA], antiphospholipid antibodies, and serum complement levels.

The Statistical package for social science SPSS 10.5 was used for data analysis. Chi square comparison of proportions was used to compare our results with other studies from Asia. The difference was considered significant if p value was less than 0.05.

## Results

### Demographic characteristics

A total of 198 patients were identified during period of 1986 and 2001 who met American Rheumatism Association criteria. Of these, 86.9% (n=172) were females and only 12.1% (n=24) were male patients. The mean age of presentation was 31 years (range 14-76 years). Mean duration of follow-up was 34 months (range 4-179 months). The comparisons of demographics with other studies are depicted in Table 1.

### Clinical findings

Malar rash was present in 29% (n=56). Discoid lupus in 14% (n=27), photosensitivity in 6% (n=12) and alopecia in 22% (n=44) patients. At the time of presentation, 53% (n=105) patients were febrile. There were variable occurrences of renal, central nervous system (CNS), serosal, haematological, and articular involvement. Serosal

**Table 1. Comparison of clinical features of SLE among Pakistan with Studies in people of Oriental (Hong Kong and Singapore) and South Asian Ethnicity (India).**

Clinical Features	Pakistan % (n=198)	Hong Kong <sup>10</sup> % (n=709)	p value	Singapore <sup>6</sup> % (n=472)	p value	India <sup>12</sup> % (1366)	p value
Malar Rash	29	56	<0.001	60	<0.001	58.5	<0.00001
Discoid Rash	14	12	0.417	10	0.1170	7	<0.001
Photosensitivity	6	35	<0.001	31	<0.001	48	<0.0001
Alopecia	22	84	<0.001	-	-	-	-
Oral Ulcers	20	11	<0.05	20	0.948	55	<0.001
Arthropathy	38	84	<0.01	51	0.3195	85	<0.001
Serositis	29	19	<0.01	21	<0.05	22	<0.05
Renal	33	50	<0.001	54	<0.001	73	<0.0001
Neurological	29	5	<0.001	4	<0.001	51	<0.0001
Seizures	4	3	0.4456	-	-	-	-
Psychosis	4	3	0.4456	-	-	-	-
Leukopenia	22	32	< 0.01	-	-	-	-
Thrombocytopenia	26	25	0.820	-	-	-	-

**Table 2. Comparison of clinical features of SLE among Pakistan with Studies in people of Arabic Ethnicity (Kuwait, Saudi Arabia and Lebanon).**

Clinical Features	Pakistan % (n=198)	Kuwait <sup>8</sup> % (n=108)	p value	Saudi Arabia <sup>18</sup> % (n=87)	p value	Lebanon <sup>7</sup> % (n=100)	p value
Malar Rash	29	43	<0.05	56	<0.001	52	<0.001
Discoid Rash	14	10	0.321	18	0.360	19	0.277
Photosensitivity	6	48	<0.001	26	<0.001	16	<0.001
Alopecia	22	44	<0.001	-	-	-	-
Oral Ulcers	20	33	<0.001	18	0.796	40	<0.001
Arthropathy	38	87	<0.001	91	<0.001	-	-
Serositis	29	-	-	56	<0.001	40	0.051
Renal	33	37	0.458	63	<0.001	50	<0.001
Neurological	29	23	0.57	25	0.543	19	0.067
Seizures	4	-	-	-	-	19	<0.001
Leukopenia	22	83	<0.001	33	0.037	17	0.33
Thrombocytopenia	26	26	0.974	20.7	0.256	33	0.198

**Table 3. Comparison of frequency of autoantibody among Pakistani patients and other populations (numbers are given in % of patient who tested positive for auto-antibody).**

	Pakistan (n=198)	Lebanon <sup>7</sup> (n=100)	Kuwait <sup>8</sup> (n=108)	Hong Kong <sup>10</sup> (n=709)	India <sup>25</sup> (n=1366)	Saudi Arabia <sup>18</sup> (n=87)	U.A.E <sup>9</sup> (n=33)	Singapore <sup>6</sup> (n=94)
ANA	86	87	94	-	98	98	89.5	-
dsDNA	74	50	58	65	67	93	97	43
Anti-Smith	50	-	13	12	31	40	33	26
Cardiolipin	35*	-	-	9	-	-	-	-

\* Anticardiolipin Antibodies were available only in 26 patients.

involvement was noted in 29% (n=56) patients. Pleural effusion was found in 19% (n=33) patients and pericardial effusion was present in 9% (n=18). Although symptomatic arthralgias were noted in almost all patients, articular involvement was noted in 38% (n=76) patients. CNS involvement was noted

in 29% (n=56) patients, of whom 15% presented with frank psychosis and 14% had seizures at some stage during the course of illness.

#### Laboratory findings at presentation

Complete blood count revealed leucopenia

in 22% (n=44), lymphopenia in 54% (n=107) and thrombocytopenia in 26% (n=51). Five percent patients presented with pancytopenia (n=9). Renal involvement was found in 33% (n=65), of which 50% had raised serum creatinine, 67% microscopic hematuria, 87% active urinary casts, and 74% proteinuria detectable on urine dipstick. Among patients with proteinuria, only 55% had proteinuria in nephrotic range. On renal biopsy, 64% of the cases had WHO class 4, 17% had class 5, 14% had class 3 and 5% had class 2 histological findings. ANA was positive in 86% (n=168) patients, Anti-dsDNA test results were positive in 74% (n=146) while 50% (n=99) tested positive for anti-Smith antibodies. No other antibodies, such as RF, ANCA, or antiphospholipid antibodies were found in clinically significant titers.

### **Outcome and Follow up**

Significant numbers of patients (40%) were either noncompliant or irregular with follow-up visits, so the ultimate outcome of their disease could not be clearly determined. The in-hospital mortality was 16% (n=32). The most common cause of death was overwhelming infections.

### **Comparison with Oriental ethnicity**

The prevalence of malar rash, photosensitivity, alopecia, arthropathy, leucopenia, and renal symptoms were found to be less when compared to Oriental populations<sup>12,13</sup>; however, serositis and neurological symptoms were more prevalent in our patients (Table 1).

### **Comparison with Arabs**

The prevalence of malar rash, photosensitivity, alopecia, oral ulcers, arthropathy, serositis and leucopenia were low in contrast to findings in Arabs.<sup>11,14,15</sup> (Table 2)

### **Comparison with Indian population**

Malar rash, photosensitivity, oral ulcers, arthropathy, renal and neurological symptoms were found to be less prevalent in our series than Indian patients.<sup>16</sup> Discoid rash and serositis was found to be more rampant in our study population (Table 1).

### **Auto-antibodies profile**

The presence of anti Smith antibodies was more prevalent in our patients when compared to other populations ( $p < 0.01$ ). The comparison of prevalence of auto-antibodies is shown in Table 3.

## **Discussion**

SLE is acknowledged as a multigenic disease in which environmental factors are likely to modulate expression of susceptibility genes.<sup>13</sup> In addition to the environment, evidence supports the concept that the geographic origin of populations and age affect the presentation and clinical course of SLE. There have been several studies dealing with late onset SLE suggesting that age at onset modifies the clinical expression of the disease in terms of onset, clinical presentation, pattern of organ involvement and serological finding.<sup>17</sup> Age also influences the serological manifestation of SLE. Anti-dsDNA antibodies and anticardiolipin tended to occur less frequently in older patients.<sup>17</sup> The mean age of onset of the disease in our series, however, was 31 years which is consistent with the reported literature from Asia.<sup>5-8, 11, 18</sup> Although females predominated the disease, the finding was more remarkable in Sri Lanka<sup>11</sup> and Oriental populations.<sup>5, 18</sup>

SLE diagnoses have increased and it seems sensible to attribute this to improved diagnostic tests and the recognition of mild disease manifestation. Although arthritis, arthralgia and rash remain the most frequent signs of SLE, there is an increase in the frequency of serositis and haematocytopenias in older patients.<sup>19</sup> The most frequent mode of presentation in our population was also arthritis and arthralgias followed by renal symptoms, malar rash, serositis, and neurological symptoms. These clinical features were even more frequent in Oriental populations<sup>5, 10, 18</sup> whereas the CNS manifestations were found to be more prevalent in our series. Conversely, individual CNS manifestations like seizures and psychosis were not found to be significant. Kasitanon et al from Thailand described a much higher proportion of seizures<sup>20</sup> while other reports found lower incidences among Chinese population.<sup>18</sup> Ward et al found that blacks had a lower prevalence of photosensitivity with a higher prevalence of discoid rash, as compared to Whites.<sup>15</sup> Similar findings were noted in another study from Singapore.<sup>5</sup>

Renal involvement in SLE may be quite diverse and may vary from no clinical abnormalities to rapidly progressive renal failure. The incidence of Lupus nephritis was found to be much higher in Chinese population<sup>6,18</sup> as compared to our findings. Furthermore, a high incidence of lupus nephritis was reported from Malaysia with 74% of patients having significant proteinuria and half of these had an

associated Nephrotic Syndrome.<sup>21</sup> Despite the fact that factors like arthritis, cutaneous manifestations and leukopenia may be protective against mortality,<sup>14,22</sup> the overall pattern generally showed higher morbidity in the Orientals than in our patients.

When compared to the Arabs,<sup>7-9</sup> our patients had lower prevalence of malar rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorders and leukopenia. However, lupus nephritis was not found to be significantly higher in Kuwait suggesting variable prevalence of Lupus Nephritis in the Arabs.<sup>8</sup> The incidence of lymphopenia in Arab population was reported to be 70%<sup>7</sup> which is significantly higher than our population. However, there was not any significant difference in other haematological abnormalities like thrombocytopenia which carries a poorer prognosis.<sup>22</sup> Moreover, the prevalence of serositis and pleural effusion in our series was similar to the study from Oman which showed that pleural effusion complicated 40% of SLE patients with serositis.<sup>15</sup>

South Asians are generally similar to Pakistani population geographically, racially, socio-economically and by culture. Paradoxically, when compared to the Indians<sup>23</sup> malar rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorders and CNS manifestations were all found to be statistically less in our population. Galapatty et al from Sri Lanka reported mucocutaneous features in 98%, alopecia in 87%, lupus nephritis in 69%, haematological disorders in 54%, neurological involvement in 42% and serositis in 25% patients.<sup>11</sup> These findings are in contrast to our findings showing that our lupus patients generally do not present as other South Asians.

About half of our patients had anti Smith antibodies which is higher than most of the available data.<sup>8-10,18</sup> This may reflect a different genetic background of our patients compared to the others. Although anti Smith antibodies are associated with a higher prevalence of lupus nephritis,<sup>16</sup> some studies have shown no differences.<sup>24</sup> There was no difference in the prevalence of other antibodies like ANA and anti dsDNA as compared to Chinese<sup>18</sup> and Indians.<sup>23</sup>

As our study was conducted in a single city in a tertiary care hospital, it may not represent the country as a whole. However, Karachi is a multiethnic city and may be a true representative of the whole country and all its races.

## Conclusion

Appreciation of the clinical differences may be important when attempting to assess for the development of certain clinical manifestations in individual patients and when attempting to define immunogenetic associations within groups of patients with SLE. This study has shown that the clinical characteristics of SLE patients in this country may be different to those of other Asian races. Although we can assume that our population is genetically, environmentally and socioeconomically similar to South Asians, yet clinical manifestations of our SLE patients are considerably different suggesting some unknown etiology. The Antibody patterns may also point to a different genetic etiology of SLE in Pakistan. We had significantly lower incidence of lupus nephritis, which is the major cause of morbidity and mortality in SLE, when compared to many other Asian studies. The Neurological manifestations of SLE, however, place Pakistani patients in the middle of a spectrum between South Asians and other Asian races. Our patients also have lower incidence of cutaneous, haematological and arthritic involvement.

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