Systemic lupus erythematosus in the multiethnic Malaysian population: disease expression and ethnic differences revisited

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*Lupus* 2013 22: 967 originally published online 11 July 2013
DOI: 10.1177/0961203313496299

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Systemic lupus erythematosus in the multiethnic Malaysian population: disease expression and ethnic differences revisited

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University of Malaya, Department of Medicine, Malaysia

Objectives: Ethnic differences in systemic lupus erythematosus (SLE) have been previously described in the multiethnic Malaysian population. However, there have since been many demographic and socioeconomic changes in the country. The aim of this study is to re-examine the clinical and immunological profiles of Malaysian SLE patients of different ethnic backgrounds. Methods: Consecutive follow-up patients at the University Malaya Medical Centre (UMMC) from July 2010 until March 2011 were included in the study. Results: The most common clinical manifestations were malar rash (61.3%), arthritis (52.3%), haematological disease (51.6%), oral ulcers (51%) and renal disease (40.6%). Ethnic Indians had fewer malar and discoid rashes but were at higher risk of arthritis, serositis, renal and neuropsychiatric disease compared to Malays and Chinese Malaysians. Antiphospholipid syndrome (APS) was less common in Chinese. A longer duration of SLE correlated with a lower SLEDAI score. Conclusion: Overall, the spectrum disease expression was similar to the earlier Malaysian study but the frequency of the more severe disease manifestations, viz. renal, haematological, neuropsychiatric involvements and serositis, were lower. This study further emphasises differences primarily between ethnic Indians and the other races in Malaysia. Lupus (2013) 22, 967–971.

Key words: Systemic lupus erythematosus; ethnicity; clinical manifestations; Indians; Malaysia

Introduction

Ethnic differences in systemic lupus erythematosus (SLE) have been described. SLE was found to be more prevalent in Asians, African-Americans and Hispanics compared to Caucasians. Differences in disease manifestations are also seen. Ethnic differences have also been noted in Asian populations. In Malaysia, a Southeast Asian nation with a multiethnic population comprising Malays, Chinese and Indians, a retrospective study of SLE patients seen between 1974 and 1990 at a university medical centre found the prevalence of SLE to be higher in Chinese, while Indians had lower frequencies of skin manifestations viz. malar rash and photosensitivity. In addition, Indians had lower survival rates compared to other races. In another study from neighbouring Singapore (which has a similar multiethnic background, although predominantly Chinese), Indians were also at lower risk of malar rash but at higher risk of oral ulcers while Malays had higher risk of renal and central nervous system (CNS) involvement compared to Chinese patients. In these two populations, the different ethnic groups have been resident in their countries for many generations and were therefore exposed to the same general environmental factors. While this may suggest underlying genetic factors as the cause for ethnic differences in disease manifestation, other factors such as behavioural factors, socioeconomic status, concomitant medical illnesses and therapy may also play a role.

Over the last 20 years, there have been significant changes in the Malaysian population with increased socioeconomic development, greater urbanisation and better access to health care. There has been greater awareness among physicians of SLE and its manifestations. The aim of our study is to re-examine the demographic, clinical and immunological profile of a new cohort of SLE patients from
the same university medical centre and to determine changes, if any, in disease pattern and ethnic differences in SLE over the last 20 years.

Patients and methods

This was a cross-sectional study of 155 consecutive SLE patients seen at the University Malaya Medical Centre (UMMC), Kuala Lumpur, from July 2010 until March 2011. The UMMC is a major tertiary medical centre in Malaysia and its referral base, although primarily from Kuala Lumpur and its surrounding areas, also includes other parts of the country. As a government-owned university hospital, it is part of the public health care system that has wide coverage. Since independence, the public health care services in Malaysia have been and remain highly subsidised by the government and patients are seen based on need, regardless of their ability to pay or other socioeconomic factors. The study was approved by the UMMC Medical Ethics committee. All patients who fulfilled the revised American College of Rheumatology (ACR) criteria for the diagnosis of SLE were included in this study. Information was obtained from patient interviews as well as review of their medical records. This included demographic, clinical, laboratory and treatment data. Current disease activity was measured using the SLE Disease Activity Index (SLEDAI) score. Age of onset of disease was defined as the age at which four or more ACR criteria were first noted by the attending physician. Ethnicity was based on that recorded on the patient’s national identity card.

The following organ involvements were looked for: malar rash, discoid rash, photosensitivity, oral ulcers, arthritis (arthritis of two or more peripheral joints, with tenderness, swelling, or effusion), serositis (pleuritis or pericarditis or evidence of effusion), renal disease (renal biopsy proven), neurologic disorder (seizures or psychosis without other causes; other neuropsychiatric manifestations) and haematologic disorder (haemolytic anaemia or leucopenia (<4000/l) or lymphopenia (<1500/l) or thrombocytopenia (<100,000/l) in the absence of offending drugs). Antiphospholipid syndrome (APS) was defined by a history of thrombosis or miscarriage with the presence of raised anticardiolipin (aCL) antibody or positive lupus anticoagulant (LA) antibody. Antinuclear antibody (ANA) with a cut-off titre of 1:80 or more using the immunofluorescence assay was defined as positive. Antibodies to double-stranded DNA (anti-dsDNA) were determined by the enzyme-linked immunosorbent assay (ELISA) method. A positive result was a value of 250 and above.

SPSS software version 18 was used for statistical analyses. Statistical significance was calculated using chi square while odds ratio (OR) and a 95% confidence interval (95% CI) were calculated for each of the various disease manifestations of SLE.

Results

Of the 155 patients studied, 85 (54.8%) were Chinese, 52 (33.5%) were Malay and 18 (11.6%) were Indians. During the same period, the ethnic distribution of all adult patients seen at the UMMC was Malays, 36.4%; Chinese, 34.4%; Indians, 24.4%; and other races, 4.8%. The mean age of onset of SLE was 28.9 ± 12.4 years. The duration of SLE ranged from two months to 44 years with a median duration of seven years (Figure 1). No difference in disease duration was seen between the different ethnic groups. A total of 139 (89.7%) were females and 16 (10.3%) were males, giving a female to male ratio of 8.6:1.

The most common clinical manifestations in descending order were malar rash (61.3%), followed by arthritis (52.3%), haematological disease (51.6%), oral ulcers (51%) and renal disease (40.6%) (Table 1). Neuropsychiatric SLE was present in 30 patients (19.3%), of whom 11 presented with stroke only and one had stroke and psychosis. Ten presented with epileptic seizures and one had, in addition to seizures, an acute confusional state and optic neuritis. Another six presented with acute confusional state, one of whom had concomitant transverse myelitis. One patient presented with psychosis alone. Overall, 26 patients (16.7%) had APS, 10 of whom (38.5%) presented with stroke. The other clinical manifestations of patients with APS included deep vein thrombosis, pulmonary embolism, miscarriage, left arm thrombosis and hepatic vein thrombosis. Discoid rash (18.1%) and serositis (7.7%) were less frequently seen. Positive ANA was detected in 148 (95.5%) while positive anti-dsDNA antibodies were observed in 143 (92.3%). The median for number of relapses was one (range zero to six).

The mean SLEDAI score seen in these patients was 3.63 (range 0–24). The majority of patients (73, 47.1%) had mild disease activity (SLEDAI score 1 to 5) or had no disease activity (52, 33.5%). Eighteen (11.6%) had moderate disease activity.
(SLEDAI score 6–10), 10 (6.5%) had high disease activity (SLEDAI score 11–19) and two (1.3%) had very high disease activity (SLEDAI score >19). A longer duration of SLE correlated with a lower SLEDAI score (Spearman correlation coefficient –3.63, \( p < 0.0001 \)).

Compared to non-Indians, Indians had a lower risk of malar and discoid rash (OR 3.46, 95% CI 1.21 to 9.98, and OR 0.86, 95% CI 0.80 to 0.93) but had higher risk for arthritis (OR 0.29, 95% CI 0.09 to 0.95), serositis (OR 0.18, 95% CI 0.05 to 0.70), renal disease (OR 0.34, 95% CI 0.12 to 0.97) and neuropsychiatric disease (OR 0.27, 95% CI 0.09 to 0.78) (Table 2). ANA and anti-dsDNA were 100% positive in Indians compared to Chinese and Malay patients. APS was significantly less common in the Chinese compared to other ethnic groups (OR 2.17, 95% CI 0.88 to 5.39). Treatments include 95.5% treated with prednisolone, 79.4% with hydroxychloroquine, 18.7% with mycophenolate mofetil, 47.7% with azathioprine, 25.2% with cyclophosphamide, 7.1% with intravenous immunoglobulin and 3.2% with intravenous rituximab.

**Discussion**

Malaysia’s racial diversity consists of three major races: Malay, Chinese and Indian. Malays are the major natives of Malaysia. Malaysian-Chinese are mainly descendants from the south China province. Similarly, Malaysian-Indians are mainly descendants of immigrants from south India. Paternal race is used to determine the identification of an individual’s race in the context of mixed race, as intermarriages are not uncommon in Malaysia. The ethnic composition of our patients differed from the previous Malaysian study in that there were higher proportions of Malays and Indians. In that study Chinese constituted 76% of patients compared to the current 54.8%. However, during the period of our study, the overall percentage of

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**Figure 1** Duration of SLE presented by patients.

**Table 1** Clinical and immunological profile of SLE in different racial groups

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Chinese</th>
<th>Malay</th>
<th>Indian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malar rash</td>
<td>61.3</td>
<td>64.7</td>
<td>65.4</td>
<td>33.3</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>18.1</td>
<td>18.8</td>
<td>21.2</td>
<td>5.6</td>
</tr>
<tr>
<td>Photosensitivity rash</td>
<td>39.4</td>
<td>40</td>
<td>40.4</td>
<td>33.3</td>
</tr>
<tr>
<td>Oral ulcer</td>
<td>51</td>
<td>48.2</td>
<td>51.9</td>
<td>61.1</td>
</tr>
<tr>
<td>Arthritis</td>
<td>52.3</td>
<td>45.9</td>
<td>53.8</td>
<td>77.8</td>
</tr>
<tr>
<td>Serositis</td>
<td>7.7</td>
<td>8.2</td>
<td>1.9</td>
<td>22.2</td>
</tr>
<tr>
<td>Renal</td>
<td>40.6</td>
<td>36.5</td>
<td>40.4</td>
<td>61.1</td>
</tr>
<tr>
<td>Neuropsychiatric abnormality</td>
<td>19.3</td>
<td>16.5</td>
<td>13.5</td>
<td>38.9</td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td>25</td>
<td>25.3</td>
<td>24</td>
<td>23.5</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>7.7</td>
<td>4.7</td>
<td>9.6</td>
<td>11.1</td>
</tr>
<tr>
<td>Seizures</td>
<td>7.1</td>
<td>7.1</td>
<td>3.8</td>
<td>16.7</td>
</tr>
<tr>
<td>Psychosis</td>
<td>1.3</td>
<td>0</td>
<td>1.9</td>
<td>5.6</td>
</tr>
<tr>
<td>Acute confusional state</td>
<td>4.5</td>
<td>4.7</td>
<td>1.9</td>
<td>5.6</td>
</tr>
<tr>
<td>Haematological abnormality</td>
<td>51.6</td>
<td>56.5</td>
<td>44.2</td>
<td>50</td>
</tr>
<tr>
<td>AIHA</td>
<td>9.7</td>
<td>11.8</td>
<td>7.7</td>
<td>5.6</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>32.3</td>
<td>38.8</td>
<td>23.1</td>
<td>27.8</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>31.6</td>
<td>31.8</td>
<td>26.9</td>
<td>44.4</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>16.8</td>
<td>11.8</td>
<td>21.1</td>
<td>27.8</td>
</tr>
<tr>
<td>Positive ANA</td>
<td>96.7</td>
<td>96.4</td>
<td>96.1</td>
<td>100</td>
</tr>
<tr>
<td>Positive anti-dsDNA</td>
<td>92.3</td>
<td>91.8</td>
<td>90.4</td>
<td>100</td>
</tr>
</tbody>
</table>

SLE: systemic lupus erythematosus; AIHA: autoimmune haemolytic anaemia; ANA: antinuclear antibody; anti-dsDNA: anti-double-stranded DNA.
adult Chinese patients seen at our hospital was 34.4%, suggesting that SLE may still be more common in Chinese. In the earlier study, the estimated prevalence of SLE in Chinese (57 per 100,000) was higher compared to Malays (33 per 100,000) and Indians (14 per 100,000).3 The female to male ratio was lower at 8.6:1 in our study compared to 12:1 in the previous study. This may suggest an increased awareness and diagnosis of SLE in males.

The pattern of organ involvement in our patients was generally comparable to the previous studies from Malaysia as well as Singapore, with malar rash, arthritis, oral ulcers, haematological and renal disease being the more common disease manifestations.3,4 However, compared to the earlier Malaysian study, major organ involvement were less frequent. Renal involvement (74% vs 40.6%), neuropsychiatric abnormality (23% vs 18.1%), haematological abnormality (81.3% vs 51.6%) and serositis (19.9% vs 7.7%) were more frequent in the earlier cohort of patients compared to the current one. Some differences in case definition were seen. For the current study, renal involvement was based on renal biopsy evidence, now a routine investigation, while in the older study renal involvement was defined by the presence of proteinuria (>0.5 g/day) or active urinary sediments with >5 red cells per high-power field and/or casts. On the other hand, neuropsychiatric involvement was less frequent in the current study despite the inclusion of other neurological disorders, e.g. stroke, in addition to convulsions or psychosis, which were the only neurological manifestations included in the earlier study. Overall, differences in case definitions alone cannot explain the reduction in the frequency of severe organ involvement. A possible explanation could be earlier diagnosis and better treatment of SLE before severe organ involvement can manifest.

When we compared our patients to other non-Asian populations, there were differences in certain clinical manifestations. For example, oral ulcers were more frequent in our patients compared to other populations3–10 while arthritis was less frequent (52.3%).3,10 Comparisons between Chinese Singaporeans and Caucasians have shown that serositis and haematological disease were more common in Caucasians and malar rash less common.11

Ethnic differences were again noted between the different races. Similar to the earlier studies from Malaysia and Singapore, Indians had lower risk of malar rash compared to Malays and Chinese but unlike previous studies, they also had lower risk of discoid rash but had no reduced risk of photosensitivity.3,4 The explanations previously put forward were either that melanin may have a protective effect or the fact that rashes were less obvious in darker-skinned individuals.3,4 While both these reasons may be valid, the lack of differences in risk of photosensitivity between races in our study and that from Singapore may be more consistent with the latter explanation. In the current study, major organ involvements were more common among Indians, viz. arthritis, serositis, renal disease and neuropsychiatric abnormality. These are differences not previously noted in the earlier Malaysian or Singaporean studies. However, in a review of SLE in India, arthritis, skin manifestations, oral ulcers, nephritis and neurological disorders were the commonest clinical manifestations in descending order among southern Indian SLE patients.12 Malar rash was noted to be significantly less common in patients from southern India compared to other parts of that country. These findings are compatible with Indian-Malaysian patients, who are mainly descendants of immigrants from south India.

The frequency of APS in this series was 16.7% while a previous serological study from our medical centre performed 20 years ago reported a similar frequency of 16.5% of patients with raised aCL antibody levels.13 In our study, we found a lower risk for APS among the Chinese compared to Malays and Indians. In the previous study, no differences were found in the prevalence of raised aCL.

Table 2  Odds ratio for selected clinical manifestations in three ethnicities

<table>
<thead>
<tr>
<th></th>
<th>Malar rash</th>
<th>Discoid rash</th>
<th>Arthritis</th>
<th>Serositis</th>
<th>Renal</th>
<th>Neurological abnormality</th>
<th>APS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indians</td>
<td>3.46 (1.21–9.98)</td>
<td>0.86 (0.80–0.93)</td>
<td>0.29 (0.09–0.95)</td>
<td>0.18 (0.05–0.70)</td>
<td>0.34 (0.12–0.97)</td>
<td>0.27 (0.09–0.78)</td>
<td>0.52 (0.16–1.84)</td>
</tr>
<tr>
<td>Chinese</td>
<td>0.75 (0.39–1.45)</td>
<td>0.89 (0.38–2.09)</td>
<td>1.57 (0.82–3.01)</td>
<td>1.04 (0.30–3.55)</td>
<td>1.62 (0.84–3.11)</td>
<td>1.30 (0.57–2.96)</td>
<td>2.17 (0.88–5.39)</td>
</tr>
<tr>
<td>Malays</td>
<td>0.81 (0.39–1.65)</td>
<td>0.60 (0.25–1.43)</td>
<td>0.94 (0.47–1.86)</td>
<td>5.28 (0.66–42.44)</td>
<td>1.03 (0.52–2.07)</td>
<td>1.58 (0.62–4.01)</td>
<td>0.58 (0.23–1.43)</td>
</tr>
</tbody>
</table>

APS: antiphospholipid syndrome.
antibody between the three ethnic groups. There were no ethnic differences in terms of SLEDAI scores. This is unsurprising as the SLEDAI scores measured the patients’ current disease activity. A longer duration of SLE correlated with a lower SLEDAI score. This could be the result of immunological response and hence disease activity diminishing with age combined with being on long-term treatment with immunosuppressive agents. This finding is in contrast to a study of SLE patients with disease duration of 10 years or more in which a high proportion of patients continued to have active disease based on their SLEDAI scores.

The current study is not strictly comparable to the previous UMMC study. We conducted a cross-sectional study on a cohort of SLE patients on regular follow-up while the earlier study was a retrospective chart review of patients seen over a period of 16 years. The median duration of SLE in our patients was seven years with a range of two months to 44 years. It is even possible that some patients from the older study were included in the current one. We were also unable to look at the survival data between ethnic groups but further follow-up of the current cohort will allow us to do so in the future. Despite these limitations, comparisons of the two cohorts from the same hospital more than 20 years apart suggest some interesting conclusions. While the patterns of clinical manifestations of SLE were generally comparable, the lower percentage of more severe disease manifestations and slightly higher percentage of males may be suggestive of greater awareness and better treatment of the disease. This study supports the earlier study in that it further emphasizes differences between ethnic Indians and the other races in Malaysia. Human leucocyte antigen (HLA) associations have been found in Malays and Chinese in Malaysia and these associations were race specific.

Further investigations into genetic risk factors in Indian Malaysians may provide reasons for the observed ethnic differences.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

None declared.

References

Corrigendum to Systemic lupus erythematosus in the multiethnic Malaysian population: disease expression and ethnic differences revisited

This article was published in Lupus 2013; 22: 967–971 by R Jasmin, S Sockalingam, TE Cheah and KJ Goh (DOI: 10.1177/0961203313496299).

The authors would like to apologize for an error made to the odds ratio of Table 2; the error also appears in the final paragraph of the results section. Corrections have been made to the following table and paragraph.

Table 2  Odds ratio for selected clinical manifestations in three ethnicities

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<th>APS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indians</td>
<td>0.27 (0.10–0.76)</td>
<td>0.24 (0.31–1.89)</td>
<td>3.66 (1.15–11.67)</td>
<td>4.61 (1.23–17.26)</td>
<td>2.57 (0.94–7.04)</td>
<td>3.52 (1.22–10.1)</td>
<td>1.91 (0.62–5.87)</td>
</tr>
<tr>
<td>Chinese</td>
<td>1.38 (0.72–2.63)</td>
<td>1.12 (0.49–2.56)</td>
<td>0.57 (0.30–1.07)</td>
<td>1.17 (0.35–3.85)</td>
<td>0.68 (0.36–1.30)</td>
<td>0.79 (0.35–1.79)</td>
<td>0.39 (0.17–0.90)</td>
</tr>
<tr>
<td>Malays</td>
<td>1.30 (0.65–2.60)</td>
<td>1.36 (0.58–3.16)</td>
<td>1.10 (0.56–2.15)</td>
<td>0.16 (0.02–1.31)</td>
<td>0.99 (0.50–1.94)</td>
<td>0.61 (0.24–1.54)</td>
<td>1.96 (0.85–4.50)</td>
</tr>
</tbody>
</table>

Compared with non-Indians, Indians had a lower risk of malar and discoid rash (OR 0.27, 95% CI 0.10–0.76 and OR 0.24, 95% CI 0.31–1.89) but had higher risk for arthritis (OR 3.66, 95% CI 1.15–11.67), serositis (OR 4.61, 95% CI 1.23–17.26), renal disease (OR 2.57, 95% CI 0.94–7.04) and neuropsychiatric disease (OR 3.52, 95% CI 1.22–10.1) (Table 2). ANA and anti-dsDNA were 100% positive in Indians compared with Chinese and Malay patients. APS was significantly less common in the Chinese compared with other ethnic groups (OR 0.39, 95% CI 0.17–0.90).