Pediatric systemic lupus erythematosus.
Retrospective analysis of clinico-laboratory parameters and their association with Systemic Lupus Erythematosus Disease Activity Index score

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ABSTRACT

Objectives: To elucidate the clinico-laboratory characteristics associated with pediatric systemic lupus erythematosus (pSLE) patients with higher Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score in a retrospective cohort of pSLE patients.

Methods: A retrospective study involving 32 pSLE patients was conducted at Hospital Universiti Sains Malaysia, Kelantan, Malaysia between 2006 and 2017.

Results: Within the group of 32 pSLE patients, 23 were girls and 9 were boys (3:1 ratio). The most common symptom was renal disorder (n=21; 65.6%) followed by malar rash (n=9; 28.1%), oral ulcers (n=7; 21.9%), prolonged fever (n=5; 15.6%) and arthritis (n=4; 12.5%). Antinuclear antibodies (ANA) were detected in all patients and 25 patients (78.1%) were positive for anti-double stranded DNA (anti-dsDNA) antibodies. Eighteen (56.3%) patients had active SLE (SLEDAI ≥6), and these patients were significantly associated with heavy pyuria (p=0.004), a high ANA concentration (1:160; p=0.040, 1:320; p=0.006), elevated ESR (p=0.006), low C3 levels (p=0.008), oral ulcers (p=0.010), heavy hematuria (p=0.017) and heavy proteinuria (p=0.017), lupus erythematosus (LE)-nonspecific lesion manifestations (p=0.019) and malar rash (p=0.044).

Conclusion: Pediatric systemic lupus erythematosus patients with higher SLEDAI score were most significantly associated with pyuria, high ANA titers, and elevated ESR.

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presentations, whereas LE-nonspecific lesions were clarified by the presence of photosensitivity, cutaneous vasculitis, oral and nasal ulcer.

Immunological laboratory investigations comprise of antinuclear antibody (ANA) (1:40-1:320), anti-double stranded DNA (anti-dsDNA) (1:10-1:320), complement 3 (C3) (0.66-1.30 g/L), and complement 4 (C4) (0.20-0.60 g/dL). Other immunological features such as red blood cell (RBC) (male: 4.5-6.0 10^12/L; female: 4.0-5.5 10^12/L) and erythrocyte sedimentation rate (ESR) (male 0-16 mm/hour; female: 0-20 mm/hour) were included. Patients were considered to have active lupus nephritis (LN) disease if they had proteinuria (> 0.5 gm/24 hours), hematuria (>5 RBCs/high power field), and pyuria (>5 WBCs/high power field).

Histological observation was categorized according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 reclassification. There are 6 histological types of LN: 1) minimal mesangial LN, 2) mesangial LN, 3) focal LN, 4) diffuse proliferative LN, 5) membranous LN, and 6) glomerulosclerosis.

All data entry and statistical analyses were performed using SPSS Statistics version 22 (IBM SPSS, Chicago, IL). The associations between the demographic features, immunological parameters, clinical features and the urine profile with the SLEDAI score were assessed using the $\chi^2$ test or Fisher’s exact test. A $p<0.05$ was considered statistically significant.

**Results.** Age at patient diagnosis ranged from 3 months to 12 years with mean and standard deviation ages of 8.44 and 3.53 years, respectively. The study group consisted of 23 (75%) females and 9 (25%) males, for a ratio of 3:1. All patients were Malay ethnicity with the most common clinical manifestations being renal disorder (65.6%), malar rash (28.1%) and oral ulcers (21.9%) (Table 1). Antinuclear antibody was determined in all patients at the lowest serum dilution factor of 1:40 to test for the presence of ANA. Most of the pSLE patients were positive for ANA at the highest titer of 1:320 (n=12; 37.5%) and 1:160 (n=8; 25%), with a sequential drop in patient frequency as the dilution factor decreased to 1:80 (n=7; 21.9%) and 1:40 (n=5; 15.6%). All pSLE patients were positive for anti-dsDNA antibodies. The greatest frequency occurred at the highest serum dilution factor at 1:320 (n=11; 34.4%) followed by 1:160 (n=9; 28.2%), 1:80 (n=5; 15.6%) and 1:40 (n=4; 12.5%) (Table 1).

Renal biopsy was performed on 20 (62.5%) of the pSLE patients. The most frequent histological finding was diffuse proliferative glomerulonephritis (class IV) followed by minimal mesangial LN (class I), focal LN (class III), and mesangial proliferative LN (class II) (Figure 1).

Elevated ESR ($p=0.006$), oral ulcers ($p=0.010$) and malar rash ($p=0.044$) were positively associated with an active SLEDAI score. Patients with LE-nonspecific lesion manifestations were also significantly associated with SLEDAI score ($p=0.019$). However, no significant differences were observed between the LE-specific lesions and both types of lesions in terms of their association with SLEDAI score (Table 2).

For immunological parameters and urine profile, high ANA concentration (1:160; $p=0.040$, 1:320; $p=0.040$, 1:80; $p=0.040$), high anti-dsDNA concentration (1:160; $p=0.040$, 1:80; $p=0.040$), low serum C3 (1:80; $p=0.040$, 1:40; $p=0.040$), low serum C4 (1:80; $p=0.040$, 1:40; $p=0.040$), elevated ESR (1:80; $p=0.040$, 1:40; $p=0.040$), anemia (1:80; $p=0.040$, 1:40; $p=0.040$), thrombocytopenia (1:80; $p=0.040$, 1:40; $p=0.040$), leucopenia (1:80; $p=0.040$, 1:40; $p=0.040$), proteinuria (1:80; $p=0.040$, 1:40; $p=0.040$), hematuria (1:80; $p=0.040$, 1:40; $p=0.040$), pyuria (1:80; $p=0.040$, 1:40; $p=0.040$), and urinary casts (1:80; $p=0.040$, 1:40; $p=0.040$) were significantly associated with active SLEDAI score.

**Table 1 -** Demographic, clinical features and immunological parameters of pediatric systemic lupus erythematosus (pSLE) patients (n=32).

| Features                | n (%) |
|-------------------------|-------|
| **Age**                 |       |
| ≥6                      | 25 (78.1) |
| <6                      | 7 (21.9)  |
| **Gender**              |       |
| Female                  | 23 (75.0) |
| Male                    | 9 (25.0)  |
| **Race**                |       |
| Malay                   | 32 (100) |
| Others                  | 0 (0.0)   |
| **Presenting symptoms** |       |
| Renal disorder          | 21 (65.6) |
| Malar-rash              | 9 (28.1)  |
| Oral ulcers             | 7 (21.9)  |
| Prolonged fever         | 5 (15.6)  |
| Arthritis               | 4 (12.5)  |
| Photosensitivity         | 2 (6.3)   |
| Blurring vision          | 2 (6.3)   |
| Vasculitis              | 2 (6.3)   |
| Alopecia                | 1 (3.1)   |
| Headache                | 1 (3.1)   |
| Serositis               | 1 (3.1)   |
| **SLEDAI**              |       |
| Active (≥6)             | 18 (56.3) |
| Inactive (<6)           | 14 (43.8) |
| **Immunological parameters** |   |
| ANA                     | 32/32 (100) |
| Anti-dsDNA              | 25/32 (78.1) |
| Low serum C3            | 22/32 (68.8) |
| Low serum C4            | 19/32 (59.4) |
| Elevated ESR            | 20/32 (62.5) |
| Anemia                  | 17/32 (53.1) |
| Thrombocytopenia        | 12/32 (37.5) |
| Leucopenia              | 4/32 (12.5) |
| Proteinuria             | 12/32 (37.5) |
| Hematuria               | 12/32 (37.5) |
| Pyuria                  | 8/32 (25.0) |
| Urinary casts           | 1/32 (3.1)  |

ANA - antinuclear antibody, Anti-dsDNA - anti-double stranded DNA, C3 - Complement 3, C4 - Complement 4, ESR - erythrocyte sedimentation rate, SLEDAI - Systemic Lupus Erythematosus Disease Activity Index.
Discussion. In this retrospective study of 32 pSLE patients, approximately half of our patients were diagnosed before the age of 10. In comparison with adult SLE patients, most studies reported a lower female-to-male ratio (3-5:1) of pSLE patients, which is comparable with our study and its female-to-male ratio of 3:1. The cohort of SLE patients was predominantly female. Its uncommon presentation in pre-pubertal and post-menopausal women suggests the role of endogenous sex hormones in SLE pathogenesis. All patients were of Malay ethnicity (100%) because the highest population in the Kelantan state of Malaysia is of Malay ethnic, which constitutes 95% of the whole population in the state. In our study, the most common clinical features were renal disorders, malar rash and oral ulcers, while the least common symptoms were alopecia, headaches and serositis. These observations resemble previous reports, where renal involvements and malar rash were the most common manifestations, while alopecia or serositis formed in a minority proportion of pSLE patients. Renal involvement occurs regularly in juvenile SLE and tends to dominate the clinical manifestations. Our study exhibited a high percentage of renal involvement (65.6%) due to LN. Antinuclear antibody was detected in all patients in our study. The elevation of anti-dsDNA antibodies was detected in 78.1% in pSLE patients in this study, corroborating the 60–97% range reported by previous studies. Complement C3 and C4 levels decreased in 68.8 % and 59.4% of our patients, respectively.

Table 2 - Association of SLEDAI score with demographic, clinical features, immunological parameters and urine profile in pSLE patients (n=32).

| Variables                      | SLEDAI score |       | P-value |
|--------------------------------|--------------|-------|---------|
|                                | Active n %    | Inactive n % |       |
| Age                            |              |       |         |
| ≥6                             | 14 (77.8)    | 11 (78.6) | 1.000   |
| <6                             | 4 (22.2)     | 3 (21.4)  |         |
| Gender                         |              |       |         |
| Female                        | 14 (77.8)    | 9 (64.3) | 0.453   |
| Male                          | 4 (22.2)     | 5 (35.7)  |         |
| Arthritis                      |              |       |         |
| Yes                            | 4 (22.2)     | 0 (0)   | 0.113   |
| No                             | 14 (77.8)    | 14 (100) |         |
| Malar rash                     |              |       |         |
| Yes                            | 8 (44.4)     | 1 (7.1)  | 0.044*  |
| No                             | 10 (55.6)    | 13 (92.9) |         |
| Oral ulcer                     |              |       |         |
| Yes                            | 7 (38.9)     | 0 (0)  | 0.010*  |
| No                             | 11 (61.1)    | 14 (100) |         |
| Prolonged fever                |              |       |         |
| Yes                            | 5 (27.8)     | 0 (0)  | 0.052   |
| No                             | 13 (72.2)    | 14 (100) |         |
| Alopecia                       |              |       |         |
| Yes                            | 1 (5.6)      | 0 (0)  | 1.000   |
| No                             | 17 (94.4)    | 14 (100) |         |
| Photosensitivity               |              |       |         |
| Yes                            | 1 (5.6)      | 1 (7.1)  | 1.000   |
| No                             | 17 (94.4)    | 13 (92.7) |         |
| Blurring vision                |              |       |         |
| Yes                            | 2 (11.1)     | 0 (0)  | 0.492   |
| No                             | 16 (88.9)    | 14 (100) |         |
| Headache                       |              |       |         |
| Yes                            | 1 (5.6)      | 0 (0)  | 1.000   |
| No                             | 17 (94.4)    | 14 (100) |         |
| Serositis                      |              |       |         |
| Yes                            | 1 (5.6)      | 0 (0)  | 1.000   |
| No                             | 17 (94.4)    | 14 (100) |         |
| Vasculitis                     |              |       |         |
| Yes                            | 2 (11.1)     | 0 (0)  | 0.492   |
| No                             | 16 (88.9)    | 14 (100) |         |
| LE-specific lesions            |              |       |         |
| Yes                            | 7 (38.9)     | 3 (21.4) | 0.446   |
| No                             | 11 (61.1)    | 11 (78.6) |         |
| LE-nonspecific lesion          |              |       |         |
| Yes                            | 9 (50.0)     | 1 (14.3) | 0.019*  |
| No                             | 9 (50.0)     | 13 (85.7) |         |
| Both types of lesion           |              |       |         |
| Yes                            | 9 (50.0)     | 3 (21.4) | 0.098   |
| No                             | 9 (50.0)     | 11 (78.6) |         |
| ANA                            |              |       |         |
| 1:40                           | 0 (0)        | 5 (35.7) | 0.052   |
| 1:80                           | 2 (11.1)     | 5 (35.4) | 0.195   |
| 1:160                          | 7 (38.9)     | 1 (7.1)  | 0.040*  |
| 1:320                          | 9 (50.0)     | 3 (21.4) | 0.006*  |
| Anti-dsDNA                     |              |       |         |
| 1:10                           | 1 (5.6)      | 0 (0)  | 1.000   |
| 1:20                           | 1 (5.6)      | 1 (7.1)  | 1.000   |
| 1:40                           | 2 (11.1)     | 2 (14.3) | 1.000   |
| 1:80                           | 5 (27.8)     | 0 (0)  | 0.052   |
| 1:160                          | 5 (27.8)     | 4 (28.6) | 1.000   |
| 1:320                          | 4 (22.2)     | 7 (50.0) | 0.101   |
Comparably with previous reports, patients with anemia presented the highest frequency followed by thrombocytopenia and leukopenia, similar with observations reported by Mohamed et al, where pSLE patients demonstrated the highest percentage of anemia followed by thrombocytopenia and leukopenia. We observed that all patients had proteinuria and hematuria with the same frequency (37.5%), 25% had pyuria and 3.1% of patients had urinary casts, comparable with previous studies.

Lupus nephritis was observed in 75-80% of patients in previous studies. There is a common agreement in literature that the active classes of biopsy proven LN are class III and IV, while class I, II, V, and VI are considered less active, requiring limited immunosuppressive therapy.

Our study demonstrated that 62.5% of pSLE had LN at the time of diagnosis, consistent with other studies in which most patients had proliferative nephritis. In this study, class IV was the most common class on the initial biopsy followed by class I, III and II. Interestingly, the majority of SLE adult patients were also class IV LN. In our cohort, a high titre of ANA was significantly associated with higher disease activity, consistent with previous studies. However, a high titre of anti-dsDNA showed an insignificant pattern (1:80; p=0.052) of association with a higher SLEDAI score. This could be partially explained by most patients in our cohort (n=25/32; 78.1%) were seronegative for anti-dsDNA. Our cohort of pSLE patients showed that low C3 level was significantly associated with higher SLEDAI score. Complement 3 and C4 are often low in SLE patients, particularly with active disease. However, in our study, low C4 did not exhibit any association with disease activity. This suggests that C4 might be a less sensitive parameter of disease activity in pSLE patients.

It was observed that an elevated ESR value was associated with higher disease activity in our study. SLE patients with active systemic inflammation often have increased non-specific markers of inflammation such as elevated ESR. For clinical presentation, we found that malar rash and oral ulcers exhibited significant associations with higher SLEDAI scores. Correspondingly, previous findings also reported that malar rash and oral ulcers were strongly associated with systemic disease activity in pSLE. In our cohort, proteinuria, hematuria and pyuria were significantly associated with higher disease activity. Prior studies suggested that proteinuria, hematuria and pyuria were associated with active renal and non-renal disease activity. Hence, these 3 urinary sediments should be considered as manifestations of active pSLE.

In conclusion, our retrospective analysis showed that SLE patients with higher SLEDAI score were more...
significantly associated with heavy pyuria, high ANA concentration and elevated ESR, and they might be appropriate measures for pSLE disease activity. Our study also implies that mucocutaneous features might require more intensive therapy and disease monitoring.

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