Utility of serum ferritin and soluble interleukin-2 receptor as markers of disease activity in childhood systemic lupus erythematosus

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Abstract

Objective: To assess the usefulness of serum ferritin and soluble interleukin-2 receptor (sIL-2r) levels as markers of disease activity in childhood systemic lupus erythematosus (cSLE) and their role in screen for subclinical macrophage activation syndrome (MAS).

Patients and methods: This is a cross-sectional analysis of prospectively collected data. Consecutive children who met the Systemic Lupus International Collaborating Clinics (SLICC) criteria were enrolled between June 2015 and June 2017. All patients interviewed and assessed for disease activity using SLE disease activity index (SLEDAI). Biochemical and serological tests including markers of disease activity and MAS were measured by standard laboratory procedure.

Results: A total of 31 (25 female; 6 male) consecutive cSLE patients with a mean age of 10.6 (±3.2) years were included. The most frequent manifestations were mucocutaneous and musculoskeletal (84%) followed by hematological (64.5%) then renal involvement (58%). Twenty-two patients had active disease (SLEDAI > 4), with a mean of 9.8. Mean serum ferritin and sIL-2r were 555 (±1860) and 2789 (±1299) respectively. Both correlated significantly with leucocyte, platelet count, transferrin, C3 and SLEDAI (p < 0.05). Additionally, sIL-2r had positive correlation with ANA, ds-DNA and C4. Both ferritin and sIL-2r had weak correlation with ESR, but no correlation with CRP. Twelve patients had a recent infection. However, they were comparable to patients without infection with regard to all clinical and laboratory features. Three patients had MAS proved by bone marrow aspiration.

Conclusion: Measurement of serum ferritin and sIL-2r might help in assessing disease activity of cSLE. Both might be good screening markers for MAS in cSLE. A larger prospective study is required to allow more definitive conclusions.

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1. Introduction

Systemic lupus erythematosus (SLE) is the prototypical model of autoimmune diseases. It is a complex disease that runs a chronic unpredictable, relapsing remitting course with an inflammatory and multisystemic nature. Because of its heterogeneous presentations and the life-threatening potentials, continuous monitoring of disease activity with assessment of clinical and laboratory tests is of paramount importance in directing prompt and effective therapeutic interventions [1–4]. However, the lack of reliable and specific biomarkers for SLE impede the correct assessment of response to treatment. Despite decays of inclining maturity in understanding SLE pathogenesis, few markers of disease activity have been widely accepted and validated in clinical practice [5,6]. For more common organ involvement in childhood SLE (cSLE) such as lupus nephritis, new promising urine biomarkers developed, hopefully these markers can be used for monitoring the response to therapy of lupus nephritis [7,8]. Current laboratory tests are clearly insufficient for monitoring the disease activity. Thus, the search for a simple and easily available markers is a legitimate objective and an ongoing demand in the clinical research of cSLE.

Serum ferritin is one of the markers that have recently gained...
much attention in adult rheumatic diseases. Several reports have suggested the usefulness of serum ferritin as a marker of disease activity in adult cohorts of different autoimmune diseases including SLE [9–14]. Furthermore, soluble interleukin-2 receptor (sIL-2r) levels could be used as a biomarker for disease activity in autoimmune diseases, it could distinguish disease exacerbation as it varied with disease activity. Moreover, recognition of macrophage activation syndrome (MAS) in patients with SLE is often challenging because of it may mimic the clinical features of the SLE or be confused with an infection. Several studies suggested that sIL-2r a reliable biomarker of MAS [15,16].

cSLE accounts for 20% of the lupus population. Despite great similarity with the adult SLE, it is axiomatic that cSLE tends to be more severe with more organ involvement and laboratory abnormalities [2,17]. It is a fact that the knowledge repertoire in cSLE has been mostly extrapolated from research in adult patients. In this study, we assessed the usefulness of serum ferritin and sIL-2r levels as markers of disease activity in cSLE and their role in screen children with SLE for subclinical MAS.

2. Patients and methods

This is a cross-sectional analysis of prospectively collected data between June 2015 and June 2017. Our cohort comprised consecutive children with SLE who are followed regularly in pediatric lupus clinic at King Faisal Specialist Hospital and Research Center, Riyadh (KFSHRC-R). All included patients fulfilled the Systemic Lupus International Collaborating Clinics (SLICC) criteria and the diagnosis made before the age of the 14th birthday [18]. Patients were interviewed and evaluated thoroughly; the disease activity was assessed by SLE disease activity index (SLEDAI) [19]. Clinically active SLE was defined as a SLEDAI score of >4. In addition to serum ferritin, sIL-2r, and markers of MAS including fibrinogen, coagulation profiles, lactic dehydrogenase, serum triglyceride level were requested; all patients had complete blood count (CBC) with differential count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), iron profile, hepatic, and renal profile, anti-nuclear antibody (ANA) profile including anti-double stranded DNA antibody, antiphospholipid antibody profile (anti-cardiolipin, Beta-2 glycoprotein I) as well as complement (C3 C4), urinalysis and urine protein creatinine ratio. All laboratory tests requested at the time of interview and assessment.

Serum levels of ferritin and sIL-2r were quantified by an enzyme immunoassay. biochemical and serological tests including markers of disease activity and MAS were measured by standard laboratory procedure. Levels of ferritin and sIL-2r were correlated with the SLEDAI score and MAS markers.

All collected data were analyzed under confidentiality practice and no personal identity needed. An informed consent was obtained from all participants and their parents. The study approved by the Research Affairs Council at KFSHRC-R.

3. Statistical methods

The results expressed as a mean ± standard deviation (SD) for continuous variables and percentages for categorical variables. We used Student’s independent t-test to compare the means of serum ferritin and sIL-2r between active and inactive cSLE patients. Mann-Whitney test was carried out to look at the correlation of serum ferritin and sIL-2 with disease activity. Statistical significance was defined as a P value of <0.05.

4. Results

Thirty-one (25 female; 6 male) consecutive SLE patients with a mean age of 10.6 (±3.2) years and mean disease duration of 3.8 (±2.4) years were included. The most frequent clinical findings were mucocutaneous and musculoskeletal manifestations (84%); in the form of oral ulceration and facial rash, and arthritis. Twenty (64.5%) patients had hematological manifestations including direct coombs positive hemolytic anemia, leucopenia and thrombocytopenia. Eighteen (58%) patients had nephritis proved by renal biopsy, 12 patients had proliferative glomerulonephritis (class III and IV) and five patients had membranous glomerulonephritis (class V).

Table 1 shows the demographic features and the frequency of clinical features with SLEDAI score. Overall, 22 patients had active disease in various organ systems (SLEDAI ≥4), with a mean of 9.8 (±9.1). The mean serum ferritin and sIL-2r levels were 555 (±1860) and 2789 (±1299) pg/ml respectively. Table 2 shows the correlation of serum ferritin and sIL-2r with SLEDAI score and other variables. Both serum ferritin and sIL-2r correlated significantly with leucopenia, thrombocytopenia, transferrin, low C3 levels and SLEDAI

| Feature                       | SLEDAI Frequency (%) |
|-------------------------------|---------------------|
| Female                        | 80.6%               |
| Mean age (years±SD)           | 10.6 ± 3.2          |
| Mean age at onset (years±SD)  | 7.5 ± 3.6           |
| Mean age at diagnosis (years±SD) | 8.2 ± 3.3          |
| Mean disease duration (years±SD) | 3.8 ± 2.4          |
| Mean duration of follow up (years±SD) | 2.7 ± 2.0          |
| Mucocutaneous                 | 84                  |
| Musculoskeletal               | 84                  |
| Hematological                 | 64.5                |
| Nephritis                     | 58                  |
| Mean SLEDAI                   | 9.0 ± 9.7           |

SLEDAI – systemic lupus erythematosus disease activity index.

Table 2 The correlation of serum ferritin and sIL-2r with SLEDAI score and other variables.

| Ferritin     | sIL-2r |
|--------------|--------|
| WBC          | 0.39   |
| 0.02          |
| 0.007         |
| Plat count    | 0.43   |
| 0.02          |
| 0.04          |
| Transferrin   | 0.87   |
| 0.001         |
| 0.01          |
| ESR          | 0.34   |
| 0.06          |
| 0.07          |
| CRP          | 0.04   |
| 0.84          |
| 0.11          |
| ANA          | 0.003  |
| 0.98          |
| 0.02          |
| dsDNA        | 0.15   |
| 0.41          |
| 0.05          |
| C            | 0.42   |
| 0.018         |
| 0.02          |
| C4           | 0.29   |
| 0.12          |
| 0.04          |
| UPC          | 0.26   |
| 0.08          |
| 0.09          |
| SLEDAI       | 0.66   |
| 0.001         |
| 0.01          |

sIL-2r = soluble interleukin-2 receptor, WBC = white cell count, ESR = erythrocyte sedimentation rate, CRP = C reactive protein, ANA = antinuclear antibody, dsDNA = double stranded DNA, C3 = complement 3, C4 = complement 4, UPC = urine protein creatinine, SLEDAI = systemic lupus erythematosus disease activity index.

* The upper number is Pearson Correlation Coefficients.

b The lower is p value P value.
score (all p < 0.05). Additionally, sIL-2r had positive correlation with ANA, ds-DNA and C4 levels. However, ferritin and sIL-2r had weak correlation with ESR, but no correlation with CRP.

Table 3 shows the mean values of the serum ferritin, sIL-2r, ESR and CRP levels in active or inactive cSLE and patients with or without recent infection (infection within one week). Twelve patients had a recent infection, three patients had more than one infection. These infections comprised respiratory tract, urinary tract infection and bacteremia. Four patients had a documented infection with Streptococcus pneumoniae, two patients with Staphylococcus aureus. Two patients had viral infections and one patient had fungal infection. The causative agent could be identified in two cases. Patients with documented infection were comparable to those without infection with regard to all clinical and laboratory features. Though, the serum levels of ferritin and sIL-2r were higher in patients with infection. However, the difference was not significant. While, the CRP levels were statistically higher in patients with infection (p < 0.05). Table 4 shows the values of the serum ferritin and sIL-2r and other variables in patients with and without MAS. Both ferritin and sIL-2r correlated significantly with markers of MAS. Moreover, bone marrow aspiration (BMA) from three patients with life-threatening conditions showed evidence of MAS.

5. Discussion

In this cross-sectional prospective study, we assessed the role of serum ferritin and sIL-2r as simple disease activity biomarkers in a cohort of children with SLE. Several studies suggested that serum ferritin is a useful marker for disease activity in adult patients with SLE, but the data about the usefulness of sIL-2r as measure of the disease activity is equivocal [9,20,21]. MAS is a life-threatening condition, which can be the presenting manifestation or mimic a flare of SLE or be confused with concomitant serious infection. Thus, high index of suspicion and proper investigations are crucial to diagnose MAS in cSLE. Several studies showed that sIL-2r is considered a good marker to detect MAS in children with systemic juvenile idiopathic arthritis (sJIA) and SLE [22,23].

Ferritin is an intracellular protein that functions as an acute inflammatory process and then leakage of ferritin from damaged inflammatory cells [26]. It has been shown that it may suppress T lymphocytes, B cells antibodies production, and decrease granulocyte phagocytosis [27]. On the other hand, some studies suggested that sIL-2r a reliable biomarker of disease activity in a broad spectrum of autoimmune disorders including MAS [15,16]. Elevated serum sIL-2r levels result from activated lymphocyte (T helper and regulatory T cells), which express high levels of IL-2r. Also, activated B cells, monocytes, granulocytes and natural killer cells express IL-2r and its shedding into the circulation [28,29].

We demonstrated that serum levels of ferritin and IL-2r were elevated in cSLE patients with active as compared to inactive disease and correlated with SLEDAI score and other markers of SLE such as total white cell and platelet count and C3 levels. Interestingly, IL-2r, but not ferritin had strong correlation with ANA, ds-DNA and C4 levels; this finding needs further investigation to assess the value of IL-2r in differentiation of active from inactive nephritis.

ESR and CRP can be raised and modestly correlated with disease activity. However, both can be high in infection [30,31]. Our results revealed lack association between serum ferritin and sIL-2r and ESR and CRP. Furthermore, serum ferritin and sIL-2r levels were higher in cSLE patients with active disease. Yet, there was no significant difference between patients with or without infection; one of the possible reasons for this unexpected result is the big variations in the serum ferritin and sIL-2r values. However, this finding needs more evaluation in other studies.

The available classification criteria of MAS developed for children with MAS complicating sJIA. Interestingly, presence of abnormal cells in form of hemophagocytic cells from BMA is not a requirement for MAS [32]. It is worth mentioning that these criteria are not validated for cSLE yet. Our results showed that both ferritin and sIL-2r correlated significantly with markers of MAS. Three patients underwent BMA as part of the comprehensive work up for their life-threatening conditions. All showed evidence of MAS.

Our study has several limitations, including a single center experience, a small sample, one visit assessment and lack of controls. Thus, all reported findings in this work should interpret in the light of these limitations.

Although no single biomarker has been identified as a perfect measure for disease activity; our results like pervious reports show that serum ferritin and IL-2r may be useful noninvasive measure of the disease activity in cSLE patients. However, whether the levels of these markers reflect the changing trend in disease activity and response to therapy cannot be determined as we did not have consecutive measurements during the follow-up visits.

Table 3

| Patient number | Ferritin ug/L | sIL-2r pg/ml | ESR mm/hr | CRP mg/L | Ferritin ug/L | sIL-2r pg/ml | ESR mm/hr | CRP mg/L |
|----------------|--------------|--------------|-----------|-----------|--------------|--------------|-----------|-----------|
| Active cSLE    | 22           | 4994.2       | 38.3      | 20.4      | 12           | 2670         | 143.3     | 14.6      |
| Active cSLE    | 22           | 529.2        | 25.2      | 6.5       | 19           | 2258.3       | 13.8      | 1.3       |
| Inactive cSLE  | 9.0          | 676.5        | 13.8      | 40.6      | 4.00         | 2258.3       | 0.07      | 0.1       |
| Inactive cSLE  | 9.0          | 676.5        | 13.8      | 40.6      | 4.00         | 2258.3       | 0.07      | 0.1       |

Table 4

| Patient number | Ferritin ug/L | sIL-2r pg/ml | ESR mm/hr | CRP mg/L |
|----------------|--------------|--------------|-----------|-----------|
| Active cSLE    | 22           | 4994.2       | 38.3      | 20.4      |
| Active cSLE    | 22           | 529.2        | 25.2      | 6.5       |
| Inactive cSLE  | 9.0          | 676.5        | 13.8      | 40.6      |
| Inactive cSLE  | 9.0          | 676.5        | 13.8      | 40.6      |

P value

| Active cSLE    | 0.001        | 0.001        | 0.002     | 0.001     |
| Active cSLE    | 0.001        | 0.001        | 0.002     | 0.001     |
| Inactive cSLE  | 0.001        | 0.001        | 0.002     | 0.001     |
| Inactive cSLE  | 0.001        | 0.001        | 0.002     | 0.001     |

sJIA – soluble interleukin-2 receptor, MAS – macrophage activation syndrome, ESR – erythrocyte sedimentation rate, CRP – C reactive protein.
Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpam.2019.07.007.

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