Thieme

B-Cell-Attracting Chemokine CXCL13 As a Marker of Disease Activity in Systemic Lupus Erythematosus (SLE)

B-Cell-anziehendes Chemokin CXCL13 als Marker der Krankheitsaktivität im Systemischen Lupus Erythematodes (SLE)

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ABSTRACT

Background A correlation was detected between the chemokine CXC ligand 13 (CXCL13) and lupus nephritis, but there is no data recorded in the literature about a relationship with other disease manifestations in systemic lupus erythematosus (SLE). Therefore, we sought to investigate the relationship between CXCL13 and overall disease activity and other disease manifestations in SLE.

Patients and Methods Fifty-seven SLE patients (51 female, 6 male) aged 18–60 years, fulfilling ≥ 4 SLICC classification criteria for the classification of SLE, were enrolled in a cross-sectional study. Disease activity was scored using the SLE Disease Activity Index (SLEDAI) scoring system. The serological workup included routine lab investigations (full blood count, liver and kidney function tests, and urinalysis) as well as ESR, CRP, anti-ds DNA, C3, C4, 24-h urine protein, and creatinine clearance. Plasma CXCL13 levels were detected by ELISA.

Results CXCL13 levels were elevated in active SLE patients. A significant positive correlation was found between the total score of SLEDAI and CXCL13 levels ($r = 0.547$, p-value < 0.0001). A statistically significant difference was found regarding the mean CXCL13 levels between the patient groups (classified according to SLEDAI score) (inactive < 3, mild/moderate ≥ 3–12, severe > 12) (p-value < 0.001). The anti-ds DNA antibody titre showed a significant positive correlation with CXCL13 levels ($r = 0.335$, p-value < 0.05). The complement levels (C3, C4) showed a significant negative correlation with CXCL13 levels (p-value < 0.001). Also there was a significant positive correlation between 24-h urine protein and urinary casts and CXCL13 levels (p-value < 0.05).

Conclusion Our study revealed elevated levels of serum CXCL13 in active SLE patients. We demonstrated a highly significant positive correlation between serum CXCL13 levels in active SLE patients and SLE disease activity, which supports the role of CXCL13 in the pathogenesis of SLE disease and its activity. Among the variants used in calculating the SLEDAI score, we detected significant relations between level of serum CXCL13 and each of total and extra-renal SLEDAI score.

ZUSAMMENFASSUNG

Hintergrund Eine Beziehung zwischen dem Chemokin-CXC-Liganden 13 (CXCL13) wurde festgestellt, um mit der Lupusnephritis zu korrelieren, aber es wurden keine Daten in der Literatur über ihre Beziehung mit anderen Krankheitsmanifestationen im systemischen Lupus erythematodes (SLE) aufgezeichnet. Deshalb haben wir versucht, die CXCL13-Relation mit der gesamten Krankheitsaktivität und ihrer Beziehung zu anderen Krankheitsmanifestationen in SLE zu untersuchen.

Patienten und Methoden Fünfundfünfzig SLE-Patienten (51 weiblich, 6 männlich) im Alter von 18–60 Jahren, die ≥ 4 SLICC-Klassifizierungskriterien für die Klassifizierung von SLE erfüllen, wurden in einer Querschnittsstudie eingeschrieben. Die Krankheit Aktivität wurde mit dem SLE-Krankheit Aktivität Index (SLEDAI) Scoring-System bewertet. Die serologische Aufarbeitung umfasste die Routine-Laboruntersuchungen (Vollblutbild, Leber- und Nierenfunktionstests und Urinanalyse) neben ESR, CRP, Anti-ds-DNA, C3, C4, 24 h-Protein im Urin und Kreatinin-Clearance. Die Plasma-CXCL13-Spiegel wurden durch ELISA nachgewiesen.

Ergebnisse CXCL13-Werte wurden bei aktiven SLE-Patienten erhöht. Eine signifikante positive Korrelation zwischen der Gesamtpunktzahl der SLEDAI- und CXCL13-Werte (r = 0,547, P-Wert < 0,0001). Ein statistischer signifikanter Unterschied zu den mittleren CXCL13-Werten zwischen den Patientengruppen (klassifiziert nach SLEDAI-Score) (inaktiv < 3, mild/mäßig ≥ 3–12, sever >12) (P-Wert < 0,001). Der Anti-ds-DNA-Antikörper-Titer zeigte eine signifikante positive Korrelation mit den CXCL13-Werten (r = 0,335, P-Wert < 0,05). Die Komplement-Niveaus (C3, C4) zeigten eine signifikante negative Korrelation mit den CXCL13-Werten (P-Wert < 0,001). Eine signifikante positive Korrelation zwischen Harn-24-Stunden-Protein und Harn-Casts und CXCL13-Konzentrationen (P-Wert < 0,05).

Schlussfolgerung Unsere Studie ergab eine erhöhte Serum-CumCL13 bei aktiven SLE-Patienten. Wir zeigten eine signifikante positive Korrelation zwischen den Serum-CXCL13-Werten bei aktiven SLE-Patienten und der SLE-Erkrankung, die die Rolle von CXCL13 bei der Pathogenese der SLE-Erkrankung und ihrer Aktivität unterstützt. Unter den Varianten, die bei der Berechnung der SLEDAI-Punktzahl verwendet wurden, wurden signifikante Beziehungen zwischen dem Serum CXCL13 und jedem der gesamten und extra-renalen SLEDAI-Score nachgewiesen.

Introduction

SLE as a prototypic systemic autoimmune disease, is characterized by diverse multisystem involvement and the production of different array of autoantibodies. Clinical features in individual patients can be quite variable, ranging from mild joint and skin involvement to severe life-threatening internal organ disease [1].

The chemokine (CXC) ligand 13 protein (CXCL13), also known as B cell-attracting chemokine-1 (BCA-1), is the most potent B-cell chemoattractant. It elicits its effect by interacting with chemokine receptor CXCR5, which is normally expressed on mature B cells and follicular T helper cells [2].

The CXCL13 expression was shown to be sufficient to induce the formation of ectopic lymphoid tissues in non-lymphoid organs, leading to exacerbation of the disease via accumulation of inflammatory cells in the kidneys in SLE [3–5].

Furthermore, it is believed that the presence of ectopic lymphoid tissues promotes the local activation of both T and B cells leading to exacerbation of the disease [6].

Moreover, CXCL13 was one of few inflammatory markers that were expressed in the lupus nephritis (LN) at an early point of the disease, suggesting a possible pathogenic role for disease manifestation [7, 8].

Therefore, this study aimed to investigate whether serum levels of CXCL13 is elevated in patients with active SLE, and correlate their levels with disease activity.

Patients and methods

Fifty-seven adultsystemiclupus erythematosus patients (6 males and 51 females)were recruited at Rheumatology and Rehabilitation Department, Assiut University Hospitals.They were diagnosed according to Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for the classification of systemic lupus erythematosus [9]. Disease activity was evaluated using SLE disease activity index (SLEDAI)[10–11]. Patients suffering from acute infections were excluded.

All patients included in this study were subjected to full history taking, General examination and systemic examination. Baseline investigations including CBC, ESR (westergreen), quantitative CRP, liver & kidney function tests, complete urine analysis. Creatinine clearance, ANA, anti-dsDNA (by ELISA), and C3&C4 (by ELISA) was also estimated.

Chemokine CXCL13 was measured by enzyme-linked immunosorbent assay(ELISA) using Quantikine® ELISA kit (Human CXCL13/BLC/BCA-1 Immunoassay) (R&D Systems, Inc., Canada), following the manufacturer's instructions. The CXCL13 was considered to be positive if > 55.2 pg/ml by ROC curve procedure (AUC = 1, sensitivity 100 %, and specificity 100 %) to discriminate diseased and non-diseased. A calculated CXCL13 cut-off value of > 134.2 pg/ml (AUC = 0.79, 66.7 % sensitivity and 100 % specificity) resulted in discriminating active SLE patients from inactive.

Thirty healthy volunteers, sex and age matched with the studied group, were enrolled in the study serving as a control group.

The above protocol was approved by the Ethics Review Board of Faculty of Medicine, Assiut University, and informed consent was obtained from all participants according to the Declaration of Helsinki.

Statistical analysis

The data were coded and entered using the statistical package for the social science program ((SPSS) version 17 Chicago, USA. The data were summarized using descriptive statistics: mean ± standard deviation (± SD), or frequencies (n) and percentages (%). Difference in plasma concentration among groups was compared with Kruskal–Wallis test (H-value). Spearman's correlation test was used to assess the correlation of CXCL13 with different SLEDAI parameters (P > 0.05 non-significant, P < 0.05 significant, P < 0.01 moderate significant, and P < 0.001 highly significant). Regression analysis was done to assess the predictors of increased CXCL13 levels. Furthermore, ROC curve was used to calculate the cut-off values of the CXCL13.

Results

Clinical and demographic data

Fifty-seven SLE patients were recruited in the study, their ages ranged between (18–60 years old), 89.5 % were females and 10.5 % were males and their mean disease duration was (4.6 months, ± 4 SD). Fifty four patient suffered a sort of SLE activity (37 patients had mild/moderate disease activity, while 17 had severe activity). Moreover, 98.2 % of the patients suffered constitutional symptoms (which included fatigue, fever, weight loss and loss of appetite). Mucocutaneous manifestations (photosensitivity, malar rash, hair loss, oral and nasal ulcers) was present in 96.5 % of the studied group, while CNS clinical manifestations (headache, psychosis, convulsion) was present in 40.4 % of them (▶ **Table 1** and ▶ **Fig. 1**).

Serum levels in SLE patients and controls

Regarding CXCL13 levels it ranged between (20.3–55.2 pg/ml) in the control group, while the range was (85.2–451.9 pg/ml) in SLE patients. A high statistical significance difference was present on comparing the mean values among both groups (▶ **Table 1** and ▶ **Fig. 2**).

Comparison between CXCL13 and SLEDAI grades

A Comparison between CXCL13 and SLEDAI grades (between control and study group, and also among patients' groups) using Kruskal-Wallis test revealed a high statistical significant difference (p-value < 0.0001) regarding the CXCL13 values in between these groups (▶ **Table 2**).

Correlations between CXCL13 and different SLEDAI parameters, SLEDAI, renal SLEDAI and non- renal SLEDAI in SLE patients

Correlation between different SLEDAI parameters and CXCL13 was calculated, and revealed a significant correlation between hair loss, malar rash, arthritis, 24 h protein in urine, urinary casts, hematuria, pyuria, C3, C4, anti-ds DNA and CXCL13. Arthritis showed statistically significant correlation (**r** = 0.328, p < 0.013), hair loss (**r** = 0.378, p < 0.004) and photosensitivity (**r** = 0.443, p < 0.001) which is a highly statistically significant correlation and lastly malar rash shows very high statistically significant correlation (**r** = 0.452, p < 0.0001). C3 and C4 had a negative significant correlation with CXCL13 (**r** = − 0.661, p < 0.0001; **r** = − 0.326, p < 0.033 respectively) (▶ **Table 3**).

A high significant direct positive correlation was found between total SLEDAI and non-renal SLEDAI on one hand and CXCL13 levels on the other hand (▶ **Table 4**), but no significant correlation between renal SLEDAI and CXCL13.

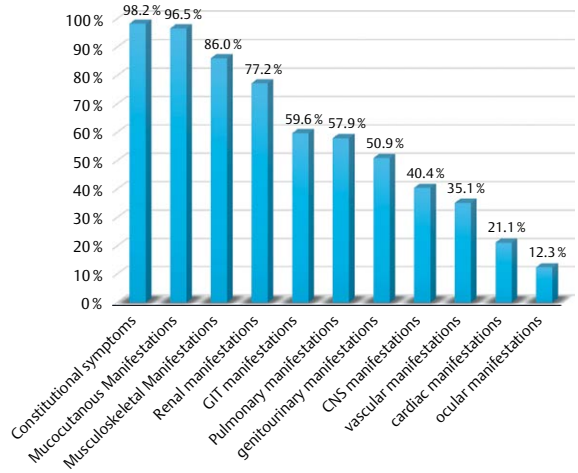
Regression analysis

Multiple regression analysis was done to detect the most significant predictors of CXCL13 levels which were found to be C3 (B = − 122.252, p < 0.0001) and malar rash (B = 64.748, p < 0.001). Hair loss, arthritis and C4 were other significant predictors of CXCL13 levels (▶ **Table 5**).

▶ **Table 1** The demographic data of SLE patients.

	Patients (N = 57)	Control (N = 30)
Sex	No. (%)	No. (%)
Female	51 (89.5 %)	26 (86.7 %)
Male	6 (10.5 %)	4 (13.3 %)
Age (years)		
Range	18–60	20–52
Mean ± SD	30.2 ± 10.7	35 ± 9.8
Duration of illness (months)		
Range	2–15	NA
Mean ± SD	4.6 ± 4	NA
Grade of activity (SLEDAI)		
Inactive (≤ 3)	3 (5.3 %)	NA
Mild/moderate (3–12)	37 (64.9 %)	NA
Severe (> 12)	17 (29.8 %)	NA

NA not available

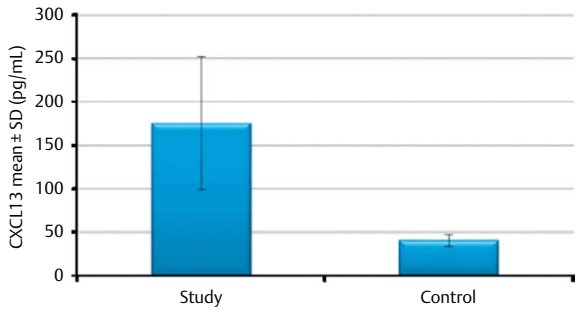


▶ **Fig. 1** Clinical manifestations of SLE patients.

Discussion

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease in which diverse immunological events can lead to a similar clinical picture, characterized by a wide range of clinical manifestations and target organ with unpredictable flares and remissions that eventually lead to permanent injury [12].

The diagnosis of SLE must be based on the proper constellation of clinical findings and laboratory evidence. Management depends on disease severity. Periodic follow-up and laboratory testing are important to detect signs and symptoms of new organ-system involvement and to monitor the response or adverse reactions to therapies.



▶ **Fig. 2** Comparison between mean CXCL13 levels in SLE patients and controls.

▶ **Table 2** Comparison between CXCL13 levels in SLE patients and controls.

CXCL13 (pg/ml)	SLE patients (n = 57)	Control (n = 30)	p value
Mean +SD	175.4 ± 76.7	39.9 ± 6.1	< 0.001 * *
Range	85.2–451.9	20.3–55.2	

Kruskal–Wallis test was used to compare the difference of CXCL13 mean levels among groups

▶ **Table 3** Correlation between CXCL13 and SLEDAI parameters.

SLEDAI parameters	CXCL13	
	r value	P value
Hair loss	0.378	0.004 * *
Malar rash	0.452	0.0001 * * *
Mucocutaneous ulceration	0.074	0.584 NS
Arthritis	0.328	0.013 *
24 h protein	0.451	0.0001 * * *
Urine casts	0.074	0.586 NS
Hematuria	0.018	0.893 NS
Pyuria	0.188	0.162 NS
C3	− 0.661	0.0001 * *
C4	− 0.326	0.033 *
Anti-ds DNA	0.335	0.011 *

r value Spearman's correlation coefficient; * Statistically significant correlation ($p < 0.05$); * * High statistically significant correlation ($p < 0.001$); * * * Very high statistically significant correlation ($p < 0.0001$)

▶ **Table 4** Correlation between CXCL13 and different SLEDAI.

Types of SLEDAI	CXCL13	
	r value	P value
SELDAI	0.547	0.0001 * * *
Renal SELDAI	0.231	0.084
Non-renal SELDAI	0.559	0.0001 * * *

r value Spearman's correlation coefficient; * Statistically significant correlation ($p < 0.05$); * * * Very high statistically significant correlation ($p < 0.001$)

▶ **Table 5** Clinical and laboratory predictors of CXCL13 levels.

	Unstandardized beta (B)	Standardized beta (ß)	Significance
Malar rash	64.748	0.396	0.001 * *
Hair loss	46.873	0.304	0.012 *
Arthritis	53.699	0.328	0.013 *
C3	− 122.252	− 0.491	0.0001 * *
C4	− 50.319	0.308	0.019 *

Multiple regression test was used; * Statistically significant correlation ($p < 0.05$); * * High statistically significant correlation ($p < 0.001$)

Assessment of disease activity poses a challenging problem as any organ system can be affected and it is well known that SLE may mimic manifestations of other diseases. As there is no single biomarker that adequately reflects disease activity, numerous composite clinical indices have been developed for assessment of disease activity [13].

B cell lymphocytes play a large role in the humoral immune response, and are essential component of the adaptive immune system. Besides their principal functions,(in making antibodies against antigens, perform the role of antigen-presenting cells (APCs) and eventually develop into memory B cells after activation by antigen interaction),they are responsible of several cytokine and chemokine production and lymphoid tissue organization [14]. So, B-cell lymphocytes play an important role in the pathogenicity of SLE. CXCL13 is the only chemokine so far which is known to specifically chemoattract B cells through the interaction with its receptor CXCR5 [15].

In the current study, the patients showed different stages of the disease, different systems affection and different durations of the disease (starting from 2 months duration up to 15 years). This supports our assumption that we have covered most of variety of patients with SLE during the study period. This is in contrary to the work of Stohl and colleagues, 2003, who mentioned that, the

patients they studied may not be completely representative of the entire SLE population, since the presence of active disease was a criterion for study enrollment [16].

Our results revealed that CXCL13 levels were significantly higher in SLE patients than controls ($p < 0.0001$), and still remained significantly elevated in inactive SLE patients (SLEDAI < 3) compared to healthy controls, probably indicating aberrant B-cell trafficking even in remission.

So, one hundred percent of our patients had elevated levels of CXCL13 levels which agreed with Schiffer et al. (2009 and 2011), Wong et al. (2010) and Ezzat et al. (2011), who approved that CXCL13 levels were significantly elevated in SLE patients (regardless their disease activity) compared to controls, suggesting a central role of CXCL13 in the pathogenesis of SLE [15, 17. In this study, our patients had a significant positive correlation (P value = 0.011) in CXCL13 serum levels with anti dsDNA antibodies levels which suggest that the increased levels of CXCL13 appear to be associated with the production of anti-dsDNA antibodies[15].

Our results coincide with the results obtained by Ezzat and colleagues (2011), which revealed that increased levels of CXCL13 in SLE patients are associated with increased production of anti-dsDNA antibodies, confirming that CXCL13 participate in disease pathogenesis as anti dsDNA antibodies do [19].

Our study established a link between CXCL13 and SLE disease activity. The total score of SLEDAI showed a highly significant linear correlation with CXCL13 plasma level of ($r = 0.547$) and (P-value = 0.0001). Additionally, there was a significant difference regarding the mean CXCL13 values between patients' groups (graded according to the SLEDAI score).

These results agreed with Schiffer et al. (2009 and 2011) and Wong et al. (2010), who mentioned that increased CXCL13 levels were associated with worsening in SLE disease activity, as well as anti-dsDNA antibody levels [15, 17. In current study, among the variants used in calculating SLEDAI score, significant relations were detected between plasma CXCL13 levels and each of mucocutaneous manifestations (in the form of malar rash, hair loss and photosensitivity), arthritis, 24 h protein, complement levels and anti-ds DNA antibodies levels while other variants didn't. This agreed with Ezzat et al. (2011) and Hafez et al. (2014), where a correlation between increased CXCL13 levels and clinical SLE activity was determined specially proteinuria [19–20].

Dendritic cells are primary source of CXCL13 secretion, which are often located in mucosal, glandular, and cutaneous regions [21. Because much of the pathology of SLE is dermal and oral, it is reasonable to speculate that overactivity of the dentiritic cells may contribute to elevated levels of CXCL13, and thus to SLE disease flares [23]. This may explain that in our study the CXCL13 levels were significantly correlated to dermatological components of SLEDAI score mainly malar rash and hair loss. This is also in agreement with McCarthy et al. (2013), who concluded that patients with skin involvement had higher CXCL13 levels than those without these clinical characteristics [24].

Although presence of significant correlation between plasma CXCL13 levels and hypocomplementemia, anti-dsDNA, and 24 h protein levels, which agree with some reports and disagree with others [15, 19], but it was not correlated to renal SLEDAI, suggesting future modifications to renal activity index depending on both plasma and urinary essential tests for more accurate nephritis activity evaluation.

Interestingly, out of our concerns, it was noticed that CXCL13 was significantly correlated with arthritis in such patients, which made us wonder about its mechanism in joint affection in SLE, and its similarity to rheumatoid arthritis immunopathogenesis [25, 26].

In conclusion, we detected elevated plasma levels of CXCL13 in all our SLE patients. A cutoff point for plasma CXCL13 levels between active and inactive SLE patients was also calculated, which prove the role of CXCL13 in the autoimmune process of SLE disease.

Among the variants used in calculating SLEDAI score, we detected significant correlation between plasma CXCL13 levels and each of anti-ds DNA antibody levels and complement levels. Also we found a significant difference in mean plasma CXCL13 levels between patients with and patients without mucocutaneous manifestations and arthritis of SLE.

Finally, our results revealed the importance of CXCL13 in SLE disease regarding its apparent role in SLE disease activity.

Interessenkonflikt

The authors declare that they have no conflict of interest.

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