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ORIGINAL ARTICLE

The Role of Fractalkine/CX3CL1 in Children with Lupus Nephritis.

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ABSTRACT

Background:- renal biopsy the gold standard for diagnosing lupus nephritis (LN) is an invasive technique, other laboratory markers lack sensitivity and specificity. **Aim**:- to evaluate serum fractalkine (CX3CL1) as a predictor for LN in children with systemic lupus erythematosus (SLE). **Methods:-** forty-four children "5 - 18 years old" newly diagnosed with SLE, 22 (50.0%) of them were complicated with lupus nephritis "diagnosed by renal biopsy", and 22 healthy age and sex matched children were included as a control group. Serum Fractalkine levels were determined using human CX3CL1 ELISA.

Results:- healthy children had lower serum fractalkine levels (median: 950.56 pg/ml, range: 591.55-1583.29**)** than both patient groups p<0.001, while there were as no significant differences between patients with LN (median: 1389.35 pg/ml, range 711.22– 16547.51) and without LN (median: 1429.39 pg/ml, range 591.55 – 4700.21), p=0.46. Moreover, serum Fractalkine was not correlated with the stage of LN (r=0.29, P=0.21) **Conclusion:-** Serum fractalkine is a poor predictor of lupus nephritis in children with SLE, although more studies are still required.

Keywords:- Biomarkers; CX3CL1; Fractalkine; pediatric lupus nephritis; systemic lupus erythematosus.

INTRODUCTION

Lupus nephritis (LN) is a major cause of morbidity and mortality in childhood- onset systemic lupus erythematosus (cSLE), it occurs in 50% to 75% of children with SLE often within the first two years of diagnosis, early diagnosis is important for the outcome of therapy [1]. Immune complex deposition and complement activation are causes of renal cell damage with subsequent release of inflammatory mediators; these mediators attract leukocytes into the inflamed renal tissue to augment inflammation and kidney damage. Therefore, the recruitment of immune cells to the inflamed kidney is a critical step in the development of LN [2].

Some chemokines are more commonly related to LN than others based on both studies of lupus-prone mouse models and SLE patients [3]. Fractalkine (Fkn; CX3CL1) "the only member of a unique family CX3C" is synthesized mainly by endothelial cells [4]. It exists in two forms; the membrane form which acts as an adhesion molecule and the soluble form (sFkn) which is a chemoatractant for inflammatory/immune cells that carry its receptor (CX3CR1) [5].

Tissue expression of CX3CL1 and CX3CR1 as well as their serum levels were up-regulated in patients with many renal disorders; CX3CL1/CX3CR1 axis was implicated in the pathogenesis of such disorders including diabetic nephropathy, IgA nephropathy, allograft rejection, and adult lupus nephritis. Moreover, CX3CL1/CX3CR1 axis was proposed to be a potential therapeutic target [6].

Although kidney biopsy is the gold standard to diagnose and classify LN it is an invasive technique. Other markers in serum and urine are widely used to predict LN, such as the anti-double stranded DNA, complements, erythrocyte sedimentation rate, but these markers often lack specificity and sensitivity for the diagnosis of lupus nephritis. Therefore, noninvasive, more specific and sensitive indicators for the early prediction of lupus nephritis are needed [7].

Serum Fractalkine has been studied previously in adults with lupus nephritis, but it has not been studied in children yet; this encouraged us to carry out this research to evaluate its efficacy to predict LN in children with SLE.

SUBJECTS AND METHODS

This case control study was conducted in the Clinical pathology and Pediatrics departments, faculty of medicine, Zagazig University, Al-sharquia governorate, Egypt, from January 2019 to January 2020. Children >1 and ≤ 18 years from both genders that were newly diagnosed with juvenile SLE were involved. Patients whose parents disagree to sign a written informed consent, attending with other complications of active SLE as vasculitis and neuropsychiatric manifestations, who suffer from any other systemic diseases, or who began therapy were excluded.

Sample size calculation and ethical approval

Assuming that serum (ng/mmol) in nephritic group 4.44±3.05 and non-nephritic group 2.37±1.88, the sample size was 44 patients 22 in each group. Using epi-info at 80% power and at 95% confidence interval [8]. This work was approved by the Zagazig University-Institutional Research Board (ZU-IRB); the number of approval (4852/10-9-2018). Work is carried out in accordance with the declaration of Helsinki. Written informed consent was obtained before enrollment.

Data collection and Routine laboratory investigations Data from history taking and clinical examination were obtained. Routine laboratory investigations results including Complete blood count (CBC), Liver and kidney function tests, Prothrombin time (PT), international normalized ratio (INR), Urine analysis, 24 hours urine protein, ESR, CRP, C3 and C4 concentrations, ANA and Anti-ds DNA were recorded.

Diagnosis of SLE and lupus nephritis Systemic lupus erythematosus was diagnosed according to the new 2019 European league against rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus (EULAR). Lupus nephritis was confirmed and classified by renal biopsy based on the International Society of Nephrology and the Renal Pathology Society classifications [9].

Measurement of Fractalkine serum levels

Two milliliters of whole blood were collected from controls and patients upon diagnosis; separated sera were stored at −20°C till the time of analysis, serum levels of Fractalkine were measured using human CX3CL1 ELISA kit (Nova Lifetech Inc. Hong Kong, China) that depends on the sandwich ELISA technique.

Statistical analysis Data analysis was carried out using SPSS version 22.0 (IBM Corp., Chicago, IL, USA). Shapiro–Wilk test was performed to test the normality of data. Normally and non-normally distributed data are presented as means ± standard deviation or medians and ranges, respectively. The t-test and one way analysis of variants were used to compare means, while Mann-Whitny and Kruskal-Wallis tests were used to compare medians. Categorical data were analyzed using Chi square or Fisher's exact test if results are less than five. Spearman coefficient (r) was applied to test the correlations, results were considered significant when p value is less than or equals 0.05.

RESULTS

This study included 44 children with SLE, 22 were presented with LN and 22 were not, their ages ranged from 5 to 18 years old, with female predominance “40 (90%) of cases were females”, there were no significant differences regarding demographic feature in between both patient groups as well as the control group. Demographic features are presented in table 1.

There were no significant differences regarding the presenting symptoms of patients among both patient groups, cases with LN presented more frequently with high RBCs, albumin, protein, and blood casts in urine. Presenting symptoms, urine analysis results, and distribution of LN stages are presented in table 2.

Apart from the kidney functions test and 24 hours protein, none of the laboratory tests showed significant differences among the patient groups. Serum creatinine, blood urea nitrogen, and 24h protein in urine were significantly increased in the LN group $p<0.001$, laboratory investigation results were summarized in tables 3 and 4.

The performance of urine analysis and 24h proteins in urine to predict LN were compared against renal biopsy, urinary sediments predicted LN at sensitivity 72.7% (95% confidence interval (CI): 49.78% to 89.27%) and specificity 68.18% (95% CI: 45.13% to 86.14%) and accuracy 70.45% (95% CI: 54.80% to 83.24%), while the 24h urine proteins “cutoff 500 mg/l” predicted LN at sensitivity 77.27% (95% CI: 54.63% to 92.18%), specificity 100.00% (95% CI: 84.56% to 100.00%), and accuracy 88.64% 95% CI: 75.44% to 96.21%).

Regarding the serum fractalkine, both patient groups had higher levels than healthy children, $p<0.001$, while there were no significant differences between patients with and without LN $p=0.46$, medians and ranges of serum Fkn level in all the studied groups are illustrated in table 5.

By testing the correlation of serum Fractalkine with all the numerical variables in both patient groups it was figured out that; there was a statistical significance positive correlation between serum Fractalkine and Albumin among patients with LN also there was a statistical significance positive correlation between serum Fractalkine and PT &

C3 and a statistical significance negative correlation between serum Fractalkine and Albumin among patients without LN, data are illustrated in table 6.

Table (1): Demographic data of the studied patient groups:

Variable		Control (*n*=22)		SLE With LN (*n*=22)		SLE Without LN (*n*=22)		F	P
Age (years)	*Mean ± SD* *Range*	13.71 ± 3.38 7.5 - 18		12.34 ± 2.49 8.5 – 17		13.96 ± 2.99 5 - 18		1.87	0.16
Variable		**No**	**%**	**No**	**%**	**No**	**%**	χ^2	**p**
Sex	*Female* *Male*	18 4	81.8 18.2	20 2	90.9 9.1	20 2	90.9 9.1	1.14	0.57

SD: Standard deviation, F: ANOVA test, χ^2: Chai square test.
LN: lupus nephritis, SLE: systemic lupus erythematosus

Table (2): presenting symptoms, urine analysis, and stage of LN among the studied cases groups:

Variable		SLE With LN (*n*=22)		SLE Without LN (*n*=22)		T	P
		No	**%**	**No**	**%**	χ^2	**P**
Symptoms	*No*	2	9.1	2	9.1	0	1
	Yes	20	90.9	20	90.9		
	Arthralgia	7	31.8	9	40.8		
	Bleeding	3	13.6	2	9.1		
	Disability to walk	5	22.7	3	13.6		
	Fever	7	31.8	2	9.1		
	Skin Rash	4	18.2	3	13.6		
	Cold like symptoms	2	9.1	0	0	20.85	0.23
	Vomiting	3	13.6	2	9.1		
	Oral ulcer	2	9.1	0	0		
	Puffiness	2	9.1	0	0		
	Edema	2	9.1	6	27.3		
	Abdominal pain	1	4.5	2	9.1		
	Pallor	1	4.5	0	0		
	Squint	1	4.5	0	0		
	Purpura	1	4.5	2	9.1		
	Loss of appetite	1	4.5	0	0		
	Jaundice	0	0	2	9.1		
	Fatigue	0	0	1	4.5		
	Thrombocytopenia	0	0	1	4.5		
Urine analysis Findings:	***Normal***	0	0	1	4.5	0	0.9
	Physical examination						
	Turbid	2	9.1	2	9.1	0	1.0
	Chemical examination						
	PH=5	1	4.5	5	22.7	0	0.2
	PH > 7.5	5	22.7	8	36.4	0.4	0.5
	Albumin	4	18.2	0	0	0	**0.05**
	Protein	11	50	0	0	12.1	**<0.001**
	Sugar	1	4.5	0	0	0	0.9
	Microscopic examination						
	↑RBCs	8	36.4	2	9.1	4.6	**0.03**
	↑PUS cell	12	54.5	12	54.5	0.09	0.7
	Blood cast	4	18.2	0	0	0	**0.05**
	Ca oxalate	0	0	3	13.6	0	0.1
Renal biopsy:	*II*	8	36.4				
	II & Eraly III	3	13.6	----	---	---	----
	III	4	18.2				
	IV	7	31.8				

SD: Standard deviation, t: Independent t test, χ^2: Chai square test. Significant p values are written in bald

Table (3): Liver and Kidney function tests among the studied cases groups:

Variable	SLE With LN (*n*=22)	SLE Without LN (*n*=22)	MW	P
Creatinine (mg/dl)	0.72 0.33 – 5.58	0.48 0.29 – 0.57	3.52	**<0.001**
24h protein (mg/l)	876.8 33.96 – 4062.4	78.45 11.56 – 469.7	5.19	**<0.001**
BUN (mg/dl)	28.25 10 – 83.3	11 6.5 – 27.7	3.64	**<0.001**
T.Bilirubin (mg/dl)	0.79 0.09 – 1.4	0.49 0.13-2.2	0.75	0.45
D.Bilirubin (mg/dl)	0.18 0.05 - 0.43	0.21 0.06 – 4.1	1.39	0.16
Albumin (gm/dl)	3.42 1.2 – 6.32	3.79 2.4 – 4.6	1.09	0.28
SGPT (IU/L)	16.15 6.6 – 198.6	23.6 9.8 – 211.6	1.53	0.13
SGOT (IU/L)	19.35 10.2 – 482.9	23 12.2 - 354.4	0.98	0.33

BUN: blood urea nitrogen
MW: Mann Whitney test
Data are expressed as median and ranges
Significant p values are written in bald

Table (4): Other laboratory findings among the studied cases groups:

Variable		(With LN) (*n*=22)	(Without LN) (*n*=22)	Test	P
CRP (mg/dl)	*Median* *Range*	2.55 0.09 – 121.7	1.83 0.9 – 40.84	MW 0.47	0.64
ESR (mm/h)	*Median* *Range*	95 29 - 140	70 20 - 145	MW 1.74	0.08
C3 (g/l)	*Median* *Range*	0.45 0.09 – 1.73	0.34 0.03 – 1.69	MW 0.47	0.64
C4 (g/l)	*Median* *Range*	0.10 0.02 – 0.40	0.08 0.02 – 0.79	MW 0.61	0.55
TLC (x10^3/mm^3)	*Median* *Range*	6.05 2.9 – 21.9	5.55 2.3 – 16.7	MW 0.11	0.92
Platelets (x10^3/mm^3)	*Median* *Range*	201 10 - 431	264 6 - 1147	MW 0.88	0.38
Hb (g/dl)	*Mean ± SD* *Range*	10.18 ± 1.16 7.6 – 11.9	10.27 ± 2.77 3.5 – 14.3	T 0.14	0.89
RBC (x10^6/mm^3)	*Mean ± SD* *Range*	4.02 ± 0.55 2.8 – 5.2	3.89 ± 0.68 2.1 – 4.7	T 0.67	0.51
INR	*Mean ± SD* *Range*	1.22 ± 0.36 0.83 – 2.54	1.21 ± 0.14 1.04 -1.52	T 0.12	0.91
PT (sec.)	*Mean ± SD* *Range*	13.32 ± 2.68 10.2 – 18.3	12.74 ± 2.14 10.2 – 17.5	T 0.79	0.43

CRP: C reactive protein, C3: complement 3, C4: complement 4, ESR: erythrocyte sedimentation rate, h: hours, INR: international normalized ratio, MW: Mann Whitney test, PT: prothrombin time, SD: Standard deviation, t: independent t test

Table (5): Serum Fractalkine level among the studied groups:

Variable	Control (n=22)	SLE With LN (*n*=22)	SLE Without LN (*n*=22)	KW	P	LSD
SFkn (Pg/ml)	950.56 591.55-1583.29	1389.35 711.22 – 16547.51	1429.39 591.55 – 4700.21	**18.47**	**<0.001**	**<0.001**[1] 0.46[2]

KW: Kruskal Wallis test
[1] P value of controls versus SLE with LN and SLE without LN
[2] P value of SLE with LN versus SLE without LN

Table (6): Correlation between S Fkn and different parameters among the studied cases groups:

Variable		Serum Fractalkine	
		SLE With LN	**SLE Without LN**
Age	r	0.04	-0.25
	P	0.85	0.26
Stage	r	0.29	---
	P	0.21	---
Creatinine	r	0.05	0.02
	P	0.83	0.93
24 h protein	r	-0.32	-0.15
	P	0.15	0.51
Protein/creatinine Ratio	r	-0.37	---
	P	0.09	---
BUN	r	-0.11	-0.01
	P	0.64	0.95
T. bilirubin	r	-0.04	-0.05
	P	0.85	0.83
D Bilirubin	r	-0.19	-0.08
	P	0.40	0.71
Albumin	r	**0.61**	**-0.45**
	P	**0.003****	**0.04***
SGPT	r	-0.38	0.36
	P	0.08	0.10
SGOT	r	-0.36	0.07
	P	0.10	0.74
INR	r	0.20	0.20
	P	0.38	0.42
PT	r	0.03	**0.58**
	P	0.88	**0.005****
CRP	r	0.07	0.12
	P	0.73	0.60
1st ESR	r	0.21	0.24
	P	0.36	0.29
C3	r	-0.22	**0.54**
	P	0.36	**0.009****
C4	r	0.43	-0.56
	P	0.25	0.06
WBCs	r	0.18	-0.21
	P	0.42	0.36
Hb	r	0.08	-0.19
	P	0.73	0.39
Platelet	r	0.15	-0.14
	P	0.52	0.54
RBCs	r	0.01	-0.24
	P	0.95	0.29

BUN: blood urea nitrogenCRP: C reactive protein, C3: complement 3, C4: complement 4, ESR: erythrocyte sedimentation rate, h: hours, INR: international normalized ratio, LN: lupus nephritis, PT: prothrombin time, r: Spearman correlation coefficient
Significant p values are written in bald.

DISCUSSION

This study was conducted on 44 children with SLE and 22 healthy children as controls. The female/male ratio in the patient group was 10/1, this ratio came close to the female/male ratio of adults rather than pediatric patients "9/1 versus 4/1, respectively" [10], the inclusion of more adolescent patients in this cohort may be an explanation of this deviation, Mohammed et al. attributed the more female predominance among Egyptian patients with cSLE to other factors such as; regional, socioeconomic, ethnic, and vitamin D deficiency in female children [11].

Serum Fractalkine was significantly higher in patient groups than the healthy control; Yajima et al. [12] reported that serum fractalkine/CX3CL1 levels were significantly more elevated in patients with SLE than in the healthy controls, this finding opens the way to further investigate serum fractalkine/CX3CL1 as a diagnostic marker for SLE, future studies focusing on this point with the inclusion of patients with other autoimmune and inflammatory disease in comparison with SLE patients are recommended.

The aim of this work was to assess the efficiency of Fractalkine serum levels to predict the renal affection in young patients with SLE, but serum Fractalkine did not differ significantly in between patients with and without nephritis and did not correlate with the stage of nephritis. So, in this cohort, serum Fractalkine failed to predict LN in cSLE patients.

Although some previous studies came to the conclusion that serum Fractalkine is a good predictor of LN, most of these studies were experimental [13-16] and two studies included adult patients; one study considered the serum level of Fractalkine; where it was significantly higher in cases with proliferative lupus nephritis (Class III & IV) and lower in cases with non-proliferative lupus nephritis (class V) [8], and another one by Yoshimoto et al [17] who detected the increased glomerular expression of Fractalkine in frozen sections from LN patients' particularly in proliferative lesions.

The conflict between previous researches and ours can be explained by the differences in patient ages, Mina and Brunner [18] discussed the differences in the pathogenesis and the disease behavior between adults and children with LN, and claimed the underlying genetic variations and consequently its biological effects to be the cause of these phenotypic differences.

The appearance of hematuria, proteinuria and casts more frequently, and the higher protein/creatinine ratio and 24h urine proteins in patients with LN of this work, as well as the performance of these markers go with previous conclusions that proteinuria is still the hallmark of LN till the present time and is used as the main urinary marker for screening for renal involvement, and the urinary sediments are also useful [19], also; the presence of combined hematuria and RBCs cast is a criterion of LN diagnosis [20].

The impaired kidney functions in some of our LN patients highlights the recommendation of Almaani et al [21] that renal biopsy is indicated with any level of proteinuria or hematuria when combined with impaired renal function that cannot be attributed to any other causes. According to Mok et al [22], the current laboratory markers for LN are unsatisfactory as the renal damage can proceed the impaired renal function and the detection of laboratory changes.

Up to our knowledge, no previous literature considered the predictive value of Fractalkine for LN in pediatric patients either in Egypt or worldwide, so, further replication studies are required to confirm or deny our results. Although the kidney biopsy still has the upper hand in the diagnosis, classification, and monitoring of LN, the search for novel biomarkers is still necessary. Urinary biomarkers including urine Fractalkine (CX3CL1) are good candidates for future researches regarding pediatric LN, as they would be more specific for renal pathologies than their serum counterparts [23].

CONCLUSION

Serum fractalkine is a poor predictor of lupus nephritis in children with SLE, but more studies are still required.

The requirements for authorship have been met. All authors contributed to the study conception and design. The original idea was the first author's; the last author contributed to patient's selection, history taking, data collection, blood sample withdrawal, sample processing, results collection, and data analysis; under the supervision of the first three authors. The first author contributed to manuscript writing and submission for publication. Authors certify that we have personally written at least 90 percent of the manuscript. Finally, the manuscript has been read and approved by all the authors. All authors are responsible for reported research

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