IInternational Journal of Psychosocial Rehabilitation, Vol.24, Issue 01, 2020
ISSN: 1475-7192

Correlation between serum caspase-3 with clinical and laboratory manifestation of SLE

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ABSTRACT

Background: *SLE is a multisystem disease that is due to dysregulation of immune system and apoptosis process. Caspase-3 is one of the important enzymes in the apoptotic pathways. In this study we try to assess correlation between serum levels of this enzyme with some clinical and laboratory manifestations of SLE.* ***Methods:*** *we have enrolled 50 patients with SLE and measured their serum caspase-3 levels end have recorded some of the clinical and laboratory manifestation. Then we correlate these with corresponding serum caspase-3 levels.* ***Results and conclusions:*** *only Serum creatinine showed significant correlation with serum caspase-3 level*

Key words*: caspase-3, SLE, apoptosis*

Introduction

Systemic lupus erythematous is a multisystem autoimmune disorder with a broad spectrum of clinical presentations. There is a peak age of onset among young women between the late teens and early 40s, and a female to male ratio of 9:1, especially in women in child-bearing years; aged 15 to 35 There is a peak age of onset among young women between the late teens and early 40s(1). In the immune system, apoptosis counters the proliferation of lymphocytes to achieve a homeostatic balance, which allows potent responses to pathogens but avoids autoimmunity(2). Caspase-3 shares many of the typical characteristics common to all currently-known caspases. The CASP3 protein is a member of the cysteine-aspartic acid protease (caspase) family. Sequential activation of caspases plays a central role in the execution-phase of cell apoptosis. Caspases exist as inactive proenzymes that undergo proteolytic processing at conserved aspartic residues to produce two subunits, large and small, that dimerize to form the active enzyme. This protein cleaves and activates caspases 6 and 7; and the protein itself is processed and activated by caspases 8, 9, and 10 (3) (2). Defects in apoptotic cell death regulation contribute to many diseases, including disorders where cell accumulation occurs (cancer, restenosis)(4). In recent years, the molecular machinery responsible for apoptosis has been elucidated, revealing a family of intracellular proteases, the caspases, which are responsible directly or indirectly for the morphological and biochemical changes that characterize the phenomenon of apoptosis(5, 6). Diverse regulators of the caspases have also been discovered, including activators and inhibitors of these cell death proteases(7). Inputs from signal transduction pathways into the core of the cell death machinery have also been identified, demonstrating ways of linking environmental stimuli to cell death responses or cell survival maintenance(8). Defects in the clearance of apoptotic cells have been described in SLE which may lead to aberrant uptake by macrophages which then present the previously intracellular antigens to T and B cells, thus driving the autoimmune process(9). Autoantigens are released by necrotic as well as apoptotic cells(10). Diagnosis can thus be elusive, with some people suffering unexplained symptoms of untreated. SLE for years(11). Relapsing autoimmune disorder of connective tissue(12). SLE is of complex clinical character and generally affects multiple organ systems(13). The prevailing clinical manifestations including glomerulonephritis, vasculitis, and arthritis occur due to

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local tissue inflammation caused by the deposition of pathogenic autoantibodies and immune complexes in various tissues(14). Common initial and chronic complaints include fever, malaise, joint pains, myalgias, fatigue, and temporary loss of cognitive abilities. However, patients may present with any of the following types of manifestations, Proteinuria is the hallmark of renal disease in lupus and is extremely common, though hematuria is less common(15). Urinary casts are often seen, reflecting renal tubular dysfunction(16). About 5%–20% of nephritic patients will progress to end-stage renal disease, although rates appear to be decreasing and survival improving as a result of improved treatment regimens, SLE is a worldwide disease(16, 17). The global incidence of SLE is reported to be between 4 and 7 in 100,000 per year(18). This disease is 10–20 times more common in women than in men and the overwhelming majority of SLE patients develop their disease between 15 and 40 years of age(12, 18). Lupus nephritis (LN) is a severe manifestation of SLE associated with a risk of terminal renal failure and mortality(14). A recent study of predictors of incident proteinuria among patients with SLE confirms the significance of age and serological manifestations for the development of incident proteinuria after SLE diagnosis, Patients were defined as having incident proteinuria if they had two or more measures of elevated urine protein (either a protein to creatinine ratio of >0.5 or a 24-hour urine collection of >500 mg) at least 30 days apart and within 180 days. Once an episode of incident proteinuria was established based on the above definition, we defined that episode as the start date of the proteinuria(19).

Subjects and Methods

This study was conducted on patients who attended hospitals with consultations for kidney and joint diseases in the Holy Najaf, Holy Karbala and Babylon hospitals from the Rheumatology and Nephrology out clinics in these hospitals. Fifty patients (7 males &44 females) with age range between 15-50 years, and duration of disease between 1 year -25 years included in this study who were clinically checked by specialist and laboratory diagnosed as SLE. All patients have been informed about the study and its aims and their agreement were taken. Specimen collection: Five ml of venous blood were drawn from patients, collected in gel tubes, slow withdrawal of the blood sample via the needle of syringe to prevent hemolysis. The sample dropped into clean disposable gel tube; serum was separated after 20 minutes at room temperature. The samples were then centrifuged at 3500 rpm for 5 minute and then stored in to separated three eppendorf tubes at freeze condition(-20C) until analyzed.

Assessment of laboratory manifestation of SLE and assessment of apoptosis marker (caspase-3) was preformed using laboratory assays with the mentioned kits:

KITS	**Source**
Human CASP3 (Caspase 3) ELISA Kit	Elabscience
Creatinine	Roche
24 hr. urinary protein (mg)	Roche
Hemoglobin	Human
WBC	Human
Rheumatoid factor	Roche
Serum Albumin	Roche
ESR	Roche
C-reactive protein	Roche

Results

A total of 50 SLE patients were enrolled in this study. The Mean age for SLE patients was 29.2 ± 8.3 (range: 15 – 50) years. Almost 60% of SLE patients married, 5 SLE patients (11.1%) had history of abortion, smoking history reported in only 3 (6.7%) SLE patients, in all comparisons of these variables, P. value > 0.05, and Family history of SLE was positive in only one SLE patient.

Table 1. Bivariate correlation matrix between demographic characteristics of the patients and caspase 3.

Demographic characteristics	**Caspase3**

	R	P. value
Age Gr	-0.133	0.220
Gender	0.147	0.226
Abortion Number	0.131	0.230
Smoking	0.211	0.058

Table 2. Bivariate correlation matrix between caspase 3 and clinical characteristics of the patients.

Clinical characteristics	**Caspase3**	
	R	**P.value**
Rheumatoid factor	-0.266	0.077
Serum Albumin	-0.024	0.876
RBC cast	-0.070	0.648
ESR	0.084	0.584
Hemoglobin	0.106	0.488
WBC	0.147	0.337
C-reactive protein	0.168	0.269
Serum creatinine	-0.321	0.031
24 hr uriner protein(mg)	0.002	0.991
SLE duration	-0.060	0.697

Statistical analysis

Data of both studied groups were entered and analyzed using the statistical package for social sciences (SPSS) version 25. Descriptive statistics presented as mean, standard deviation, standard error, range, frequencies and proportions. Correlation coefficient (R) is an indicator of the strength and direction of correlations ; its value ranged zero (complete no correlation) to one (perfect correlation) the higher R value close to one indicated stronger correlation, the positive (no sign) R value indicated a direct (positive) correlation and the negative signed R indicated an inverse correlation. Level of significance of ≤ 0.05 was considered as significant difference or correlation. Results and findings were presented in tables and figures with explanatory paragraphs using the Microsoft Office 2010 for windows.

Discussion

The current study focused on the association the serum caspase 3with clinical and laboratory manifestation of SLE. This is a novel study we did not found pervious study that use serum level of caspase- 3to assess it role in patients with SLE. We do not find so much study to compare with these results these are a novel study. Apoptosis is a form of programmed cell death that is controlled by aspartate-specific cysteine proteases called caspases (20). we examined the level of Caspase- 3in sera patients using ELISA technique and a clarify the relationship between caspase-8 levels and clinical and laboratory manifestation of SLE. The current study showed the difference between male and female ratios in SLE patients. The male to female ratio was 10:40. Stanescu I-I, Calenic B,(21) they showed difference between male & female, expression of caspase 8 in gene level was lower in female than male The reason for this difference between male and female patients is not clear, but differences in sex hormones may be involved. In contrast to our finding a study of Zandman-Goddard G and Peeva E, they showed that the level of prolactin was increased in female and male SLE patients (22). We studied the relation with some immunological factors, these show no relation.

The current study showed significant correlation between serum caspase-3 level and Serum creatinine, the p. value < 0.05(0.031). This results nearly agree with (23) (26) Yang B and El Nahas AM , that consist with this study. A The current results agree with (24) Wen S, Wang Z-H, That confirmed a relationship between caspase 3 and serum creatinine .Present study showed no significant correlation between serum caspase- 3level and SLE rheumatoid factor, the p. value > 0.05 (0.077). This study also found that there is no significant correlation between Serum Albumin, Hemoglobin, WBC, 24hr uriner protein and C-reactive protein with serum caspase-3, the p. value > 0.05 (0.876, 0.488, 0.3370.991, and 0.269) respectively. The current study showed no significant correlation between serum caspase-3 level and SLE duration, the p. value > 0.05(0.697). Also, we checked other feature like, RBC cast and ESR, we not found positive correlation with serum caspase-3, the p.value is (0.648 and 0.584) respectively, was close to the statistical value 0.05, But it is not considered a positive statistical relationship. These differences are explained by the increase in kidney failure, such as decreased kidney function efficiency, and thus increased protein loss. This is consistent with a previous study in lupus patients by Petrackova A and Smrzova A, they showed increased organ damage, and active LN, with many novel candidate proteins detected. Their exact role and suitability as biomarkers in SLE deserve further investigation (25) .This indicates an increase in kidney damage associated with an increased disease effectiveness that is inversely proportional to the caspase 3, As explained Rastin M and Mahmoudi M in their research(26), which confirmed increased kidney damage is directly proportional to the effectiveness of the disease.

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