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Low Level of Activated Protein C and Protein S in Patients With Systemic Lupus Erythematosus are Associated With Thrombosis

KEYWORDS

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ABSTRACT *Thrombosis is a well-known clinical entity in patients with Systemic Lupus Erythematosus (SLE), and it is multifactorial. In this study we analyze activated protein C and protein S levels in a patient of SLE as a risk factor for thrombosis. A prospective case-control study was performed in a pathology department KGMU, Lucknow in year 2014-2015. 40 diagnosed patients with SLE and 40 control of same age and sex were included in this study. Plasma protein C and protein S activity were studied in above patients. After analysis, thrombotic episodes were seen in 15% of SLE patients. Reduced plasma protein C and protein S level were found to be a risk factor for thrombosis and hence it may be advisable to suggest screening tests for thrombotic risk factors at the time of SLE diagnosis to prevent life threatening thrombotic complications.*

Introduction: Systemic lupus erythematosus (SLE) is an autoimmune disease in which organ and cells undergo damage initially mediated by tissue binding autoantibodies and immune complexes and leads to various clinical manifestations. Ninety percent of patients at the time of diagnosis are female of childbearing age. Prevalence of SLE in united state at the time of diagnosis is 10 to 400 per 1, 00,000 depending upon race and gender [1]. SLE is rare in India with prevalence is less than 3.2 per 1,00,000 and the median age of onset in Indian SLE patients is 24.5 years and the gender ratio of female to male is 11.1 [2].

One of the major complication in SLE patients is arterial and/or venous thrombosis with prevalence >10%. This prevalence may exceed 50% in high risk patients [3]. Antiphospholipid antibodies are detected in 60% of patients of SLE with history of thrombosis [4]. Protein C (PC), protein S (PS), and antithrombin deficiencies are rare but carry a higher risk for venous thrombosis [5].The PC pathway is one of the most important anticoagulant systems. PC is activated on endothelial cells by thrombin bound to thrombomodulin. The activated PC exerts its anticoagulant function by proteolytic cleavage of the procoagulant protein factors Va and VIIIa [6].

Objective: To study the analysis of plasma protein C and protein S level in patients of Systemic lupus erythematosus.

Material and methods: This is a type of prospective study of one year duration from August 2014 to August 2015. 40 diagnosed cases of patient with SLE attending Rheumatology OPD, KGMU, Lucknow in year 2014-2015 had taken. 40 normal individuals of same age and sex had taken as control. SLE patients those were taking vitamin K, antithrombotic and antiplatelet drugs including aspirin, oral contraceptives not included in the study. In the present study we measured level of PC and PS with proper tests in cases and controls. Data were entered into Microsoft excel and analyzed using Epi Info 7.1.3.0 statistical software. Data was expressed in terms of percentages, mean and SD. Chi- square and t test were used to test for the association of plasma protein C and protein S level with thrombosis.

Results: In this study we divided SLE patients on the basis of history of thrombosis into two Groups (Table-1). PC levels were found to be normal (≥70 IU/dL) in 67.50% Cases and 97.50% Controls and in rest of the Cases (32.50%) and Controls (2.50%) were found to be below normal (<70 IU/dl). Difference in PC level of Cases and Controls was found to be statistically significant (p<0.001). PS levels were found to be normal (≥ 65 IU/dL) in 67.50% Cases and all the Controls (100.0%) in rest of the cases PS levels were found to be below normal (<65 IU/dL). Difference in PS level of Cases and Controls was found to be statistically significant (p<0.021) (Table-2).

Mean PC and PS levels were higher in Group II as compared to Group I difference was found to be statistically significant. Comparison of levels of PC and PS between Subgroup IIA and Subgroup IIB and it was found that PC and PS were found to be higher in Subgroup IIA than Subgroup IIB and difference was found to be statistically significant. Comparison of levels of PC and PS between Group I and Subgroup IIA it was found that PC and PS were found to be higher in Group I as compared to Subgroup IIA to be statistically significant. Comparison between Group I and Subgroup IIB levels of PS and PC were lower in Group I as compared to Subgroup IIB difference was found not to be statistically significant (Table- 3,4).

Discussion: Thrombotic events in the patients of SLE may leads to various serious complications such as deep vein thrombosis, recurrent abortions, gangrene, pulmonary embolism, cardiovascular manifestations, stroke etc. As described by Burgos et al that one of the most common factor for causing thrombosis is antiphospholipid antibodies (APLA) which are responsible for majority cases. In several other risk factors, thrombophilic factors (PC, PS, Homocysteine and Fibrinogen) and platelets also have role in thrombosis but they contributes minority of cases [7].

Freyssinet JM et al. suggested that an IgM lupus anticoagulant neutralizes the enhancing effect of phospholipids result in a reduced activation of PC which could be responsible for the occurrence of thrombotic complications in a patient with SLE [8]. In a study by Nojima J et al it was found that Patients with SLE frequently have some APLA to

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PC and PS and these antibodies having antigenic specificities to different phospholipids which leads to thrombotic complications in SLE, alone or in combination [9]. In the study of Simmelink MJ et al it was found that presence of lupus anticoagulants in plasma was a major risk factor for thrombosis it interfere with activation of PC, a natural antithrombotic in plasma[10].

The study of Guermazi S et al suggested that an auto-immune mechanism could account for low PS activity in patients with SLE. Auto-antibodies to PS may form immune complexes, inducing increased clearance of PS or interfering with the PC-PS system [11]. The study of Ginsberg JS et al confirms an association between APLAs and reduced free PS levels and demonstrates that patients with SLE and acquired free PS deficiency generate more thrombin than patients with SLE and normal free PS levels and which was responsible for thrombotic diathesis [12].

In the present study PC activity is decreased in 32.5% (13 patients) of cases as compared to control and the 15% (6 patients) of patients who had history of thrombosis also had decreased PC activity. This correlation was statistically highly significant with p value<0.001. Hence this concluded the relation between thrombosis and decreased level of PC activity. When we studied intergroup comparison it was found that mean value of PC activity was decreased in group I and Subgroup IIb and these differences are statistically significant between Group I and Group II (p value <0.001), Group I and Subgroup IIa (p value <0.001), Subgroup IIa and Subgroup IIb (p value <0.001).

In the present study PS activity is also decreased in 32.5% (13 patients) of cases as compared to control and the 15% (6 patients) of patients who had history of thrombosis also had decreased PS activity. This correlation was statistically highly significant with p value <0.001. Hence this concluded the relation between thrombosis and decreased level of PS activity. When they studied intergroup comparison it was found that mean value of PS activity was decreased in group I and Subgroup IIb and these differences were statistically significant between Group I and Group II (p value <0.001), Group I and Subgroup IIa (p value <0.001), Subgroup IIa and Subgroup IIb (p value <0.001).

When we compare between group 1 and group 2 it was seen that in group 1 having all patients (100%) with history of thrombosis have decreased PC and PS activity while in group 2 with no history of thrombosis only 20.59% of patients have decreased PC and PS activity. Hence there was correlation between thrombosis and decreased PC and PS activity and this correlation was statistically significant (p value is 0.001). In this study, it was seen that PC and PS values were reduced in both patients with thrombosis(Group I) and without thrombosis(SubgruopIIb) hence it shows that PC and PS alone were not responsible for thrombosis but some other factors were also responsible for thrombosis.

Conclusions: Risk of thrombosis is higher in SLE patients. In this study it was found that reduced level of plasma PC and PS activities in patients of SLE are correlated with thrombosis. Hence it may be advisable to suggest screening tests for thrombotic risk factors at the time of SLE diagnosis and start appropriate antithrombotic therapy if required to prevent life threatening thrombotic complications, because the patients without history of thrombotic manifestations, but having thrombotic risk factors may developed thrombosis in future.

Table-1 Group wise Distribution of Cases

	Description	No.	%
Group I	H/o of Thrombosis with decreased Protein C & Protein S levels	6	15.00
Group II	No History of Thrombosis	34	85.00
Subgroup IIA	No history of Thrombosis and normal Protein C & Protein S levels	27	67.50
Subgroup IIB	No history of Thrombosis and decreased Protein C & Protein S levels	7	17.50

Table-2 Comparison of Protein C and S levels among Cases and Controls

Variables	Total subjects	Cases (n=40)		Controls (n=40)		Statistical significance	
		No.	%	No.	%	χ^2	P
Protein C							
>70	66	27	67.50	39	97.50	12.468	<0.001
<70	14	13	32.50	1	2.50		
Protein S							
>65	67	27	67.50	40	100.00	15.522	<0.001
<65	13	13	32.50	0	0.00		

Table-3 Comparison of Mean Protein C and S value among Cases

	Group I			Group II			Subgroup IIA			Subgroup IIB		
	No.	Mn	SD	No.	Mn	SD	No	Mn	SD	No.	Mn	SD
Protein C	6	50.20	12.10	34	105.12	37.50	27	117.58	31.02	7	57.06	13.10
Protein S	6	25.94	23.77	34	75.55	27.43	27	86.66	14.64	7	32.69	22.62

Table-4 Association of Protein C and S value among Cases

	Group I and Group II		Subgroup IIA and Subgroup IIB		Group I and Subgroup IIA		Group I and Subgroup IIB	
	't'	'p'	't'	P	't'	p	't'	P
Protein C	3.521	0.001	5.001	<0.001	5.180	<0.001	0.974	0.351
Protein S	4.152	<0.001	7.741	<0.001	8.172	<0.001	0.524	0.611

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