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Estimation of C-Reactive Protein, Immunoglobulin's and Complements in SCD Patients

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Abstract: *Sickle cell disease (SCD) comprises an inherited blood disorder that is life long and affects many people globally. Despite progress in therapy, SCA is a considerable cause of mortality and morbidity. This study was designed to measure the immunological and inflammatory parameters of patients with sickle cell disease (SCD) and to found if there is any role of it in the pathogenicity of the disease. This study included A total of 32 patients, their ages ranged from 16 to 55 years patients with Sickle cell disease who have been evaluated during vaso occlusive crisis and had been followed up till they attained steady state, and there are 32 normal control subjects matched with patients in age and sex. In general there was elevation in all parameters the study were included in patients than control and particularly in crisis, despite the IgM value which was insignificantly decrease, but the statically significant elevation reported only in CRP, IgG, IgA.*

Keywords*:* c - reactive protein, Immunoglobulin's, Sickle cell disease

1. INTRODUCTION

The immune system is of importance in sickle cell disease Review of literature shows that sickle cell patients in other parts of the world have a variety of abnormalities in their specific and non-specific immune systems[1,2] C-reactive protein (CRP) is found in the plasma, It is the most commonly assessed marker of acute and chronic inflammation [3].Increase in CRP levels is likely to vaso-occlusion and hence blocking the blood flow to organs [4] . Antibodies are specialized proteins that specifically recognize and bind to one particular protein.antibody production and binding to a foreign substance or antigen, often is critical as a means of signaling other cells to engulf, kill or remove that substance from the body [4]. Total IgG and IgA levels are usually raised in SCD patients [5] while others have noted impaired *in vitro* function of B-Lymphocytes [6].

The complement system involves a large number of plasma proteins that are cleaved sequentially by protease enzymes to generate active fragments. These function as opsonins or chemo attractants, and the terminal components can kill some pathogens directly by creating pores in their membranes. The cascade can be activated either via the classical pathway, following binding of IgM or IgG to surface antigens, or the alternative pathway, in which C3b interacts directly with the pathogen cell surface, then recruiting further downstream components [7] . Deficiencies in the alternative pathway of the complement system and factor B reported despite of inconsistently demonstrate any deficiencies in the amount of complement components, but early studies did suggest a reduced functional activity of the alternative pathway, with lower levels of factor B (the first protein recruited by C3b) and impaired opsonization of yeast *in vitro* [8,9]

This study compared differences in the levels of, complements, CRP, immunoglobulins in SCD patients in painful crisis episodes and compared with their levels in steady state from side and healthy control from the other side. The aim of this study was to evaluate these immunological and inflammatory parameters and correlate their disturbance if found with the disease and its pathogenecity.

2. MATERIALS AND METHODS

in three subject groups namely SCD patients in painful crisis then follow them up in steady state and healthy control subjects which age and sex matched with patients (Table 1) 3ml of blood were withdrawn from each patient during painful episodes and also during steady state and also from control group subjects; the following investigations were done for each patient with SCD and for each control subject: Total immunoglobulin, complement and C-reactive protein (CRP).

IgG, IgM, IgA, C3, C4 and CRP Which analyzed by ARCHITECT *C* 4000 fully automated analyzer SN C461520, REF 02P24-01 were evaluated by using these kits:
IMMUNOGLOBULIN IgA A9D98-20304565/R06
IMMUNOGLOBULIN IgG G9D99-2030-4513/R4
IMMUNOGLOBULIN IgM M1E01-2030-3962/R3
COMPLEMENT C3-9D96-2030-3982/R4
COMPLEMENT C4-9D97-2030-3965/R4
C-REACTIVE PROTEIN 8G65-2130-4143/R1
All the test above analyze protocol related to Immunoturbidimetric principle.

3. RESULTS

The results of the current study is an output from 32 SCD patients (14 males and 18 females), their ages range from 16 – 55 years. Twenty two of them are SS, two are splenoctomized and one with splenomegaly. Ten of them are SF, two are splenoctomized and one with splenomegaly. The patients are recruited during crisis state then follow them up

in a steady state. There were 32 normal control subjects, matched with the patients in age and sex (Table 1).

Table 1. Age and gender distribution of subjects

Variables	Subject		Total	P-value
	Case N=32	Control N=32		
Mean age ± SD				
	30.2 ± 11.5	30.1 ± 11.9	9.8 ± 4.2	.816
Age-group				
16- 25	14 21.9%	14 21.9%	28 43.8%	.986
26-35	8 12.5%	7 10.9%	15 23.4%	
36-45	6 9.4%	7 10.9%	13 20.3%	
46-55	4 6.3%	4 6.3%	8 12.5%	
Gender				
Male	14 43.8%	14 43.8%	28 43.8%	1.000
Female	18 56.3%	18 56.3%	36 56.3%	

As an inflammatory marker, CRP was highly elevated in crisis than steady state and control groups, being 4.10 mg/dl in crisis patients compared to 0.68 and 0.25 mg/dl in steady state and control groups respectively. The *P*-value is 0.004, as shown in Table 2.

Table 2. Descriptive Statistical results of CRP in all groups.

Parameters		N	Mean	Sig.
CRP (mg/dL)	Crisis	32	4.10	.004
	Steady	32	0.68	
	Control	32	0.25	
	Total	96	1.79	

There is statistically significant difference in C3 level in patients compared to control (P-value =0.10). The difference was more prominent during steady state that shows the lowest value compared to patients during crisis and control group; 114, 127 and 138 mg/dl respectively. No such differences were reported in C4, as shown in Table 3.

In general, immunoglobulin IgA and IgG are significantly higher in patients, particularly during crisis, compared to control group. Insignificant lowest of IgM in crisis and steady groups than control (*P* value= .481)

Table 3. Descriptive Statistical results of complement and Immunoglobulin in all groups.

Parameters		N	Mean	Sig.
C3(mg/dL)	Crisis	32	127.72	.010
	Steady	32	114.03	
	Control	32	138.37	
	Total	96	126.48	
C4(mg/dL)	Crisis	32	25.41	.703
	Steady	32	23.41	

	Control	32	24.30	
	Total	96	24.41	
IgA(mg/dL)	Crisis	32	347.59	.008
	Steady	32	319.21	
	Control	32	228.63	
	Total	96	301.74	
IgG(mg/dL)	Crisis	32	1833.75	.000
	Steady	32	1877.21	
	Control	32	1219.37	
	Total	96	1659.57	
IgM(mg/dL)	Crisis	32	110.66	.481
	Steady	32	116.00	
	Control	32	130.96	
	Total	96	118.65	

4. DISCUSSION

In this study patients with SCD in crisis showed significantly elevated in CRP values compared with steady state and healthy control groups as shown in other studies[10,3]. Increase in CRP levels is likely to vaso-occlusion and hence blocking the blood flow to organs [10].

There is evidence that patients with sickle cell anemia have moderately increased in C-reactive protein during their symptom-free steady state and significantly increased during painful vaso-occlusive crisis [11,3.12].CRP level was high in steady state patients compare to control but this elevation didn't reach to significant value.

Patients in steady state and crisis showed significantly reduction in C3 values compared with healthy control group specially between steady and control while there is no significantly difference values in C4 among three groups, early work did suggest a reduced functional activity of the alternative pathway, with lower levels of the active form of factor B (the first protein recruited by C3b) .[8] study in 1999 did show an inverse correlation between complement activity and the number of crisis suffered by SCD patients[13]. In patients with severe variant SCD C3 were reduced, these differences however did not reach significance ($P > 0.05$) [14].

In immunoglobulin's levels evaluation there is significantly elevated IgG values in patients with SCD in crisis and steady state groups compared with healthy control group and significantly elevated IgA values in patients with SCD in crisis group compared with healthy control and steady state groups while there is reduce IgM in SCD patients in steady state and crisis compared with healthy control group but this reduction did not reach significance ($P > 0.05$) .

The total spontaneous production of IgG and IgA by mononuclear cells is increased in asymptomatic patients with sickle cell disease [15,16].Chronic inflammation in sickle cell disease may lead to polyclonal activation of B cells[17]. (Merck, Sharp, and Dohme, West Point, Pennsylvania) also reported impaired in vitro spontaneous IgM synthesis in SCD patients compared with controls. Both SCD and control subjects had similar spontaneous IgM levels in a study done in Venezuela [16].

From this study we conclude the adaptive immune response in SCD is impaired despite the apparent increase in immunoglobulin level and cell counts. Also the SCD is a state of immune dysregulation that leads eventually to a chronic inflammatory status, during the steady state of the disease, with bouts of exacerbations during sickling crises, and we recommend for further studies to highlight the important points that could not be covered in this study like different cells functions, particularly phagocytic function and lymphocyte subset functions .

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