Natural Inhibitors and Lipids in Patients with Sickle Cell Disease

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ABSTRACT

Microvascular occlusion in sickle cell disease (SCD) is a multifactorial process. Disordered coagulation may play a role in the pathogenesis of vaso occlusive crisis (VOC). The aim of this study was to evaluate the patients and to investigate their Protein C (PC), Protein S (PS) and AT-III levels during normal and crisis periods. A total of 18 patients with SCD were included in this study at the Antalya State Hospital, Thalassemia Center. The mean number of VOC episodes of the patients per year was 4.1 – 3.2. Complications in patients included 4 cases of osteonecrosis (23.5%), 2 cases of cholealithiasis (11.7%), 2 cases of leg ulcers (11.7%), and 3 splenectomies (17.6%). The patients during noncrisis periods have lower cholesterol and higher triglycerides levels than the controls ($p< 0.001$). Hepatic and renal functions were normal in all patients. The mean totals of the PS, PC and AT-III levels were statistically lower both in non crisis and in crisis periods than the control ($p< 0.001$), but there was no statistical difference between the levels durining noncrisis and crisis periods.

In conclusion, PC, PS and AT-IIII deficiencies in patients with SCD are certain. However, these deficiencies do not change during noncrisis and crisis situations and does not play a role on the period of crisis. Abnormal lipid patterns may be a predisposing condition for a crisis.

Key Words: Sickle cell disease, Natural inhibitors, Lipids.

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INTRODUCTION

In sickle cell disease (SCD), vaso-occlusion is a complex process involving cellular, vascular, and humoral factors and, possibly, thrombotic events. Major organ failure, such as autosplenectomy, and end stage renal failure, generalized osteonecrosis, stroke, retinopathy, chronic lung disease, and leg ulcers are direct consequences of sickle cell evoked vaso-occlusive crisis (VOC)[1].

Disordered coagulation of SCD is characterized by the evidence of activation of coagulation increased levels of prothrombin fragment F1+2, D-dimers and thrombin-antithrombin-III (AT-III) complexes[2,3]. Naturally occuring anticoagulants, protein C (PC) and protein S (PS) have been reported to be low in steady state[4,5,6,7]. There is a strong association between PC activity and antigens with serum lipids[8].

The aim of this study was to evaluate the pati-

ents with SCD and to investigate their PC, PS, AT-III and serum lipids levels during steady state and in crisis.

MATERIALS and METHODS

In the Antalya State Hospital, Thalassemia Center, a total of 18 patients with SCD (9 female, 9 male) aged 2-46 years (mean – SD: 26.3 – 10.5) participated in this study. The mean number of VOC in patients was 1-12/year (mean – SD: 4.1 – 3.2).

The patients were evaluated for clinical, hematological, hepatic, and renal functions, and natural inhibitors and lipids. Natural inhibitors were studied in three groups of subjects; 18 patients with steady state, 10 patients in crisis and 15 healthy subjects. Protein C antigens, total Protein S and AT-III levels were assayed with commercial Elisa Kits (Thrombonostika Protein C-Organon Teknika), (Thrombonostika Protein S-Organon Teknika) and (Chromostrate™ Antithrombin III assay-Organon Teknika). Serum lipids were measured in 18 patients with SS, and 20 healthy subjects were matched for age and sex by using the commercial Elisa Kits (Olympus System Reagent).

Student t test was used for statistical analysis.

RESULTS

In Table 1 the features and complications of patients are shown: 4 osteonecrosis (23.5%), 2 cholelithiasis (11.7%), 2 leg ulcers (11.7%), 3 splenectomy (17.6%). Hepatic, renal function tests and fibrinogen levels were normal in 18 patients in steady state.

The patients in steady state have been found

Table 1. The features of patients with sickle cell disease

Patient no	Age (year)	Sex	VOC (no/year)	Crisis	Steady state	Complications
1	43	F	2	-	+	Bilateral femur osteonecrosis
2	2	M	3	-	+	-
3	16	M	3	-	+	Splenectomy
4	22	F	3	+	+	Cholelithiasis
5	18	F	1	+	+	Left knee osteonecrosis
6	36	F	6	+	+	Bilateral femur osteonecrosis
7	25	M	8	+	+	Leg ulcer
8	23	F	12	+	+	-
9	31	M	3	+	+	-
10	21	F	2	-	+	-
11	30	M	10	-	+	-
12	18	M	2	-	+	-
13	46	F	2	-	+	Osteonecrosis + cholelithiasis
14	30	M	1	+	+	Leg ulcer
15	31	F	3	+	+	Splenectomy
16	31	F	2	+	+	Splenectomy
17	24	M	6	-	+	-
18	20	M	8	+	+	-
Mean – SD	26.3 – 10.5		4.1 – 3.2			

Table 2. Serum lipid levels in the patients with SCD in steady state

	Cholesterol (mg/dL)	Triglycerid (mg/dL)	HDL-CHOL (mg/dL)	LDL-CHOL (mg/dL)
Control				
n: 40	160.1 – 25.3	73.4 – 25.8	45.4 – 8.0	100.0 – 22.9
Patient				
n: 18	121.5 – 44.5*	157 – 36.7*	39 – 4.2	82.5 – 40.3

*p< 0.001

Table 3. Protein C, protein S and at-III levels in the patients with SCD at the steady state and crisis

Natural inhibitors	Steady state (n: 18)	Crisis (n: 10)	Control (n: 15)
Protein C (IU/mL)	0.46 – 0.12*	0.44 – 0.11*	0.92 – 0.3
Protein S (%)	49.4 – 16.6*	47.3 – 9.7*	70.6 – 19.3
AT-III (%)	117 – 31.9*	111 – 33.5*	130.8 – 20.7

*p< 0.001

with lower serum levels of total cholesterol and higher triglycerides than the control (p< 0.001) (Table 2).

The mean total PS, PC and AT-III levels were statistically lower in patients in steady state and in crisis than in the control (p< 0.001), but there was no statistical difference between the periods of steady state and crisis (Table 3).

DISCUSSION

Major organ damage in 785 patients with SCD have been reported: strokes (8.8%), chronic renal failure (4.1%), sickle chronic restrictive lung disease (4.2%), priapsim (6.7%), retinopathy (5.6%), generalized or localized osteonecrosis (9.4%) and devastating leg ulcers (10.4%) were clearly related to VOC[1]. We observed organ complications such as osteonecrosis (23.5%), cholelithiasis (11.7%), leg ulcers (11.7%) and splenectomy (17.6%) in 18 patients with SCD.

Hagger et al. showed that PC levels in patients with SCD was reduced in steady state but unchanged in crisis, while PS and AT-III levels were normal both in the steady state and crisis[3]. Nsiri et al. reported that PC, PS and AT-III levels were reduced in steady state and further diminished in crisis and they also showed that Factor VIII, D-dimer, plasminogen activator inhibitor (PAI-1) antigens were significantly increased in patients with SCD[4]. Wright et al. reported that a prolongation of the PT time, low Factor V and VII levels, the absence of PIVKA and reduced concentrations of PC and PS in SCD[9]. Other studies have also shown that PC, PS and AT-III levels were low only in the steady state[5,6,7].

In our study, PC, PS and AT-III levels were statistically lower both in the steady state and in crisis than in the control group (p< 0.001), but there was no statistical difference between these levels in steady state and crisis.

Microvascular occlusion in SCD is a multifactorial process. Disordered coagulation and atheroma besides natural inhibitors, may play a role in the pathogenesis of VOC. The appearance and progression of atheraoma in these patients may explain the alteration of plasma lipid patterns[2,10]. Although hepatic, renal, and coagulation tests such as the PT, aPTT, fibrinogen, and Factor V levels were with in normal limits in our patients, we found lower total cholesterol and higher triglycerides in patients with SCD than in the controls. MacCallum et al. reported that PC activity and antigens were strongly associated with serum lipids. Total PS antigen concentrations were associated

with total cholesterol in healthy adults[8]. There may be a relationship between decreased PC and PS levels and low plasma levels of total cholesterol in patients with SCD.

In conclusion, PC, PS and AT-IIII deficiency is present in patients with SCD and may be due to either decreased production or increased consumption, but this deficiency does not seem to play a role in the period of crisis. Abnormal lipid patterns may be a predisposing condition for crisis.

REFERENCES

1. Powars D. Sickle cell anemia and major organ failure. Hemoglobin 1990;14(6):573-98.
2. Francis RB. Platelet coagulation and fibrinolysis in sickle cell disease: Their possible role in vascular occlusion. Blood Coagul Fibrinolysis 1992;2:341-53.
3. Hagger D, Wdff S, Owen J and Samson D. Changes in coagulation and fibrinolysis in patients with sickle cell disease compared with helathy black controls. Blood Coagul Fibrindysis 1995;6(2):93-9.
4. Nsiri B, Gritli N, Bayoudh F, Messaoud T, Fattoum S and Machghoul S. Abnormalities of coagulation and fibrinolysis in homozygous sickle cell disease. Hematol Cell Ther 1996;38(3):279-84.
5. Francis RB. Protein S deficiency in sickle cell anemia, J Lab Clin Med 1988;111(5):571-6.
6. El-Hazmi MA, Wrasy AS, Bahakim H. Blood protein C and S in sickle cell disease. Acta Haematol 1993;90(3):114-9.
7. Marfaing-Koka A, Boyer-Neumann C, Wolf M, Leroy Matheron C, Cynober T,Tchernia G. Decreased protein S activity in sickle cell disease. Nouv Rev Fr Hematol 1993;35(4):425-30.
8. MacCallum PK, Cooper JA, Mart n J, Howarth DJ, Meade TW and Miller GJ. Associations of protein C and protein S with serum lipid concentrations. Br J Haematol 1998;102:609-15.
9. W right JG, Malia R, Cooper P, Thomas P, Preston FE and Serjeant GR. Protein C and S in homozygous sickle cell disease: Does hepatic dysfunction contribute to low levels? Br J Haematol 1997;98:627-31.
10. Borgna Pignatti C,Carnelli V,Caruso V, Dore F, De Mattia D, Di Palma A, Di Gregorio F, Romeo MA, Longhi R, Mangiagli A, Melevendi C, Pizarelli G, Musumeci S. Thromboembolic events in beta thalassemia major: An Italian Multicenter Study. Acta Haematol 1998;99:76-9.

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