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Hemostatic Profile among Sickle Cell Sufferers during the Steady State in Cameroon

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ABSTRACT

Sickle-cell anemia is characterized by a hypercoagulable state with a perturbed coagulation profile during vaso-occlusive crises, as well as during inter-critical periods. Some studies have been done in several countries on the coagulation profile during inter-critical periods in patients suffering from this hemoglobinopathy, but there are no reports on Cameroonian sickle-cell patients during the inter-critical period. In this prospective study, we included 68 blood samples homozygous SS sickle-cell patients, 11 samples from heterozygous patients (SF patients and 21 AS patients). Standard techniques were used for the measurements of blood counts, prothrombin time, activated partial thromboplastin time and fibrinogen levels in all samples. The study was carried out from February to August 2016. The mean platelet count in homozygous SS patients was 438 ± 158 G/L and was significantly higher than that of AS samples (279 ± 94 G/L, p=0.000) and of SF samples (392 ± 115 G/L, p=0.037). The mean prothrombin time was 15.7 ± 2.1 seconds (s) for SS samples and was significantly different from that of AS (13.8 ± 1.4 s, p=0.000) samples but not significantly different from that of SF samples (15.3 ± 1.6 s, p=0.525). Activated partial thromboplastin time and mean fibrinogen levels in SS samples (34.2 ± 8.9 s and 2.8 ± 0.9 g/L, respectively) were not statistically different from those of AS samples (32.4 ± 6.5 s, p=0.373 and 3 ± 0.7 g/L, p=0.240, respectively) and of SF samples (30 ± 5.9 s, p=0.436 and 2.7 ± 0.5 g/L, p=0.359, respectively).

The coagulation profile of Cameroonian sickle cell sufferers in the inter-critical period shows more abnormal values in SS and SF patients than in AS patients. However, the prothrombin time, activated partial thromboplastin time and fibrinogen levels remain within normal limits.

Keywords: Coagulation, Sickle-cell anemia, Platelets, Prothrombin time

Abbreviations: APTT: Activated Partial Thromboplastin Time; g/L: grams per liter; G/L: 100^3 per mm^3, s: Seconds; PT: Prothrombin Time

INTRODUCTION

Sickle Cell Anemia is a hereditary hemoglobinopathy transmitted in autosomal recessive fashion. It results from a mutation of the beta-globin chain gene on chromosome 11, a mutation in which glutamic acid is replaced by valine in position 6 [1]. It is characterized by a hypercoagulable state in which several perturbations during and in-between vaso-occlusive crises cause an increase in the activation of the coagulation system, platelets, prothrombin time and thus occurrence of thrombosis [2-5]. Decreased natural anticoagulant proteins C and S [6], increased prothrombin time and hyperfibrinogenemia have also been reported in the absence of vaso-occlusive crises.

Performing these coagulation tests offers a predictive value on the clinical presentation of SCA patients. For example, increase in fibrinolytic activity correlates with the frequency of vaso-occlusive crises [7]. The absence of studies in our

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context on the coagulation profile of these patients during and in between crises is the motivating factor behind this study. The aim was to determine certain coagulation parameters (platelets' count, PT, APTT, fibrinogen levels) in homozygous sickle-cell subjects during inter-critical periods and to compare these values with those of heterozygous subjects in Yaounde. The findings from this study could contribute in the establishment of baseline values for coagulation parameters during inter-critical periods and also in improving on the management of these patients.

MATERIALS AND METHODS

The study was carried out at the National Center for the Management of Sickle-Cell Anemia, the sickle-cell anemia unit of the Chantal Biya Foundation and the Hematology Laboratory of the University Teaching Hospital in Yaoundé, over a period of seven months. Stable patients were SS and SF patients who were without pain necessitating pain-killers for a minimum period of four weeks [1], between the last day of the previous crisis and the first day of the next vaso-occlusive crisis. Carriers of sickle-cell trait were also included in the study.

With the aid of a pre-conceived data-collection form, demographical (age, sex), hematological (platelet counts, hemoglobin electrophoresis) and hemostatic parameters (PT, APTT, fibrinogen levels) of each subject were recorded. For each subject, two venous blood samples were collected in EDTA and citrated tubes. Complete blood counts were done in EDTA tubes with MINDRAY BC 5300 analyzer (Medical Electronics Technology Research Institute Co., Ltd., Shenzen, China) within 3 h following blood collection. Samples collected in the citrated tubes were used for coagulation tests (PT, APTT, fibrinogen levels). The samples were centrifuged at 1200 rpm for 15 min to obtain platelet-poor plasma, which was introduced into a Stago START 4 coagulation analyzer, version 2002, from France for haemostatic tests. Thromboplastin (Neoplastin®) used for measurement of prothrombin time and fibrinogen (Fibrinogène®) were obtained from Cypress Diagnostics while C.K. Prest® was used for measurement of APTT (supplied by Stago, France). All coagulation tests were done in duplicates for each plasma sample between two to four hours following the collection. Results were expressed in terms of means (in seconds, s) for PT and APTT. Fibrinogen levels were measured in grams per liter (g/L).

Ethical clearance and authorizations for research were obtained from the participating centres and the national review board.

Quantitative variables were analyzed as continuous variables and means were used to evaluate central tendencies and distribution. Descriptive analysis of demographic, hematological and hemostatic parameters between the subgroups was also carried out. Data were entered in CSPRO version 6.1 software and statistical analysis was done with SPSS 16.0. Means and standard deviations were compared using ANOVA tests. The Student T test enabled us to compare the groups two-by-two. Statistical significance was set at $p<0.05$.

RESULTS AND DISCUSSION

One hundred blood samples were collected from sickle-cell subjects aged 2 to 56 years predominantly the Sudanese ethnic group. The homozygous sicklers represented 68% of the participants **(Table 1)**. A total of 82.6% homozygous had an abnormal number of platelets and 89.6% had an abnormal prothrombin time. Thrombocytosis was found only in SS **(Table 2)**. The means of platelets and prothrombin time of SS sicklers were 438 G/L and 15.7 s, respectively in homogenous sicklers compared to 279 G/L, p=0.000 and 13.8 s; p=0.000, respectively in heterogenous sicklers AS and 392 G/L; p=0.037 and 15.3 s; p=0.525 in SF. Our study showed that hemostatic abnormalities in Cameroonian sickler are predominantly an increase of platelet count in eight patients over ten, homozygous are more affected than heterogenous and a prolonged prothrombin time is present in half the patients **(Table 3)**.

The raised platelet count in sicklers has previously been reported with a high tendency of homozygotes to have thrombocytosis [8,9]. This thrombocytosis is probably a consequence of the loss of the function of splenic sequestration which results from autosplenectomy in these patients. The spleen is the main site of destruction of platelets so in the event of splenectomy reactive thrombocytosis occurs. According to Girot et al. [8], this thrombocytosis could be a manifestation of hyposplenism.

The increase of prothrombin time and APTT in sicklers was also reported by many authors [10,11]. PT explores the extrinsic pathway of the coagulation cascade. The main factor in this pathway is factor VII which is synthesized by the liver [12]. APTT explores the intrinsic pathway and some of the important coagulation factors implicated in these are factors VIII and IX. Possible explanations of increase of PT and APTT are reduction in synthesis of these factors, their increased consumption and hepatocellular dysfunction observed in sickle cell anemia [13,14].

Table 1. Socio-demographic characteristics of a hundred sicklers during the steady state at the Yaounde National take care sickle cell center and hematology laboratory of University Teaching Hospital, 2016.

Parameters	Frequency	Percentage
AGE (years)		
2-5	14	14
5-10	18	18
10-16	29	29
Total of children	61	61
16-21	4	4
21-26	9	9
26-31	7	7
31-36	7	7
36-41	6	6
41-46	3	3
46-51	2	2
51-56	1	1
Total of Adults	39	39
SEX		
Male	34	34
Female	66	66
ETHNIC GROUPS		
Bantous	3	3
Semi-Bantous	36	36
Sudanese	61	61
SICKLERS' GROUPS		
AS	21	21
SS	68	68
SF	11	11
TOTAL	100	100

Bantous: From Center, South, East and Littoral regions
Semi-Bantous: From West, North-West, South-West regions
Sudanese: From Adamaoua, North and Far-North regions

Table 2. Frequencies of hemostasis abnormalities in a hundred of sicklers during the steady state at the Yaounde National take care sickle cells center and Hematology Service of University Teaching Hospital in 2016.

Sickler's groups	Platelets			PT			APTT			Fibrinogen		
	Normal N (percentage)	Abnormal N (percentage)	P-Value	Normal N (percentage)	Abnormal N (percentage)	P-Value	Normal N (percentage)	Abnormal N (percentage)	P-Value	Normal N (percentage)	Abnormal N (percentage)	P-Value
SS	30 (55.5)	38 (82.61)	0.001	33 (54.1)	35 (89.8)	0.001	58 (67.5)	10 (71.45)	0.883	49 (63.6)	19 (82.6)	0.11
SF	5 (9.3)	6 (13.04)		9 (14.8)	2 (5.1)		10 (11.6)	1 (7.2)		11 (14.3)	0 (0)	
AS	19 (35.2)	2 (4.35)		19 (31.1)	2 (5.1)		18 (20.9)	3 (21.4)		17 (22.1)	4 (17.4)	
Total	54	46		61	39		86	14		77	23	

Table 3. Means of hemostasis parameters in a hundred of sicklers during the steady state at National take care sickle cells center and hematology service of University Teaching Hospital in 2016.

Hemostatic Tests	Platelets (G/L)		PT (s)		APTT (s)		Fibrinogen (g/L)	
	Median	Range	Median	Range	Median	Range	Median	Range
SS N=38	438	280-596	15.7	13.6-17.8	34.2	25.3-43.1	2.8	1.9-3.7
SF N=11	392	277-507	15.3	13.7-16.9	30	24.1-35.9	2.7	2.2-3.2
AS N=21	279	185-373	13.8	12.4-15.2	32.4	25.9-38.9	3	2.3-3.7
All Population	399	244-554	15.3	13.2-17.4	33.4	25.1-41.7	2.8	2-3.6
p-value	0.000		0.001		0.241		0.471	

N: Frequency; Platelet's normal range: 150-400 G/L; Prothrombin time's normal range: 12-13.5 s; APTT's Normal range: 30-33 s; Fibrinogen normal range: 2-4 G/L

LIMITATIONS

We recognize some limitations in this study. Measurement of coagulation factors and transaminases was not done in our study but this does not void the validity of our results. However our sample size should be enlarged to confirm these results.

CONCLUSION

Based on our study, Cameroonian sicklers during steady state have a prolonged prothrombin time and increase in platelets' count. Future larger prospective studies to determine whether abnormal coagulation findings in sicklers are associated with a decrease in coagulation factors and transaminases are necessary in our context.

Just like the complete blood count, prothrombin time measurement should become a routine test in the evaluation of sickle cell anemia patients in order to evaluate their liver function. The early detection of liver dysfunction amongst these patients will permit that they are managed adequately.

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