No Correlation Between The Expression Of Stress Reticulocytes (CD49d+ And CD36+) In Sickle Cell Anemia And The Clinical Severity

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Abstract

The complex physiopathology of sickle cell disease involves many factors, among them adhesion molecules such as the 41 integrin or CD 49d and CD36. These antigens are found on immature reticulocytes or stress reticulocytes. We investigated whether there were links between the clinical manifestations and the presence of stress reticulocytes and the expression of CD 36 and CD 49d. We evaluated 60 SSFA2 homozygous sickle cell patients with complete blood count, the presence of total reticulocytes, total stress reticulocytes, and CD 36 and CD49d antigens with immunophenotyping by flow cytometry. Out of the 308, 845/uL reticulocytes, 48.2% and 42.5% expressed respectively CD 36 and CD 49d. In over 90% of patients, stress reticulocytes were found. The presence or absence of complications, or of moderate or severe clinical manifestations, was not correlated with the expression of CD36 and CD 49d. From a clinical point of view, there was no difference between subjects expressing or not the CD 36. Even if the level of stress reticulocytes, CD 49d + and CD 36 + reticulocytes were high, the clinical status was not correlated with the expression of adhesion molecules.

INTRODUCTION

The classical pathophysiology of sickle cell disease, based on the polymerization of hemoglobin (Hb) S leading to sickling of blood cells, is now complemented by new data based on the adhesion of stress reticulocytes to the vascular endothelium leading to vaso-occlusive events (1). Some of the molecules involved in these interactions have been identified, such as the 4 (CD 49d) 1 (CD 29) integrin or very late activation antigen (VLA) 4 and CD36, exclusively present on stress reticulocytes, and CD47 on mature red blood cells (2). The results of in vivo or in vitro studies on the relationship of stress reticulocytes on clinical status and the expression of adhesion molecules are contradictory. Some authors (3, 4) state that the presence or absence of CD 36, and CD 49d had no effect on the clinical manifestations of sickle cell disease. Styles (2) and Browne (5), on the contrary, established a link between the expression of these adhesion molecules and clinical manifestations. More recently, attention has been focused on basal cell adhesion molecule-1/Lutheran (BCAM-1/Lu), and on intercellular cell adhesion molecule 4 (ICAM-4) (6, 7).

In this report we investigated the relationship between the number of stress reticulocytes and the expression of CD 36 and CD49d. We correlated the expression of these molecules on these cells with the severity of sickle cell disease in black African homozygous sickle cell patients not treated with hydroxyurea in Abidjan. To our knowledge no study of this kind has been carried out in black Africa.

MATERIALS AND METHODS

This was a cross sectional study carried out at the central laboratory and clinical hematology department of the University Hospital of Yopougon in Abidjan. Between August 2010 and February 2011 we evaluated 60 sickle cell patients who had given their informed consent. The patients were SSFA2 homozygous sickle cell patients who had a complete medical record, and who were regularly followed at the University Hospital of Yopougon in Abidjan. We did not include subjects who were transfused in the three months preceding the investigation as well as subjects for whom the samples were hemolyzed or contained a clot, or samples whose immuno-phenotyping tests were not performed within 48 hours of phlebotomy (3, 8).

Blood was collected by venipuncture performed at the elbow in a tube containing ethylene diamine tetra-acetate

(EDTA). We performed a complete blood count with Sysmex XT-2000i analyzer. The determination of the level of reticulocytes and of their degree of maturity was performed with immunophenotyping by flow cytometry with the FACSCalibur Flow Cytometer of Becton Dickinson. The distribution of reticulocytes according to the degree of maturity with thiazole orange subdivides them into mature reticulocytes (low fluorescence region or LFR), reticulocytes of intermediate maturity (medium fluorescence region or MFR), and into very immature reticulocytes (high fluorescence region or HFR). Stress reticulocytes, corresponding to the immature reticulocytes fraction (IRF), consist of the sum of the MFR and HFR reticulocytes (9).

We used the FACSCalibur to demonstrate the CD 36 and CD49d antigens present on the surface of reticulocytes using the following reagents: anti-CD36 monoclonal antibodies coupled to fluorescein isothiocyanate (FITC), Ig M isotype, kappa (FITC), CD49d monoclonal antibodies coupled to phycoerythrin (PE), IgG1 isotype, kappa (PE),

Retic-CountTM or thiazole orange, saline phosphate, bovine serum albumin and the fragment F (ab') 2 of Ig G 1 (2, 3).

VLA-4 is composed with CD 49d (4) and CD 29 (1). Both components were measured by Styles (2) using flow cytometry. He found that the results were virtually identical and therefore only CD 49d results were reported (2).

Our results were presented in the form of tables using the CellQuest software, Microsoft Excel 2007 and Epiinfo6. We used the Student t-test risk for comparison of means at an = 5% (significance, p= <0.05).

RESULTS

Of 60 SSFA2 homozygous sickle cell patients, 32 were male, 28 were female, with an average age, 15.12 ± 10.57 (2-43 years). The electrophoretic profile showed mean Hb S: 86.4 ± 5.1% (73.6 to 95%), mean Hb F 11.2 ± 4.8% (2.5 to 23.6%), and mean Hb A2: 2.4 ± 0.9% (0.6 to 5.9%). All patients received the same maintenance treatment composed of anti-anemic drugs (folic acid), and vasodilator, pentoxifylline. Thirty eight patients (66.7%) had been hospitalized at least once a year for an average length of hospital stay of 1.97 days (0-11d). More than half (63.3%) had been transfused at least once a year with an average of 0.7 units of RBC (0-3u). Twenty five patients (41.67%) presented with complications involving the eye, bones, head and neck, lung, or heart.

Mean hemoglobin level was 6.3 ±1.8g/dl (1.9 - 9.9g/dL), and the total WBC count was 18 992 ± 13 116/l (5 290 – 74 190/uL) with an absolute neutrophil count of 9 442 ± 6 296/l (1750-34130 /uL). The average eosinophil count was within normal range at 455 ± 1059/l (0 – 7730/uL).

The level of reticulocytes was very high with the average count of 308 845/uL of which 48.2% and 42.5% respectively expressed the CD 36 and CD 49d (Table I). CD 36 + and CD 49d + reticulocytes were, in 90% of cases, stress reticulocytes. However, the composition of these reticulocytes was different depending on the marker that was present. CD 36 + reticulocytes consisted of 65% reticulocytes of intermediate maturity (MFR), while 64.9% of CD 49d reticulocytes were very immature cells (HFR) (Table I).

SS patients without complications had a level of total reticulocytes and CD36+ reticulocytes higher than subjects with complications (Table II, p = 0.02). The presence or absence of complications had no effect on the production of stress reticulocytes (Table II).

CD 36 + and CD36- subjects had the same epidemiological and clinical profile (Table III). Apart from the total reticulocytes which were much higher in CD 36 + subjects than in

CD36 - subjects (p = <0.001), there was no difference between both populations (Table III).

We used clinical parameters such as the presence of complications or the presence of a low level of Hb F to identify SS patients with a good or a bad profile (Table IV). These subjects presented a level of Hb S higher than 90%. Besides, these patients demonstrated more severe anemia and more leukocytosis. Clinically the number of hospitalizations and annual transfusion were correlated with severity, but these parameters showed no correlation with regard to total reticulocytes and CD49d stress reticulocytes (Table IV). The level of CD 36 + reticulocytes was higher in subjects with a better profile (p = 0.02).

DISCUSSION

Data on age and sex were similar to other studies carried out in Abidjan. Most sickle cell patients were teenagers or young male adults (10, 11). The frequency of painful crises requiring hospitalization and the length of stay are clinical

criteria used to assess the severity of sickle cell disease (12). Platt (12) showed that the number of painful episodes in the year is a measure of the clinical severity of the disease and is associated with early death especially in patients over 20 years.

Hydroxyurea is a cancer chemotherapy agent that decreases the frequency of sickle cell disease crises. Hydroxyurea may exert its therapeutic effect by generation of nitric oxide (anti-inflammatory) and by increasing the level of anti-sickling Hb F (2, 6, 13). It also produces a significant reduction of α4 β1 integrin and CD 36 on sickle cell reticulocytes (2, 6, 7). Hydroxyurea is not part of the armamentarium used in Côte d'Ivoire for the treatment of sickle cell patients. Maintenance treatment is based on folic acid drugs and vasodilators (10). In a crisis, the therapeutic management, we follow four simultaneous steps. The patient will be transfused in case of an intense hemolytic syndrome, and triggering factors will be suppressed. Pain is treated with non-steroidal anti-inflammatory drugs, specifically, Ketoprofen at 1 to 2 ampoules twice daily by infusion in 100 to 250 mL of glucose solution (10, 11). Vasodilators are used to promote increased blood flow. These therapies do not directly alter the percentages of Hb F, number of reticulocytes, the expression of CD 36 and CD 49d in these patients.

The complete blood count demonstrated abnormalities commonly described as severe anemia and leukocytosis (10, 11, 14). Leukocytes play a significant role in vaso-occlusion and physiopathology of sickle cell disease. Leukocytosis is correlated with an increased rate of early death, acute chest syndrome and death (12, 14). Unlike Canalli (14), we found no eosinophilia.

The very high level of reticulocytes (Table II) approximates the results of other authors such as Styles (2), Lee (3) and Maier-Redelsperger (15), who demonstrated high reticulocytosis ranging between 259,000/µl (3) and 320,000/µl (2, 15).

Out of the mean level of 308,845 reticulocytes, 48.2% (159, 249/µl) and 42.5% (109,193/µl) respectively expressed the CD 36 and CD 49d (Table I). These results were part of an interval having as lower bound values of Lee (3) and as upper bound those of Styles (2). In fact Lee (3) found 24.1% (76, 867/µl) of CD 36 + reticulocytes and 22.1% (70 806/µl) of CD49d + reticulocytes. For Styles (2) there were 55.3% (245, 000/µl) of CD 36 + reticulocytes and 29% (129, 000/µl) of CD 49d + reticulocytes. Just as Styles (2) and Lee (3), we found that there were more CD 36 + reticulocytes than CD 49d. However, it seems that the adhesion of red blood cells to the endothelium performed through VLA-4 would be more tenacious than that involving the CD36 (2). We also noticed that the profile of these reticulocytes was not the same. 65% of CD 36 + MFR and 64.9% of CD 49d + reticulocytes were HFR (Table II). Supporting this hypothesis is the finding that the youngest reticulocytes have the greatest expression of VLA-4 (2, 16).

The presence or absence of complications had no effect on either the production of stress reticulocytes or on the expression of CD 49d (Table II). We also found that CD 36 + and CD 36 - subjects had the same epidemiological and clinical profile (Table III). The absence of CD 36 does not result in milder clinical manifestations (Table III).

We grouped the parameters that allowed us to select patients with more severe sickle cell disease (Table IV). They were patients with complications and with a lower level of Hb F, less than 10% (2, 3, 12). They were transfused more often and had more frequent hospitalizations in (Table IV). However, the only difference between this group with a worse prognosis and those with a moderate form was the level of CD 36 + reticulocytes that surprisingly was higher in subjects with a better profile ($p = 0.016$). The contribution of CD 36 has-been called into question with the finding that sickle cell patients who have low levels of CD 36 on reticulocytes and mature red blood cells can have a normal clinical course (3, 4). Tring-Trang-Tanh (4) measured the adhesion of red blood cells with under-expressed levels of adhesion molecules. Tring-Trang-Tanh (4) showed that there is dissociation between adhesiveness and adhesion molecules. It is therefore conceivable that ICAM-4 and CD 36 although in reduced amounts, might be activated by an abnormal constitutive phosphorylation (4). More recently, studies based on quantitative expression analysis of adhesion molecules on red blood cells and during erythroid differentiation in patients undergoing hydroxyurea therapy, surprisingly revealed that Lu/BCAM level was enhanced, although α4β1, CD36 and ICAM-4 (to a lower extent) levels were indeed reduced. CD47 and CD147 expression were also enhanced in hydroxyurea treated patients (6, 17). Based on these findings Cartron (6) suggested that the signaling cascade leading to receptor activation rather than the expression level of adhesion molecules may be the critical factor regulating cell adhesion, although both mechanisms are not mutually exclusive.

CONCLUSION

The complex pathophysiology of sickle cell disease involves several factors, including adhesion molecules such as the 41 integrin (CD 49d) and CD36. Although a number of adhesion molecules and their targets that mediate adhesion events have been identified, the mechanisms involved are incompletely resolved. It seems that among factors that determine cell adhesive properties, the number and affinity (low and high) of receptor-ligand interactions may both play a role in vivo. In addition it is likely that the signal cascade leading to receptor activation rather than the quatitative expression level of adhesion molecules may be the critical factor regulating cell adhesion, although both mechanisms are not mutually exclusive.

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TABLES

Table 1

Main properties of reticulocytes of sickle cell patients

Parameters	Patients SSFA_2		
	All patients m ± sd (range)	**CD 36 $^+$ m ± sd (range)**	**CD 49d$^+$ m ± sd (range)**
	n=60 (100%)	**n=48/60 (80%)**	**n=60 (100%)**
Total reticulocytes (%)	14.8 ± 9 (1.58 - 40.13)	48.2 ± 13 (18.1 - 75.8)	42.53 ± 13.63 (4.4 - 82)
Total reticulocytes / (µl)	308,845 ± 176,224 (55,616 – 922,983)	159,249 ± 111,369 (26,637 – 571,870)	109,193 ± 88,650 (13,514 – 460,004)
LFR (%)	48.15 ± 13.85 (9.3 -78.9)	9 ± 6.8 (1.3 -29.82)	7.9 ± 14 (2.2 -84.1)
MFR (%)	34.93 ± 7.99 (14,8 - 50,6)	65.1 ± 8.2 (45.6 - 81.3)	27.4 ± 7.6 (10.8 - 43.7)
HFR (%)	16.9 ± 9.5 (2.3 – 41.7)	25.9 ± 7.7 (14 - 49.2)	64.9 ± 13.8 (3.4 – 84.6)
IRF (%)	51.8 ± 13.3 (17.1 - 79)	91 ± 6.8 (70.2 - 98.7)	92.1 ± 14 (15.9 – 97.8)

m±sd: mean ±standard deviation
LFR: low fluorescence reticulocytes or mature reticulocytes
MFR: medium fluorescence reticulocytes or semi-mature reticulocytes
HFR: high fluorescence reticulocytes or immature reticulocytes
IRF: index reticulocytes fraction or stress reticulocytes (MFR+HFR)

Table 2

Effect of complications on total reticulocytes, CD 36 and CD 49d

Parameters	With complications	Uncomplicated	p
All SSFA_2 patients	**n=25**	**n=35**	
Total reticulocytes (%)	15.6 ± 10.4	14.2 ± 8	0.573
Total reticulocytes (/µl)	300,182 ± 176 236	315, 033 ± 146 991	**0.02***
HFR (%)	16.8 ± 9.8	17 ± 9.4	0.941
IRF (%)	50.6 ± 14.6	52.6 ± 12.5	0.568
CD 36$^+$	**24/25 (96%)**	**24/35 (68.6%)**	
Total reticulocytes (%)	47.4 ± 14.2	48.7 ± 12.4	0.746
Total reticulocytes (/µl)	138,002 ± 83,688	173,169 ± 125,738	**<0.001 ***
HFR (%)	26.1 ± 9.5	25.7 ± 6.4	0.86
IRF (%)	90 ± 7.5	91.7 ± 6.4	0.401
CD 49d$^+$	**25/25 (100%)**	**25/25 (100%)**	
Total reticulocytes (%)	41 ± 17.6	43.6 ± 10	0.40
Total reticulocytes (/µl)	111 086 ± 89 802	107 840 ± 89 107	0.60
HFR (%)	63.2 ± 19.7	66.2 ± 7.3	0.40
IRF (%)	88.7 ± 21.3	94.6 ± 2.2	0.20

m±sd: mean ±standard deviation
p: Student t-test
* Significant difference
HFR: high fluorescence reticulocytes or immature reticulocytes
IRF: index reticulocytes fraction or stress reticulocytes (MFR+HFR)

Table 3

Effect of the absence or presence of CD 36 on certain clinical and biological parameters

Parameters	Presence n=48	Absence n=12	p
Age (years)	19.54±11 (2 - 43)	19.42±6,08 (2 -18)	0.09
Sex ratio M/F Male/ Female	1.29 27/21	0.71 5/7	0.56
Hb S (%)	86.24±5.4 (73.6 - 95)	87.15±3.7 (77.1-90,5)	0.59
Hb F (%)	11.26±4.97 (2.5 - 23.6)	10.7±3.91 (6.7-21.5)	0.72
Hb A_2 (%)	2.42±0.88 (0.6 - 5.9)	2.14±0.70 (1- 3.8)	0.31
Number of crisis/year	2.42±0.90 (1-4)	2.33±1.07 (1 - 4)	0.78
Number of hospitalization days/year	2±2.95 (0 – 11)	1.67±1.78 (0 – 4)	0.71
Number of hospitalizations/year	0.96±1.11 (0 - 6)	0.92±0.79 (0 – 3)	0.90
Number of transfusions	0.65±0.57 (0 - 2)	0.83±0.58 (0 – 2)	0.31
Hb (g/dl)	6.41±1.79 (1.9 -9.9)	5.92±1.7 (3.5 – 8.2)	0.48
WBC (/µl)	19 375±13 947 (5 500 – 74 190)	17 462± 9 397 (5 290 – 36 710)	0.65
Total reticulocytes (%)	15.04±8.56 (1.58 – 39.99)	13.85±11.02 (2.57 - 40.13)	0.68
Total reticulocytes (/µl)	323,237±178,637 (55,616 – 922 983)	251,278±160 313 (74, 273 – 694,249)	**<0.001***
HFR (%)	17.39±9.57 5 (3.59 – 41.71)	15.06±9.08 (2.26 - 27.72)	0.44
IRF (%)	52.77±12.74 (21.15 - 79)	48.25±15.4 (17.08 -71.71)	0.31

m±sd: mean ±standard deviation
p: Student t-test
HFR: high fluorescence reticulocytes or immature reticulocytes
IRF: index reticulocytes fraction or stress reticulocytes (MFR+HFR)

Table 5

Comparison between two groups of sickle cell patients with moderate or severe clinical manifestations

Parameters	Severe form n=10	Milder form n=8	P
Age (years)	19.6±1.64 (7 - 43)	20.86±13.37 (2 - 37)	0.83
Sex ratio (M/F) Male/Female	0.67 4/6	1.67 5/3	0.64
Hb S (%)	91.3±2.48 (88.8 - 95)	84.54±2.43 (80.6 – 87.3)	**<0.001***
Hb F (%)	7.08±2,61 (2.5 - 9,7)	13.1±2.15 (10.8 – 16.9)	**<0.001***
Hb A_2 (%)	2.42±0.87 (1 – 4.4)	2.36±0.45 (1.7 – 3.1)	0.87
Number of crisis/year	2.2±0.92 (1 – 4)	2,63±0,74 (2 – 4)	0.30
Number of hospitalization days/year	2.2±2.15 (0 – 6)	1,38±2,88 (0 - 8)	0.40
Number of hospitalizations/year	1.2±0.63 (0 - 2)	0.88±0.64 (0 - 2)	**0.02** *
Number of transfusions	1.1±0.32 (1 - 2)	0,5±0,54 (0 - 1)	**<0.01***
Hb g/dl	5.24±1.43 (3 – 6,9)	7,71±0,34 (7,3 – 8,2)	0.04 *
White blood cells/µl	21,158±12,549 (5.500 – 45,660)	20,547±21,108 (6.400 – 70,770)	**0.03***
Total reticulocytes %	18.07±12.57 (7.25 – 40.13)	12.16±6,58 (4.48 – 22.51)	0.24
Total reticulocytes /µl	301,142±173,521 (158.050 – 694,249)	306,433±147,732 (138,880 – 535,854)	0.50
IRF (%)	47.57±15.20 (37.88 – 68.57)	51.14±16,62 (22,77 - 66.38)	0.65
CD 36+			
Reticulocytes %	46.63±11.42 (32.19 – 64.95)	47.47±18.10 (21.49 – 62.69)	0.92
Reticulocytes /µl	134,322±83,818 (65.949 – 257,152)	166,926±125,844 (29,843 – 335,905)	**<0.02***
IRF (%)	89.2±7.85 (76.59 – 98.49)	92,6±2,3 (89,51 – 94,73)	0.35
CD 49d+			
Reticulocytes %	40.32±19.02 (4.35 – 64.64)	40,02±11,08 (21,63 – 54,16)	0.97
Reticulocytes /µl	102,910±84,805 (13.514 – 233,581)	101,783±74,903 (13,879 – 231,561)	0.93
IRF (%)	87.63±25.23 (15.94 – 97.84)	94.12±23 (89.54 – 97.68)	0.39

m ± sd: mean ± standard deviation
p: Student t-test
* Significant difference

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