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Research Article

Variation in Pain and Clinical Indices among Patients with Sickle Cell Disease in Ghana

Ababio GK[1], Acquaye J[2], Ekem I[2], Aleksenko L[3] and Quaye IK[4]*

[1]Department of Medical Biochemistry, University of Ghana, Ghana

[2]Department of Hematology, University of Ghana, Ghana

[3]Department of Pathology, University of Namibia, Namibia

[4]Department of Biochemistry and Microbiology, University of Namibia, Namibia

***Corresponding author:** Quaye IK, Department of Biochemistry and Microbiology, University of Namibia, PBAG, 13301, Windhoek, Namibia

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Abstract

Background: Patients with Sickle Cell Disease (SCD) have acute pain episodes that vary between patients. We examined whether differences exist in socio-demographic profiles, blood indices and pain attributed fear of movement in SCD.

Methods: The study included 287 patients with SCD attending the outpatient SCD clinic of the Korle-Bu Teaching Hospital, Accra, Ghana. We documented socio-demographic information, clinical history and pain location at enrolment. Blood sample was also taken for hematological analysis. We used the numeric descriptor, verbal and visual analog scales to determine the site and spectrum of pain intensity, and the Tampa Scale of Kinesiophobia (TSK) to assess pain attributed fear of movement.

Results: Patients with SCD were more literate than their healthy controls ($\chi 2$, p=0.0001). By genotypes, patients with HbSS were younger in age and had lower BMI, p=0.0001, 95% CI: -10.1 – 3.6; and p=0.01, 95% CI -4.13- 0.46. Pain was the most common clinical manifestation in both HbSS and HbSC (17.7% and 25.7% respectively) disease, presenting mainly as musculoskeletal pain (81.3%). Patients with HbSS were anemic, with indicators of hemolytic episodes and elevated WBCs and Platelets (p=0.0001.), depicting an inflammatory state. The disease profile of patients with HbSS was generally severer (OR= 1.695, 95% CI: 1.035-2.776 p=0.036) with a higher score of pain attributed fear of movement (p=0.0001, 95% CI: 2.2 – 6.0).

Conclusion: Pain is a significant index of disease in patients with SCD, particularly in those with HbSS genotype leading to fear of movement. Efforts at involving patients in coping strategies and pain mitigation in management are warranted.

Keywords: Pain and sickle cell disease; Sickle cell disease; Fear of movement; Ghana

Abbreviations

SCD: Sickle Cell Disease; SCA: Sickle Cell Anemia; HbSS: Hemoglobin SS mutant; HbSC: Hemoglobin SC mutant, RBC: Red Blood Cell; MCV: Mean Cell Volume; MPV: Mean Platelet Volume; Hct: Hematocrit; Plt: Platelet; WBC: White Blood Cell; Hb: Hemoglobin; MCH: Mean Corpuscular Hemoglobin; LDH: Lactate Dehydrogenase; BMI: Body Mass Index; TSK: Tampa Scale of Kinesiophobia

Introduction

Sickle Cell Disease (SCD) is a co-dominant genetic disorder [1,2] characterized by the HbS variant of β-globin gene [3]. The common forms of SCD are HbSS, HbSC, HbSD, HbSE and HbS β°/β Thalassemia [4], due respectively to missense mutations E6V (β6 GAG→GTG), E6K (β6 GAG→AAG), E26K (β26 GAG→AAG), E22V (β22 GAG→GTG) and β°/+. The homozygous HbSS variant is referred to as Sickle Cell Anemia (SCA), which is one of the most commonly inherited genetic disorders, in the world [5]. In SCA, HbS polymerization under low oxygen tension leads to dehydration, rigidity and increased red cell density [6]. This phenotype increases vaso-occlusion risk in small blood vessels, impairs blood flow and leads to tissue necrosis so that in reperfusion, an inflammatory response is elicited inducing acute pain episodes [7,8]. Patients with SCA have the highest episodes of pain which is reported to increase in frequency from 6 months of birth and dominates the clinical presentation [9,10]. Most hospitalizations in SCD are due to pain crisis, largely acute episodic nociceptive pain [11-13]. In general the major clinical indices known to contribute to heightened pain are genotype (SCA verses HbSC) [14], hemolysis [15], decreased hematocrit or anemia [16] and decreased fetal hemoglobin (HbF) [17]. There is evidence that these factors do not necessarily translate into heightened pain. For example it is reported that chronic hyper-hemolysis is associated with fewer episodes of pain [18,19]. In addition, in a study of pain involving 3578 patients in the Cooperative Study of Sickle Cell Diseases (CSSCD), 5.2% had 3-10 painful episodes annually that required medical care, while 39% had no pain [19]. Clearly gaps exist in the knowledge of patient factors associated with pain, which requires more data collection from different populations. As mentioned previously, while genetic factors are important in disease phenotype, environmental factors, in particular sociodemographic factors are also major contributors. We reasoned that differences in socio-demographic factors between

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patients may contribute partially to the observed variation in pain manifestation, in addition to disease genotypes and hematological profiles. We also hypothesized that heightened pain episodes in SCD could lead to a morbid state with regards to fear of movement which may differ by genotypes (HbSS and HbSC). So we have characterized differences in demographic, hematological indices and pain attributed fear of movement in patients with SCD (HbSS and HbSC) in Ghana.

Materials and Methods

Study subjects

We enrolled 294 patients with sickle cell disease presenting to the SCD clinic of the Korle-Bu teaching Hospital Accra, Ghana, and 624 controls who qualified to donate blood at the national blood transfusion center, consecutively. The sample size was determined using the formula: N=Z2 (P) (1-P)/ (Error) 2, where Z= standard score for the confidence interval of 95% and equals 1.96. P is the sample proportion of the prevalence of an S allele which is 0.78 and for C allele 0.22 in the population studied. Assuming an error of 5% in this estimate, the sample size per group with an SS and SC genotypes are respectively 175 and 98. The enrolment followed ethical approval by the University of Ghana Medical School Ethical Committee and patients' informed consent. Inclusion criteria depended on subjects having SCD and undergoing follow up visits at the Center for Clinical Genetics, Korle-Bu Teaching Hospital. Patients with sickle cell disease and with acquired hemolysis or known glucose-6-phosphate dehydrogenase deficiency (G-6-PD) were excluded. Non-sickle cell disease subjects declared medically fit to donate blood at the National Blood Donation Center, Korle-Bu Teaching Hospital, and Accra, served as controls.

Demographics

At enrolment, demographic data (age, education) and clinical information (previous infection or disease) were obtained from each subject with a questionnaire either verbally and/or from their folders. Anthropometric measurements (weight (kg) and height (m)) for BMI were also taken.

Pain assessment

We defined pain as that occurring at the extremities, back, abdomen, chest and ribs, head and neck that lasted a minimum of 30 minutes and which could not be explained during a clinic visit except SCD. Pain intensity was assessed over the preceding seven days. We used the Numeric Rating Scale (NRS), Visual Analogue Scale (VAS) and Verbal Descriptors Scale (VDS) to designate the pain intensity, while the Tampa Scale of Kinesiophobia (TSK) was used to assess pain associated disability attributed to fear of movement and musculoskeletal pain. We defined musculoskeletal pain in our context as: back pain, head and neck pain, chest and ribs and general bodily pains. The NRS, VDS and VAS included a body diagram and mood cartoons to enable the patient indicate the exact location of the pain and feeling about the pain. Responses were categorized into four tiers according to the WHO analgesic ladder: without pain (0), mild pain (1-3), moderate pain (4-7) and intense/severe pain (8-10).

Blood collection and analysis

Four millimeters (4ml) blood was drawn from an antecubital vein by means of a plastic syringe and dispensed into EDTA (ethylenediamine tetra -acetic acid) tubes and immediately mixed gently over a roller. This was used to determine the Full Blood Count (Red Blood Cells, Mean Cell Volume, Hematocrit, Hemoglobin, Mean Platelet Volume, Platelet count and White Blood Cells). The Swelab TMAlfaLyse 1504125 (Stockholm, Sweden) analyzer was used for the Full Blood Count, after a control sample had been used to standardize the analyzer. Hb phenotyping was done by cellulose acetate electrophoresis.

Table 1: Baseline demographic data of patients and controls.

¶SCD	BMI (kg/m^2)$_{(n)}$	Age (years)$_{(n)}$	Education(n: ≥ secondary) χ^2 (%)
HbSS	19.9±3.5 $_{(186)}$	25.1±12.8 $_{(186)}$	48(25.8%) SS *vs* Control, p=0.0001
HbSC	22.2±5.1 $_{(101)}$	32.0±13.7 $_{(101)}$	20(19.8%) SC *vs* Control, p=0.0001
Controls	27.0± 3.5 $_{(588)}$	31.6±8.6 $_{(588)}$	31(5.3%)

¶SCD: Sickle Cell Disease; HbSS: Hemoglobin SS mutant; HbSC: Hemoglobin SC mutant; BMI: Body Mass Index

Statistical analysis

Data were captured into an excel spreadsheet and analyzed with Graph Pad Prism and EPI Info. Differences between the means of the hematological indices were determined by student's t-test. The association between the groups of patients with different types of SCD (HbSS and HbSC) and pain were assessed by Chi-square and Fisher's exact tests with Odds ratio and 95% Confidence interval.

Results

A total of 294 patients with sickle cell disease and 624 control subjects were enrolled into the study. Those lost to follow up were seven (7) patients and 36 control subjects to give a final patient population of 287 (186 HbSS, (77 males, 109 females) 101 HbSC (32 males, 69 females) and 588 control subjects (518 males, 70 females). Patients and control subjects lost to follow up declined later to participate in the study. Details of the demographic variables for all subjects are presented in Table 1. Subjects with HbSS genotype were the youngest and had the least BMI (mean ± SD; age: 25.1 ± 12.8; BMI: 19.9 ± 3.5 p=0.0001) in the group. Subjects with HbSC genotype were comparable in age to the controls although their BMI was also lower (age: 32.0 ± 13.7, 31.6 ± 8.6; p=.0001; BMI: 22.2 ± 5.1, 27.0 ± 3.5, respectively). Out of the 588 control subjects, 100 were randomly sampled for Hb phenotyping and were found to consist of HbAA (63), HbAS (28) and HbAC (9). The age and BMI of these control sub groups were similar. Patients with SCD were more likely to have attained at least a secondary education than the control subjects, HbSS *vs* controls, OR=6.2, 95% CI: 3.8-10.2 χ^2, p=.0001; HbSC *vs* controls, OR=4.4, 95% CI: 2.4-8.2, p=0.0001.

The clinical manifestations and disease seen in the patients at presentation to the clinic are presented in Table 2. Pain was the most common clinical manifestation in both patients with HbSS and HbSC (17.7% and 25.7% respectively). Nociceptive pain (aching, sharp, throbbing, cramping and dull) accounted for 94.4% of pain in the general SCD population in this study, with the rest being neuropathic (shooting, tingling and burning). When all the clinical manifestations were combined for patients with HbSS and HbSC genotypes, patients with HbSS have a higher odds of having severe disease, (OR=1.695, 95%CI: 1.035-2.776 p=0.036). With respect to the location of pain, a hundred and sixty (160) subjects with SCD

Table 2: Common clinical manifestations and disease in the SCD patients.

Clinical manifestation/disease	$HbSS_{(186)}$ n(%)	$HbSC_{(101)}$	χ^2
Body Pains	33 (17.7)	26 (25.7)	NS
Fever	13 (7.0)	7 (6.9)	NS
Jaundice	11 (5.9)	3 (3.0)	NS
Dizziness	9 (4.8)	6 (5.9)	NS
Chest Pains	6 (3.2)	5 (5.0)	NS
Cough	4 (2.2)	3 (3.0)	NS
Pallor	3 (1.6)	2 (2.0)	NS
Disease			
Malaria	26 (14.0)	8 (7.9)	NS
Leg Ulcer	5(2.6)	1(1.0)	NS
Flu Like Illness	4(2.2)	1(1.0)	NS

Table 3: TSK assessment of pain avoidance by fear of movement between patients with HbSS and HbSC.

Model/Phenotype	HbSS(n)	HbSC(n)	p-value	Controls(n)	P
Inferences from TSK	22.8±7.9 (163)	18.7±6.8 (92)	0.0001	14.2±3.8 (100)	0.0001

¶TSK; Tampa Scale of Kinesiophobia; HbSS: Hemoglobin SS mutant; HbSC: Hemoglobin SC mutant

responded to the questionnaire. The most commonly indicated sites were limbs (19.4%), back (lumber and sacral regions) (9.4%), head and neck (8.1%), chest and ribs (5%), abdomen (0.63%) and general body pains (6.9%). About 18.1% of the patients had no pain. Excluding abdominal pain, musculoskeletal pain accounted for 81.3% of all pain indications. Painful crises lasted between 3.5 hours to five days. In the TSK Table 3 analysis, we observed that both patients with HbSS and HbSC genotypes have significant fear of movement to avoid pain. This pain avoidance strategy is higher in patients with HbSS genotype (p=0.0001, 95% CI: 2.2 – 6.0).

The indices of hemolysis between patients with HbSS and those with HbSC with respect to controls are presented in Table 4. In general, patients with HbSS genotype were anemic with lower Red Blood Cells (RBCs) count, Hematocrit and Hemoglobin concentrations; while Mean Cell Volume (MCV), Mean Corpuscular Hemoglobin (MCH) and Lactate Dehydrogenase (LDH) were elevated significantly, an indication of hemolytic episodes. In addition White Blood Cells (WBCs) and Platelets were significantly elevated depicting an inflammatory state. The intensity of pain by genotypes in relation to the hematological profile is presented in Table 5. There were no differences in the variables categorized by pain intensity for either patients with HbSS or HbSC genotypes except for Platelets that were significantly reduced in patients with mild pain in HbSS genotype, p=0.0007).

Discussion

In the present study we interrogated some demographic profiles of patients with SCD in Ghana and clinical variables associated with pain. We determined that the population of patients with HbSS genotype presenting at the SCD clinic are young, lean and relatively well educated. In SCD both genetic and acquired factors contribute to the variation in clinical conditions and hospitalizations [20,21]. Among the acquired factors, a patient's socio-economic condition has been identified as the most important. It is most probable that within the Ghanaian setting, the relatively higher educational standard of the patients points to a family background that is high earning and therefore are conscious of a healthy life style. Previous reports indicated that patients with HbSS variant are young but generally have lower than normal anthropometric measurements [22,23]. In a recent report from Brazil most of the patients with HbSS genotype were found to have lower socioeconomic backgrounds contrasting our findings. The relatively higher education of the subjects in Ghana is also good for management as the patients can be guided and informed on their participatory role to attaining a good quality of life. Our study affirmed that SCA as opposed to HbSC disease presents a severer disease condition characterized by anemia and inflammation [24,16]. Considering that the patients with SCD had a good BMI, major contributory factors to the anemic condition could be hemolysis, loss of rbcs and inflammation [25,26]. In hemopoiesis, the common myeloid progenitor gives rise to the megakaryocyte, erythrocytes and myeloblast from which the wbcs are derived. The myeloblast can also respond to a feed in from the common lymphoid progenitor to increase WBC production in an inflammatory state [27]. So in the coexistence of anemia and elevated platelets and wbcs, as seen in the present study, one could envisage a change in hemopoiesis at the progenitor level (megakaryocyte erythrocyte progenitor and common myeloid progenitor) towards increased megakaryocyte and

Table 4: Indices of hemolysis in patients with SCD with respect to controls.

¶Clinical variable	HbSS Patients n=186	HbSC Patients n=101	p-value (SS x SC- t-test)	Controls N=588	p-value (SS x Control-student t test	p-value (Control x SC-student t test)
RBC (10^{12}/L)	3.0±1.0	4.1±0.9	0	4.8±1.3	0	0
MCV(fl)	80.5±10.6	75.9±10.0	0	82.2±27.8	0	0.025
MPV	7.8±2.4	7.9±0.7	0.683	8.6±10.3	0.294	0.495
Hct(%)	23.2±5.2	31.3±6.9	0	39.2±15.5	0	0
Plt(10^9/L)	456.0±313.4	255.3±182.6	0	220.0±65.5	0	0
WBC(10^9/L)	14.2±7.4	8.8±6.6	0	5.1±1.4	0	0
Hb(g/dL)	8.0±1.8	10.9±2.2	0	13.4±1.6	0	0
MCH(pg)	28.0±4.2	26.7±4.0	0.011	28.4±2.4	0	0
LDH	298.3±129.0 (19)*	166.8±81.5 (16)*	0.001	182.4±67.4 (21)*	0.001	0.528

*actual numbers used; ¶SCD: Sickle Cell Disease; SCA: Sickle Cell Anemia; HbSS: Hemoglobin SS mutant; HbSC: Hemoglobin SC mutant; RBC: Red Blood Cell; MCV: Mean Cell Volume; MPV: Mean Platelet Volume; Hct: Hematocrit; Plt: Platelet; WBC: White Blood Cell; Hb: Hemoglobin; MCH: Mean Corpuscular Hemoglobin; LDH: Lactate Dehydrogenase

Table 5: Pain intensity by SCD genotype in relation to hematological indices.

	RBC (N)	MCV	Hct	Plt	WBC	Hb
¶*HbSC*						
No pain (0)	4.3±0.8 (22)	76.1±8.3 (22)	32.8±6.4 (22)	280.0±210.0 (22)	8.4±4.2 (22)	11.0±2.0 (22)
Mild (1-3)	4.1±0.8 (21)	74.8±11.7 (21)	31.3±5.4 (21)	251.1±122.6 (21)	8.4±3.2 (21)	11.1±1.9 (21)
Moderate (4-7)	3.9±0.6 (29)	78.6±6.7 (29)	30.8±4.1 (29)	236.8±95.6 (29)	8.2±3.6 (29)	10.8±1.3 (29)
Severe (8-10)	4.2±0.6 (25)	74.4±6.6 (25)	30.9±4.8 (25)	221.6±147.7 (25)	8.9±3.3 (25)	10.9±1.6 (25)
HbSS						
No pain (0)	3.0±0.9 (35)	80.8±10.4 (35)	23.2±4.9 (35)	476.7±165.6 (35)	13.1±6.9 (35)	8.0±1.7 (35)
Mild (1-3)	2.8±0.7 (29)	80.8±9.9 (29)	22.0±4.6 (29)	411.3±243.5 (29)	13.3±5.0 (29)	7.6±1.5 (29)
Moderate (4-7)	3.0±1.5 (44)	80.8±13.0 (44)	22.3±5.5 (44)	487.9±249.2 (44)	15.2±9.8 (44)	7.6±1.9 (44)
Severe (8-10)	3.1±0.9 (59)	80.5±10.7 (59)	24.3±5.2 (59)	440.3±161.9 (59)	14.3±6.0 (59)	8.3±1.8 (59)
Controls (588)	4.8±1.3	82.2±27.8	39.2±15.5	220.0±65.5	5.1±1.4	13.4±1.6
Units	10^{12}/L	Fl	%	10^{9}/L	10^{9}/L	g/dl

¶SCD: Sickle Cell Disease; SCA: Sickle Cell Anemia; HbSS: Hemoglobin SS mutant; HbSC: Hemoglobin SC mutant; RBC: Red Blood Cell; MCV: Mean Cell Volume; Hct: Hematocrit; Plt: Platelet; WBC: White Blood Cell; Hb: Hemoglobin; MCH: Mean Corpuscular Hemoglobin

leukocyte production respectively, driven by periodic inflammatory conditions. As expected in anemic and inflammatory states, fever, jaundice and leg ulcers were common in the patients with SCD.

Severe nociceptive musculoskeletal pain was the most prominent presenting clinical manifestation in SCA. This indicates that injury to muscle tissues, discs; nerves and ligaments are primary conditions underlying the pain syndrome [28-30]. These injuries increase the activation of inflammatory mediators and the response to the injury [31] leading to pain. The inflammatory state in sickle cell disease is driven by hemolysis, heme release and interactions between sickledrbcs and wbcs that increase adhesion to the vascular endothelium, vaso-occlusion and recurrent ischemia reperfusion injury in multiple organs [32-34]. Ischemia reperfusion injury leads to oxidative stress, increased expression of adhesion molecules on the endothelium and release of platelet activating factor which activates platelets and sustain inflammation [35]. The acute episodic and chronic pain not only reduces life expectancy [36] but as in the present study induces a disability in the patients in the form of fear of mobility. The observed pain induced fear of mobility is particularly interesting considering that the majority of the patients were young and not affected by other conditions of disability that will normally be associated with the elderly. In addition it is interesting that the number of patients who complained of pain were lower in SCA than in HbSC disease. These observations may relate to the severity of SCA anemia as a whole with its attendant hemolytic and inflammatory states compared to HbSC disease. As previously reported, it appears that increased hemolysis correlates inversely with the number of pain episodes [18,19]. The TSK scale is also known to correlate not only with fear of movement and disuse but also to depression [37]. Not surprisingly several reports, including the Pain in Sickle Cell Epidemiology Study (PiSCES) present evidence of depression in patients with sickle cell disease that relates to the totality of the disease severity [38-41]. These call for standardized approaches on care of patients with sickle cell disease that takes a holistic approach on clinical presentation, including pain attributed fear of movement and depression.

Conclusion

We conclude that pain is a significant index of disease in patients with SCA in particular and efforts at involving patients in coping strategies, pain mitigation and fear of movement are warranted.

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