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Pathology Section

Clinical and Laboratory Predictors of Frequency of Painful Crises among Sickle Cell Anaemia Patients in Nigeria

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ABSTRACT

Introduction: The severity of Sickle Cell Anaemia (SCA) in terms of frequency of painful Vaso-Occlusive Crises (VOC) may be affected by clinical and haematological parameters amongst others. Elucidation of these factors in a given disease prevalent environment is necessary for prompt and effective management of patients with frequent painful VOC.

Aim: This study aimed at determining the clinical and laboratory predictors of frequency of painful VOC among SCA patients in Enugu, Southeastern Nigeria.

Materials and Methods: It was a cross-sectional study of 100 consecutive SCA patients receiving care at the University of Nigeria Teaching Hospital, Enugu, Nigeria between May 2012 and February 2014. The eligible patients were categorized into two groups namely; Group A and Group B. Group A/study group (severe disease) comprised SCA patients who had experienced three or more painful crises (≥3 crises) in the last one year preceding the study but, currently in steady state, while Group B/control group (mild–moderate disease), comprised SCA patients matched for age, sex, highest educational status, and occupation but who have had no painful crisis or had only one or two painful crises (0–2 crises) in the last one year preceding the study and currently in steady state.

Results: The overall mean age of the patients was 18.4±12.2 (range=2-52) years. The mean values of the haematological parameters including haemoglobin concentration, white cell count, platelet count, and neutrophil count were significantly higher in those with severe crises than mild-moderate crises ($p<0.05$). Sickle cell related complications including Avascular Necrosis (AVN) and leg ulcers were significantly higher in the study group than the control group ($p<0.05$).

Conclusion: There was significant association between the frequency of crises and haemoglobin level, platelet and neutrophil counts and some clinical parameters: AVN, nephropathy and stroke. Future preventive interventions for reduction in frequency of crisis amongst patients with SCA could be targeted at controlling the blood levels of the identified haematological parameters.

Keywords: Clinical parameters, Frequency of crisis, Laboratory parameters

INTRODUCTION

Across Africa, SCA, a condition where an individual inherits two abnormal haemoglobin S genes from both parents is prevalent. The prevalence varies from 10% in Northern Ghana to 30% in Northern Nigeria [1]. Patients with SCA have various clinical manifestations such as acute painful crisis, AVN of joints, leg ulcerations, jaundice, episodes of severe anaemia and also Cerebro-Vascular Accidents (CVA). They have exacerbations of clinical symptoms called crisis, which are of several types viz, vaso-occlusive, aplastic and sequestration crises. The commonest form is the VOC which is also the commonest reason for hospital visit [2]. Recurrent episodes of these crises lead to complications such as stroke, nephropathy, avascular necrosis of bone, pulmonary hypertension and retinopathy.

VOC in SCA also leads to injury to multiple organ systems. It is a known fact that large numbers of sickled red cells lodging in the microvasculature appear not to be the only link to causation of vaso-occlusion rather, other factors play significant roles such as excessive tendency of both sickle and non sickled red cells to adhere to vascular endothelium and subsequent activation of other cell lines such as platelets and leukocytes [3,4].

Several factors have been shown to be associated with the initiation of VOC among SCA patients. These factors range from: haematological, epigenetic, socioeconomic, environmental, cultural, nutritional, psychosocial, physical and mental stress causes [4], even among siblings with SCA, it is known that the severity of the clinical manifestations of the disease varies from one person to another. In other words, despite the genetic identity at the site of the sickle haemoglobin mutation, all patients with SCA do not manifest similar disease severity [5]. Elucidating the clinical and laboratory factors that affect the disease severity in any given disease prevalent environment may help the clinicians in counselling and prompt management of patients with SCA in that environment. It could also help the policy makers in designing strategies for reducing the frequency of painful crises and clinical severity of the disease in a given area.

This study therefore aimed to determine the clinical and laboratory predictors of frequency of painful crisis and clinical severity of SCA patients in Enugu, Southeastern Nigeria where the prevalence of SCA is high.

MATERIALS AND METHODS

The study was carried out at the adult and paediatric special sickle cell clinics of the University of Nigeria Teaching Hospital (UNTH) Ituku-Ozalla, Enugu, Nigeria between May 2012 and February 2014. The approval for the study was sought and obtained from the Institutional Review Board before the commencement of the study.

It was a cross-sectional study of eligible consecutive SCA patients attending the adult and paediatric outpatient haematology clinics of the hospital. The patients were recruited after informed written consent had been obtained. Also, consent was sought from parents/caregivers of the paediatric patients. The patients were categorized into two groups namely; group A and Group B. Group

A formed the study group (severe disease) comprising SCA patients who have had three or more sickle cell painful crises (≥3 crises) in the last one year preceding the study but currently in steady state, while Group B which formed the control group (mild-moderate disease), comprised SCA patients matched for age, sex, highest educational status, and occupation but who have had no painful crisis or had only one or two painful crises (0–2 crises) in the last one year preceding the study and currently in steady state. This classification was adapted from studies by Darbari DS et al., and Nebor D et al., [6,7]. For each group, the exclusion criteria included: blood transfusion of patient in the last four months, treatment with hydroxycarbamide or any agents/herbal remedies that may affect membrane PUFA composition, and patient being currently in painful crisis.

Patients were interviewed and examined for presence if any, of complications of sickle cell disease. Detailed clinical, pertinent personal history and other relevant information were obtained from the SCA patients themselves (for the adults) or from their guardians (for the children) using a questionnaire specifically designed for the study. The data obtained included: enrolment identity number, gender, age, residence, ethnicity, weight, height, occupation, steady state haemoglobin, number of painful crisis and sickle cell-related hospital admissions in the last one year preceding the study, sickle cell-related complications, and history of blood transfusion.

The severity of SCA was assessed in each group by evaluating for sickle cell related complications (AVN, chronic osteomyelitis, chronic leg ulcers, priapism, gall stone, acute chest syndrome, cerebrovascular accident, nephropathy and retinopathy), number of hospital admissions and blood transfusions in the last one year preceding the study, and by investigating for certain laboratory parameters (white cell count, haemoglobin concentration, platelet count and neutrophil percentage) [8]. Sickle cell vaso-occlusive events (painful crisis) was defined as the development of acute severe pains in SCA patients due to ischemia or infarction occurring in the bones, joint, lungs, kidney, spleen, eye or central nervous system that brings patients into hospital for care [9]. A patient was regarded to be in “steady state” if the patient has been free of overt painful crisis, fever or infection for more than four weeks preceding the study [10,11].

STATISTICAL ANALYSIS

Using a 3.1% prevalence of HbS obtained from a previous study in Ibadan, Southwestern Nigeria [12], at a confidence limit of 95% (d = 5%) and ‘Z’ of 1.96, the minimum sample size (n) for each group was 46.1. However, considering an attrition rate of 10% for possible drop outs, the required sample size was approximately 50 for each group.

Data analysis was done using the Statistical Package for Social Sciences (SPSS) computer software version 16.0 for windows. Continuous variables were analysed using the student’s t-test. Discrete variables were analysed using chi-square and Fisher-exact tests and associations expressed using odds ratio, and confidence intervals as applicable. All tests were two-sided, and statistical significance was considered to be at probability value of <0.05.

RESULTS

Sociodemographic characteristics: All the 100 SCA patients (50 in each group) recruited into the study completed the study. The mean age of the paediatric patients was 8.1±4.3 (range: 2-17) while that of the adult patients was 28.9±7.8 (range: 19-52). The overall mean age of the patients was 18.4±12.2 (range: 2-52) years. The mean height and weight of the paediatric patients were 128.4±17.5 (range: 88-162) cm and 29.2±9.4 (range: 12-63) kg respectively while that of the adult patients were 161.4±12.8 (range: 156-175) cm and 62.3±15.2 (range: 47-92) kg respectively. The overall mean height and weight of the patients were 143.4±25.03 (range: 88-

Variable	Variable sub-group	Group A (%)	Group B (%)
Age	1-10	9 (18)	7 (14)
	11-20	10 (20)	11 (22)
	21-30	24 (48)	23 (46)
	31-40	4 (8)	5 (10)
	41-50	2 (4)	3 (6)
	51-60	1 (2)	1 (2)
Sex	Male	25 (50)	25 (50)
	Female	25 (50)	25 (50)
Educationa status l	< Primary	11 (22)	10(20)
	Primary	9 (18)	9 (18)
	Secondary	12 (24)	11 (22)
	Tertiary	18 (36)	20 (40)
Occupation	Pupil	6 (12)	5 (10)
	Students	15 (30)	14 (28)
	Trading	3 (6)	5 (10)
	Civil servants	5 (10)	4 (8)
	Unemployed	21 (42)	22 (44)

[Table/Fig-1]: Sociodemographic characteristics of patients.

Variable	Group A	Group B	p-value
Family history of SCA:			
Yes	32 (64%)	30(60%)	0.84
No	18 (36%)	20 (40%)	0.84
Number of siblings with SCA:			
None	32 (64%)	36 (72%)	0.52
One	11(22%)	8 (16%)	0.61
≥2	7 (14%)	6 (12%)	0.77
At least one	18 (36%)	14 (28%)	0.52
Intake of folic acid/paludrine for anaemia/malaria prophylaxis	48 (96%)	47 (94%)	0.65
Intake of omega 3 fatty acid supplements and/or fish oil	43 (86%)	39 (78%)	0.43

[Table/Fig-2]: Relationship between frequency of crisis and some patients’ characteristics*.
*t-test for continuous variables; $\chi 2$ for categorical variables

Variables	Group A (n = 50)	Group B (n = 50)	p-value
Sickle cell related complications			
AVN	14(28%)	5 (10%)	0.04
Chronic leg ulcer	9 (18%)	3 (6%)	0.03
Priapism**	7 (28%)	1 (4%)	0.04
Nephropathy	2(4%)	0 (0)	-
Retinopathy	2 (4%)	0 (0)	-
Chronic osteomyelitis	5 (10)	1 (2%)	0.20
Gall stones	4 (8%)	1 (2%)	0.36
Acute chest syndrome	2 (4%)	0 (0)	-
Number of hospital admissions	4.86 ± 1.43	0.93 ±0.54	< 0.001
Number of blood transfusions	2.13 ± 0.53	1.33 ± 0.48	< 0.001
Haematological parameters			
Haemoglobin level (g/dl)	8.5 ± 1.45	7.8 ± 1.29	0.01
WBC (X 10^9)	11.28 ± 2.47	10.25 ± 2.33	0.03
Neutrophil (%)	52.70 ± 9.59	48.60 ± 8.56	0.03
Platelet (X 10^9)	269.6 ± 11.85	263.9 ± 11.63	0.02

[Table/Fig-3]: Association between some clinical and laboratory factors and frequency of crises in SCA*.
* Fisher-Exact-test for categorical data and t-test for continuous data
**n = 25 (for the males in each group); AVN = Avascular necrosis

175) cm and 44.34±22.12 (range: 11.0-92.0) kg respectively. Other sociodemographic characteristics of the two groups are as shown in [Table/Fig-1].

The proportions of patients with family history of SCA, siblings with SCA, intake of folic acid and paludrine, and intake of omega 3 fatty acids supplements and/or fish oil, were not significantly different in the two groups. Details are as shown in [Table/Fig-2].

Clinical and laboratory factors: Thirty two patients (64%) in Group A had at least one sickle cell related complication in the last one year preceding the study as against 8 (16%) patients in Group B. The observed difference was statistically significant (OR=9.33; 95% C1=3.60-24.17; p<0.001). The proportion of patients with AVN, chronic leg ulcer, and priapism; the mean values of number of hospital admissions and blood transfusions; and the mean values of haematological parameters, are significantly higher in cases with severe crises than mild-moderate crises. Details are as shown in [Table/Fig-3].

DISCUSSION

The mean age of the paediatric and adult patients was 8.1±4.3 and 28.9±7.8 respectively with significant proportions being in the 10-20 (21%) and 20-30 (47%) age categories. These findings are similar to previous report on SCA from the study area [13].

It was observed in this study that patients with severe crises had significantly higher mean haemoglobin concentration than those with mild-moderate crises. This may be explained by the potentially deleterious effect of a higher haematocrit on blood rheology in larger vessels, causing impairment in blood flow with resultant tissue ischemia and increased risk of painful crises [3,4]. The degree of sickle haemoglobin polymer formation which is a function of haemoglobin concentration has been shown to correlate closely with the severity of haemolysis and sickle cell crises [14]. Thus, while maintenance of adequate haemoglobin concentration remains critical in the management of SCA, this study did not determine the level of haemoglobin at which the increased risk of painful VOC may occur. A future study on the cutoff haemoglobin level that increases this risk may guide in clinical practice.

It was also found in this study that patients with severe crisis had significantly higher mean white cell count and neutrophil count than those with mild-moderate crises. This observation was not surprising as many complications of sickle cell disease are associated with high white cell count which is a distinct risk factor for acute chest syndrome [15], CVA and early sickle cell disease related deaths [3]. Furthermore, a high absolute neutrophil count has been shown to have a statistically significant relationship with clinical severity of SCA including the frequency of crises [15,16].

With respect to platelet count, this study demonstrated a significant association between platelet count and frequency of crises. Previous studies also documented an association between clinical severity of sickle cell disease e.g., stroke and high levels of platelet count [16]. This may be related to the activation of platelet at increased numbers during steady state in patients with haemoglobin SS. Though, the exact cause of platelet activation is not known, it is postulated that platelet activation leads to release of substances that are thrombogenic and vasoactive [3].

This study also demonstrated a significant association between the degree of crises and occurrence of sickle cell related complications. In fact, a patient with severe degree of crises has over a nine fold risk of developing sickle cell related complications compared to a patient with mild-moderate degree of crises. This may be related to the effect of chronic oxygen deprivation on body tissues which leads overtime to end organ damage. The painful crisis often precedes the onset of most complications of the disease such as acute chest syndrome and acute multi-organ failure [4]. AVN (21%), followed by leg ulcer (12%) was the commonest sickle cell related complication observed in this study, and this finding is in keeping with that of previous related studies [4,13]. The least frequent complication in both groups was acute chest syndrome, occurring generally in 1-4% of the patients. This finding is also in agreement with a previous related study [4].

The higher frequency of blood transfusion seen among those patients with severe degree of crises may be due to the higher frequency of sickle cell related complications such as nephropathy and chronic leg ulcers found in this study. Also, any further assault on the already existing pathology gives rise to further depression of an existing chronic anaemia and thus, will attract blood transfusion [3,4].

The wide confidence intervals of some outcome measures in this study suggest that a larger sample size would have improved the study's precision and external validity; however, it is likely that it would have had only a minimal effect on the magnitude and direction of the estimates. The HbF levels in the two groups, the haplotype, and the compound heterozygosity are possible areas of future studies that may explain the differences in the degree of crisis and other clinical severity in SCA.

LIMITATION

Despite the comprehensive matching for the known biological factors that could affect disease severity; the limitations of this study include the possibility of some other currently unknown confounding factors that might affect disease severity.

CONCLUSION

There was significant association between the frequency of crises and the levels of haemoglobin concentration, white cell, and platelet counts, and some sickle cell related complications including avascular necrosis and leg ulcers. Since most complications of SCA including frequency of crisis are associated with raised levels of haematological parameters, future preventive interventions may be targeted at controlling the blood levels of these parameters in these patients.

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