PULMONARY HYPERTENSION AMONG PATIENTS WITH SICKLE CELL ANEMIA IN KANO, NORTHWESTERN NIGERIA: CLINICAL AND LABORATORY CORRELATES

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Abstract

Context:

With increasing life expectancy due to improvements in healthcare for patients with sickle cell anemia (SCA), pulmonary hypertension (PH) is emerging as one of the leading causes of morbidity and mortality in adult patients with SCA.

Aim:

The study aims to determine the prevalence of PH and the clinical and laboratory correlates of PH among adult patients with SCA in Kano, North-Western Nigeria.

Settings and Design:

A cross-sectional study was conducted among 211 patients with SCA aged ≥16 years.

Materials and Methods:

Demographic and clinical data were obtained using a structured questionnaire and a review of clinical records. Complete blood count (CBC) and biochemical markers of hemolysis were determined using standard methods. Tricuspid regurgitant velocity (TRV) as a marker of PH was obtained using a 2D echocardiography. PH was defined as TRV ≥2.5m/sec.

Statistical Analyses Used:

Data was analyzed using SPSS v21.0 and a *p*-value <0.05 was considered significant.

Results:

The prevalence of PH was 31.8%. Patients with PH were significantly older (*p*=0.036), had more blood transfusion (X^2=7, *p*=0.003), less hospitalization (X^2=8.8, *p*=0.001), less VOC (X^2=6.7, p=0.000) and more priapism (X^2=10, p=0.036) compared to those without PH. Platelet count (r=0.416), reticulocyte count (r=0.451), serum LDH (r=0.682), and serum bilirubin (r=0.810) had a positive correlation with PH while hemoglobin (r=-0.661) had a negative correlation with PH.

Conclusion:

PH is common in adults with SCA in our environment and it is significantly associated with less frequent painful crises and more transfusions, high serum LDH, and bilirubin. Routine screening and early intervention are needed to prevent morbidity and mortality and improve quality of life.

Keywords: Pulmonary Hypertension, Sickle Cell Disease, Hemolytic markers, clinical correlates

Introduction

Recent advances in the management of sickle cell anemia (SCA) have increased patient survival, unmasking chronic complications as individuals with SCA age. [1,2] Among these complications, pulmonary hypertension (PH) stands out as a relatively common, severe, and potentially fatal outcome of sickle cell disease (SCD), serving as an independent risk factor for mortality. [1,3] Pulmonary hypertension is estimated to affect 20-30% of patients with SCD and is characterized by elevated pulmonary artery pressure and pulmonary vascular resistance. [4] While a definitive diagnosis of PH requires right heart catheterization, Doppler echocardiography is a valuable non-invasive screening tool. This method can identify abnormalities indicative of PH, including right atrial enlargement, right ventricular dilation or hypertrophy, Tricuspid Regurgitation Velocity (TRV), and right to left septum shift.

Studies in tertiary care SCD centers in the United States using Doppler echocardiography have revealed that 20% to 30% of patients screened exhibit signs of PH. [5] Recent echocardiographic screening studies have suggested a higher-than-expected prevalence of hemoglobinopathy-associated PH. [6] However, the burden of PH and its clinical correlates among adult SCA patients in our specific environment, particularly in Kano, North–Western Nigeria, remains unexplored. Assessing these factors

is crucial for clinicians, aiding in identifying patients who would benefit from diagnostic echocardiography, enabling early management, and mitigating potential morbidities and mortalities. Thus, our objective is to determine the prevalence of PH and its clinical determinants in adult SCA patients in Kano, North–Western Nigeria.

Materials and Methods

Study design and population

This descriptive cross-sectional study involved 211 patients attending the adult Hematology Clinic of Aminu Kano Teaching Hospital (AKTH) from March to July 2021.

Inclusions and exclusions

We included all patients aged 16 years and above diagnosed with homozygous SCA (HbSS) using cellulose acetate electrophoresis at alkaline pH and presenting in a steady state, defined as the absence of acute illness (pain crisis, fever, acute chest syndrome, or other SCA-related complications) or transfusion in the preceding 4 weeks. [1] We excluded participants with a history of chronic lung diseases like tuberculosis, heart failure and SCD-related chronic organ damage (liver and kidney).

Ethics

Ethics approval for the study was obtained from the Research and Ethics Committee of AKTH (Approval No. AKTH/MAC/SUB/12/P-3/VI/1689, 4th February 2016). Informed written consent was obtained from the participants before recruitment into the study.

Demographic and Clinical Data

Demographic and clinical data was collected using a structured questionnaire and a review of clinical notes.

Laboratory Analyses

Blood samples for CBC were collected in the standard way using appropriate bottles and analyzed with a Sysmex hematology analyzer (Japan). The reticulocyte count was manually estimated from a peripheral blood smear stained with methylene blue and expressed as a percentage of the total red cell count. Biochemical markers of hemolysis (serum bilirubin, lactate dehydrogenase, and aspartate transaminase) were determined by spectrophotometry using Randox kits (UK) following the manufacturer's instructions.

Echocardiography

According to the American Society of Echocardiography guidelines, all

echocardiographic measurements were performed by a qualified cardiologist. [7] The measurements were performed using the 2D thoracic echocardiogram (Sonoscape 1800i machine, China). Tricuspid regurgitation was assessed in the parasternal right ventricular inflow, the parasternal short-axis, and apical four-chamber views to determine the highest velocity. Continuous wave Doppler of the peak tricuspid regurgitant jet velocity was used to estimate the right ventricular to right atrial systolic pressure gradient using the modified Bernoulli equation, in conjunction with echocardiographic estimation of Right Atrial Pressure in which TRV of <2.5 m/s and ≥2.5 m/s as normal and PH respectively. [7]

Statistical Analysis

Data was analyzed with Statistical Package for Social Sciences (SPSS) version 21.0 (IBM Corp. Armonk, NY), and the result was presented as mean with standard deviation and proportion with percentage as appropriate. Chi-square (χ^2) and logistic regression analysis at a 95% confidence interval were employed to test for association and estimate risk respectively. *P* – value of less than 0.05 was accepted as a significant statistical relationship

Results

Bio-demographic characteristics

Two hundred and eleven (211) patients participated in the study aged between 16-44 years of whom the mean age was 21.93 ± 5.31. The majority (80) of the participants were between the ages of 20-24 (37.9%). A significant number of the participants were students 136 (64.5%) while 15 (7.1) were self-employed. Other bio-demographic characteristics of the participants are depicted in Tables 1 and 2.

Clinical Characteristics of the Participants

The mean age at diagnosis of the participants in the study was 15.52 ± 7.78 months and other clinical parameters of the study participants are depicted in figures 3 to 5. Figure 3 shows that the majority of the participants 136 (46.50%) had 1-4 episodes of bone pain crisis that required hospital admission in the preceding year while only 15 (2.4%) had ≥ episodes of similar bone pain crisis within the same period. Figure 4 shows that the majority of the participants 135 (64.00%) had been admitted once in their lifetime with 96 (45.50%) and 4 (1.90%) having 1-4 and ≥ 15 admissions in the preceding year respectively. Among the 211 participants, more than half of 123 (58.30 %) had a positive history of blood transfusion. Of those who had a transfusion in the past, 95

(45.00%) were transfused 1-4 times in their lifetime as depicted in Figure 5 respectively. The majority of the participants 136 (64.5%) had a positive history of dyspnoea but only 35 (16.60%) admitted improvement of dyspnoea upon transfusion. Among the male participants, 27 (34.60%) had at least an episode of priapism at one time in their life.

Hematological and Hemolytic Parameters

Table 2 shows the hematological and hemolytic parameters of the participants. The mean hemoglobin, total white blood cell count, and platelet count were 7.97 ± 1.37g/dL, 12.71 ± 4.05 × 10^9/L and 347 ± 149.25 × 10^9/L respectively. The mean total and direct bilirubin, LDH, and Reticulocyte of the study participants are 16.50 ± 9.39 U/L, 8.50 ± 4.85 U/L, 229.66 ± 156.38 U/L and 5.08 ± 7.42(%) respectively as shown in table 2.

Echocardiographic Parameters

Selected echocardiographic parameters of the participants in the study are depicted in Table 1. The mean Pulmonary Artery Systolic Pressure, Right Atrial Pressure, Right Atrial Diameter major and minor, and Estimated Central Venous Pressure were 27.26 ± 13.21mmHg, 6.00 ± 2.81mmHg, 38.38 ± 7.22mmHg, 39.04 ± 7.54mm, and 11.02 ± 2.80mm respectively.

Prevalence of PH

A total of 67 of 211 participants (31.8%) had PH (Table 1). Figure 2 shows the classification of PH among the participants.

Clinical and Laboratory Correlates of PH

Male sex (p= 0.036), higher number of blood transfusions (p= 0.003), lower number of bone pains (p= 0.000, X^2 = 6.7*)*, and hospital admission (p= 0.031, X^2 = 8.8), had a statistically significant association with the development of PH. A total of 30 (38.46%) of the male participants had PH as against 37 (28.03%) of the female participants. As the frequency of bone pains and hospitalization increases, the occurrence of PH decreases, for instance, 4 (80%) and 3 (75%) of participants with >15 bone pains and hospital admissions in the last year had a normal TRV as against only 33 (34%) and 34 (35%) of participants with 1-4 bone pains and hospital admissions within the same period respectively as depicted in Table 2.

The number of lifetime transfusion correlate well with the development of PH (*P* = 0.003, X^2*=7.02) as* 3 (75%) of all participants with > 15 blood transfusions had PH. About 21

(51%) of patients who had a history of syncope have PH (p= 0.012, X^2= 7.8) as shown in Table 3.

Patients with PH had a lower Hb (p=0.037) and higher platelet count (p= 0.026) than those without PH, while other hematological parameters were not significantly different between the two groups (p >0.05) as depicted in Table. There was a significant positive correlation between the development of PH and the platelets (r = 0.416, p=0.026) while hemoglobin (r = -0.661, p =0.037) had a significant negative correlation with the development of PH among participants.

The results of the association between hemolytic markers and PH are presented in Table. Patients with PH had a higher total and direct bilirubin (p = 0.001 and p =0.004), higher LDH (p= 0.006), and higher reticulocyte count (p=0.026) than those without PH as depicted in Table 17. There was a significant positive correlation between the development of PH and total and direct bilirubin (r = 0.810, p= 0.001 and r= 0.400, p= 0.004), reticulocyte (r= 0.451, p=0.017), LDH (r= 0.682, p= 0.006).

Table 1: sample characteristics of participants

	Frequency (Number)	**Percentage (%)**
Age (years)		
16 – 19	79	37.4
20 – 24	80	37.9
25 – 29	25	11.8
30 – 34	19	9.0
35 – 39	3	1.4
40 – 44	5	2.4
Gender		
Male	78	37.1

Female	132	62.9
Occupation		
Students	136	64.5
Civil Servant	17	8.1
Self Employed	15	7.1
Unemployed	43	20.4

Table 2: Hematological and hemolytic parameters of study participants

Parameters	**Mean ± SD**
Hematological parameters	
Hemoglobin (g/dl)	7.97±1.37
PCV (%)	23.26±4.70
MCV (fl)	90.34±7.92
WBC (x 10^9/L)	12.71±4.95
ANC (x 10^9/L)	5. 96±2.24
Platelets (x 10^9/L)	347.10±148.25
Hemolytic markers	
Reticulocyte count(%)	5.08 ± 7.42
Total bilirubin (U/L)	16.50 ± 9.30
Direct bilirubin (U/L)	8.50 ± 4.85
LDH(U/L)	229.66 ± 156.38

PCV = packed cell volume, MCV = mean cell volume, WBC = white blood cell count, ANC = absolute neutrophils count, LDH = lactate dehydrogenase

Table 3: Prevalence of PH

Parameter	**Frequency (%)**
MPAP (mmHg)	
Normal	149 (70.6)

High	63 (29.4)
TRV (m/s)	
Normal	143 (68.1)
High	67 (31.8)

MPAP = mean pulmonary artery pressure, TRV = tricuspid regurgitant velocity

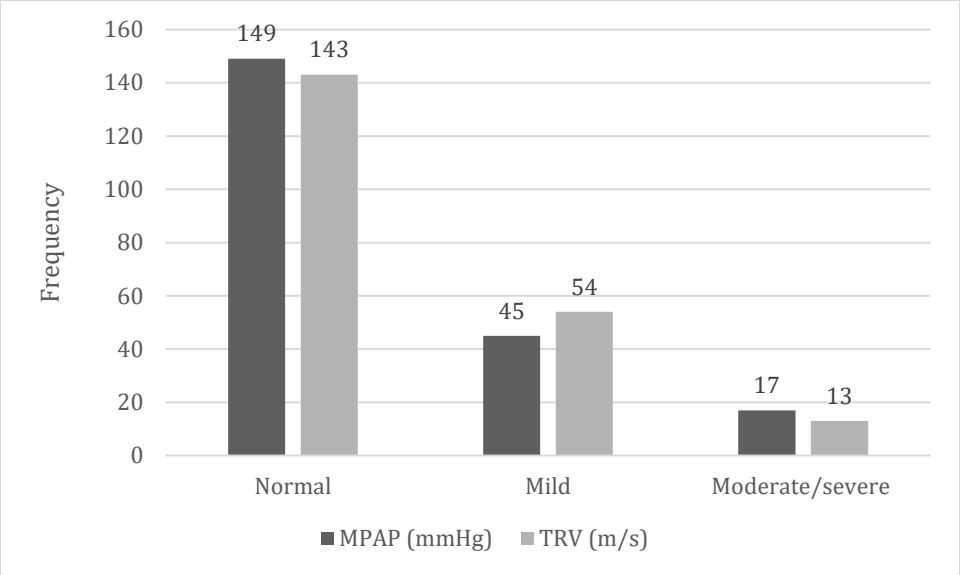

Figure 1: Classification of PH

Key: MPAP = mean pulmonary artery pressure, TRV = tricuspid regurgitant velocity

MPAP (mmHg) Classification: normal (< 25), mild (25 – 34.9), moderate (35 – 44.9), severe (≥ 45)

TRV (m/s) Classification: normal (< 2.5), mild (2.5 – 2.9), moderate/severe (≥ 3)

Table 4: Clinical correlates of PH

Parameter	Normal TRV	PAH	P-value
Hospitalizations/ year			0.031
No hospitalization	49	27	
1-4	63	34	
5-9	22	3	
10-14	7	2	
≥ 15	3	1	

History of blood transfusion			0.013
Yes	83	40	
No	60	27	
Number of blood transfusions per lifetime			0.003
No Transfusion	55	25	
1-4	63	31	
5-9	14	5	
10-14	8	5	
≥ 15	1	3	
Dyspnea			0.013
Yes	102	33	
No	41	34	
Improvement in dyspnea after Blood Transfusion			0.064
Yes	24	28	
No	10	13	

Table 5: Comparison of hematological parameters of participants with and without PH

Parameter	**Normal TRV** **Mean ± SD**	**PAH** **Mean ± SD**	**P-value**
Hb (g/dL)	9.84± 1.38	6.03±1.33	0.037
PCV (%)	30.40±4.86	19.99±9.83	0.026
MCV (fL)	88.99±7.13	90.98±8.22	0.089
WBC (x10^9/L)	12.69±4.35	12.76±3.36	0.904
ANC (x 10^9/L)	6.04±2.84	5.78±1.92	0.435
Platelet (x 10^9/L)	244.59±192.07	348.30±143.46	0.026

Statistically significant p <0.05

MPAP = mean pulmonary artery pressure, TRV = tricuspid regurgitant velocity

Hb = Hemoglobin, PCV = Packed Cell Volume, MCV = Mean Cell Volume, WBC = White Blood cell Count, ANC = Absolute Neutrophil Count

Table 61: Correlation between hemolytic markers and PH

Parameter	Correlation Coefficient (*r*)	*p-value*
Reticulocyte (%)	0.451	0.009
TBIL (U/L)	0.810	0.001
DBIL (U/L)	0.400	0.004
LDH (U/L)	0.682	0.006

Statistically significant $p < 0.05$

TBIL = Total bilirubin, DBIL = Direct bilirubin, LDH = Lactate Dehydrogenase

Discussion

The prevalence of PH is high among this population of adults with SCA. This is consistent with previous reports of 28-32% in other environments. [8–12] With increased longevity from reduced childhood mortality and better care of SCA patients, cardiovascular complications in patients with SCA are increasingly more evident, with the notable development of progressive proliferative systemic vasculopathy including PH.[8] Although other studies reported a much lower prevalence of 3.6 to 25% than our study, this low value may be due to the lower sample size of their research compared to the present study, and most likely the resolution power of a machine used may also be a contributory factor to these variations.

The findings of more blood transfusion among SCA patients with PH and the association of the development of PH with blood transfusion per life in this study were earlier reported. [13,14] This is likely due to the ongoing hemolytic process releasing the contents of red cells into circulation leading to low hematocrit and subsequent need for transfusion as well as the development of chronic organ injury. [4] This study also shows a significant association between the number of transfusions per lifetime and the development of PH. Hagar *et al*[15] reported a similar finding that chronic transfusion was found to be independently associated with

PH. Potoka *et al*[8], reported that a major risk factor for developing chronic organ injury including PH is SCA. Machado also reported that patients with PH have a higher number of RBC transfusions. [16]

This provides support to the hypothesis that PH arises secondary to chronic hemolytic anemia and end-organ dysfunction (renal and liver disease) rather than secondary to episodes of acute chest syndrome and related pulmonary fibrosis and this can be further buttressed by less hospitalization among SCA with PH reported in this study as VOC was shown to be the commonest cause of hospital admission. [17–19] The finding of a high prevalence of PH among patients with low vaso-occlusive crisis was similarly reported by other studies. [8,15]

The main hematological findings in this study are in keeping with previous reports of steady-state hematological parameters of patients with SCA in Nigeria. [20] These results largely depict moderate anemia, leucocytosis, reticulocytosis, and platelet count on the upper limit of normal. This study shows that patients with PH had a significantly lower hematocrit compared to those without PH. This is similar to previous studies. [11,16,20] This association may be due to the effect of cell-free hemoglobin resulting from chronic hemolysis with a resultant low hematocrit. [14]

The study shows no significant association between WBC count among the participants with PH and those without which is similar to the work of Gladwin *et al*.[14] However, a significant relation was found between PH and high platelet count in this study, which is similarly reported by Pashankar *et al*.[21] Gladwin *et al*, and Machado *et al* disputed this association. [14,16] Thrombocytosis is a feature of SCA in the steady state. It represents bone marrow response to hemolysis, autosplenectomy, and inflammatory response as well as SCA being a chronic inflammatory state. Elevated platelet count contributes to hypercoagulability seen in SCA. This phenomenon may be explained by the circulating young, metabolically active giant platelet seen on blood film. [22]

Data from this study reveals a significant association between markers of red cell destruction including reticulocytosis, higher serum LDH, and higher total and indirect bilirubin with high TRV. Hemolysis-induced endothelial dysfunction has been reported as an important proposed mechanism of PH. This association may be due to the effect of

cell-free hemoglobin resulting from chronic intravascular hemolysis leading to impaired nitric oxide bioavailability. [16,21] Erythrocyte Arginase is also released during the hemolysis which acts on L-Arginine changing it to ornithine, leading to depletion of plasma arginine, the obligate substrate of NO synthase. These findings corroborate well with the work of Gladwin *et al*,[14] where they found variables independently associated with PH in adults with SCD include, high steady-state LDH, and high serum direct bilirubin. Aliyu *et al*,[9] also found an association between high tricuspid regurgitant jet velocity and markers of red cell destruction (low hemoglobin and high serum LDH). An association between the development of PH and the intensity of hemolytic anemia has been observed in prospective screening studies of patients with SCD. [9] Although this hypothesis has been challenged in editorials, strong clinical and experimental evidence suggests that hemolysis is related mechanistically to PH. Hemolysis releases plasma-free hemoglobin that inactivates the intrinsic vasodilator nitric oxide and arginase-1, depleting L-arginine, the substrate for the synthesis of nitric oxide. [23] The result of these combined pathologic processes is a state of decreased nitric oxide bioavailability and resistance to NO-dependent vasodilation.

Conclusion

PH is common in adults with SCA in our environment and is significantly associated with less frequent painful crises, more transfusions, and markers of hemolysis. Routine screening and early intervention are needed to prevent morbidity and improve quality of life and life expectancy.

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