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One Year Retrospective Review of Bone Pain Crisis among Adult Sickle Cell Disease Patients in Benin City, Nigeria

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Abstract:
Introduction: *Sickle cell disease (SCD) poses a major public health challenge in sub-Saharan Africa particularly Nigeria and other parts of the world. Bone pain crisis (BPC) is a major clinical manifestation of SCD among others. BPC rate has not been evaluated in SCD subjects in our environment.*
Objective*: This study aimed at assessing the rate of BPC among Nigerian SCD subjects in Benin City, to identify possible associated factors and control practices in the study group.*
Methodology: *Data were collected from a total of 73 SCD adult patients seen at Haematology Outpatient Department of the University of Benin teaching Hospital using a structured interviewer administered questionnaire. Descriptive and inferential statistics were analyzed using Statistical Package for Social Sciences (SPSS) version 16. P value was set at 0.05.*
Results: *BPC was reported in 98.6% of the subjects and it accounted for 71.4% of hospital admissions. An average BPC rate of 2.58 ± 0.43 per annum was found. BPC rate was higher in between 15 – 29 years of age, males, haemoglobin SS phenotype and higher leucocyte count, though it was not statistically significant. Use of hydroxyurea did not alter BPC rates significantly.*
Conclusion: *There is a significant pain burden associated with increased hospitalization among SCD subjects in Benin City, Nigeria. The clinical utility of Hydroxyurea in Nigerian subjects should be evaluated and standardized for optimal benefit.*
Keywords: *Sickle cell disease, bone pain crisis, Sickle cell anaemia, Vaso-occlusive Crisis, Benin City, Nigeria.*

I. Introduction

Sickle cell disease (SCD) is a chronic haemolytic disease characterized by intra-corpuscular precipitation of sickle haemoglobin molecules into tactoids, deforming the red cell into a sickle or crescent morphology, with resultant chronic haemolysis, vaso-occlusive events and progressive organ damages [1, 2].

SCD predominates in sub-Saharan Africa, south-east Asia, Middle East areas, the Mediterranean Basin and is also found in other parts of the world due to migration and inter-racial marriages [3, 4]. SCD affects 2 – 3% of Nigerians of over 160 million [5]. A recent study in Benin City reveals a prevalence rate of 2.39% [6].

The genetic aberration underlying SCD is a single base change (point mutation) from adenine to thymidine, which encodes a neutral, less polar, hydrophobic molecule, valine in replacement for glutamate at the 6 position of the beta-globin chain. In SCD, the sickle mutation is inherited as homozygous or as a compound heterozygous state [7, 8].

The clinical manifestationsof SCD is pleiotropic, affecting virtually every organ system in the human body [1]. Typically, SCD runs a chronic (steady state) course, which may be interrupted by acute exacerbations, termed 'crisis'. The commonest SCD crisis is bone pain crisis (BPC) [1, 9]. BPC is the most consistent and characteristic manifestation of SCD. As such, pain management is a mainstay in the care of affected persons. Pain management strategies include use of analgesics, rehydration, treatment of underlying precipitating factors, use of disease modifying interventions such as hydroxyurea and in severe and recurrent cases may become an indication for red cell exchange and haemopoietic stem cell transplant (HSCT). HSCT is curative though, its use requires careful patient selection, availability of a matched donor and it is expensive beyond the reach of majority of affected persons in our environment. Hydroxyurea, an FDA (USA) approved drug in 1998 for SCD, has shown immense therapeutic benefits in treatment of SCD, including pain control [10 – 13]. Chronic blood transfusion or red cell exchange is also indicated in pain management; though its use may be complicated by red cell alloimmunisation and iron overload [14].

BPC greatly impairs the quality of life among affected persons and is a predictor of severe disease (disease outcome) [9, 15]. The exact burden of SCD BPC among Nigerian patients is yet to be clearly defined. The objective of this study therefore is to estimate BPC rates among SCD patients in Benin City, determine its associated factors (if any), evaluate the current measures at controlling it, as well as, proffer strategies at reducing its frequencies.

II. Methodology

This is a cross-sectional study conducted at the University of Benin Teaching Hospital (UBTH). Consenting SCD patients seen at the Adult Haematology Out-patient department over a period of six months were recruited for this study. Subjects were recruited consecutively during routine clinic visit (health maintenance visits) after detailed explanation of the purpose of the study. All patients were prediagnosed on the basis of their clinical features and haemoglobin electrophoresis patterns and are receiving routine care in the unit. Data were collected using a structured interviewer-administered questionnaire (and case notes when necessary). Information collected included demographics, bone pain characteristics in the last one year including precipitating factors and interventions, haematological parameters in their steady state and pattern of SCD complications.

Body mass index (BMI) was calculated as a ratio of weight (in kg) divided by square of height (in meters). Underweight is defined by BMI less than 18.5, normal/healthy weight between 18.5 and 24.9, overweight between 25 to 29.9 and obesity over 30.

All data were inputted and analyzed using Statistical Package for Social Sciences (SPSS) version 16. Descriptive statistics was performed using the appropriate tools. Difference in mean rates of BPC between age groups, sex, hydroxyurea use, water intake among others were tested using Students T test and analysis of variance (ANOVA) as appropriate. P value was set at 0.05. Results were presented in tables.

III. Results

A total of 73 SCD respondents participated in this study including 68 (93.2%) Hb SS and 5 (6.8%) Hb SC subjects. The median age of participants was 29 years; the modal age group of respondents was 20 – 29 years accounting for 42.5%, followed closely by age group 30 – 39 years (31.5%) as shown in table 1. Male respondents were 34 (46.6%) while females account for 39 (53.4%) giving male to female ratio of 1:1.15. The median age at diagnosis of SCD was 7 years. The median BMI of participants was 20.82 Kg/m^2. Fourteen (19.2%) were underweight while 5 (6.8%) were obese.

Forty five (61.6%) comply with the regular use of their routine medication; 43 (58.9%) take less than 3 litres of water or water-based fluid recommended for adequate hydration daily.

Twenty four (32.9%) of the subjects reported less than one episode of BPC per annum, 27 (37%) reported 1 – 2, while 22 (30.1%) experience 3 or more BPC per year (Table 2). The average BPC rate among the participants is 2.58 ± 0.43 per annum. Seventeen of the respondents (23.3%) experience chronic pain. In 34 (46.6%) of the subjects, the pain was described as moderate in severity. The most frequently reported BPC trigger is physical stress in 30 (41.1%), followed by spontaneous occurrence in 23 (31.5%), fever/malaria in 18 (24.7%) and cold in 18 (24.7%). Self injection of opiods was reported in 15 (20.5%) of the subjects. Analgesic use by the study subjects were as shown in table 1. Forty (54.7%) of the subjects had been hospitalized in the preceeding one year while BPC was responsible for the hospitalization in 29 (71.4%) of cases.

Thirty three (45.2%) of the participants are on hydroxyurea therapy but 17 (23.3%) use it regularly. The average duration of use was 21.7 ± 23.58 months. Twenty (27.4%) of them attested to have benefitted its use. The mean haemoglobin concentration level among the subjects is 8.43g/dl (see table 3). Mean total leucocyte count and platelet counts were 9.81 x 10^3 and 289,000/ul respectively. Most common reported SCD clinical manifestation was bone pain crisis (98.6%), followed by chronic leg ulcers (31.5%), Peptic ulcer disease/Dyspepsia (31.5%) and AVN (23.3%) as shown in Table 4. Past history of priapism was positive in 11 (32.4%) of males.

No statistically significant association was found between BPC rates and variables including age groups, sex, haemoglobin phenotype, water intake, compliance with routine drugs, body mass index (Table 5). However, the rate of BPC was observed to be higher in male subjects, younger age groups and those with Hb SS phenotype. Similarly, subjects with one or more BPC per year were observed to have a higher leucocyte, granulocyte and haematocrit levels (Table 6).

IV. Tables And Figures

Table 1: Patient Characteristics

Patient Characteristics	Frequency (n=73)	Percentage (%)
Age (Years)		
15 – 19	7	9.6
20 – 29	31	42.5
30 – 39	23	31.5
40 – 49	9	12.3
50 – 59	2	2.7
≥ 60	1	1.4
Mean age ± SEM = 30.14 ± 1.11, Median age = 29		
Sex		
Males	34	46.6
Females	39	53.4
Age at Diagnosis (Years)		
Infancy	10	13.7
1 – 14	55	75.3
>14	8	11
BMI (kg/m2)		
Underweight	14	19.2
Normal	54	74.0
Overweight	5	6.8
Hb Phenotype		
SS	68	93.2
SC	5	6.8
Water Intake		
<3L	43	58.9
≥3L	30	41.4
Routine Drugs		
Regular	45	61.6
Non Regular	28	38.4
Home-Based Analgesia (Multiple Responses)		
None	15	20.5
Mild Non-Opioid	27	37
NSAIDS	22	30.1
Weak Opioids	18	24.7
Strong Opioids	2	2.7

Table 2: Bone Pain Characteristics

CHARACTERISTICS	FREQUENCY(n=73)	PERCENTAGE (%)
Frequency of BPC per annum		
< 1	24	32.9
1-2	27	37
3 or more	22	30.1
Mean BPC rate ± SEM: 2.58 ± 0.43		
Chronic Pain Syndrome		
Yes	17	23.3
No	56	76.7
BPC Severity		
Mild	20	27.4
Moderate	34	46.6
Severe	19	26
BPC Trigger (Multiple Responses)		
Spontaneous	23	31.51
Physical stress	30	41.09
Emotional stress	7	9.59
Fever/malaria	18	24.66
Hot climate	2	2.74
Menstruation	3	4.11
Cold	18	24.66
Inactivity	2	2.74
Pregnancy	2	2.74
Self Opioid Injection		
Yes	15	20.5
No	58	79.5
Hydroxyurea Use and Compliance		
Regular Use	17	23.3
Not regular Use	16	21.9
Non-use	40	54.8
Hydroxyurea Benefit		

Yes	20	27.4
No	13	17.8
Non-Use	40	54.8
Number of hospitalization in the preceeding one year		
None	33	45.2
1 – 2	35	47.9
3 or more	5	6.8
BPC hospitalizations in the preceeding one year		
None	44	60.3
1 – 2	26	35.6
3 or more	3	4.1

Table 3: Haematological Parameters

Haematological Parameters	MEAN ± SEM	Median	Range
Haemoglobin(g/dl)	8.43±0.25	8.65	3.9 – 12
Haematocrit	26.08±0.79	26.85	11.8 – 38
WBC count (x 10^3)	9.81±5.24	8.50	3.2 - 18.8
Granulocyte (x 10^3)	5.68±3.99	4.65	1.3 – 12.9
Lymphocyte (x 10^3)	2.98±1.69	2.80	0.6 – 6.2
Platelet (x 10^3)	289±143	257	62 – 554

Table 4: Reported SCD Clinical Features And Complications

REPORTED SCD CLINCIAL FEATURES AND COMPLICATIONS	Frequency (n =73)	%
Bone Pain Crisis	72	98.6
Chronic Leg Ulcers	23	31.5
PUD/Dyspepsia	23	31.5
Avascular Necrosis	17	23.3
Priapism	11*	32.4*
Gall Stone	6	8.2
Osteomyelitis/Septic Arthritis	6	8.2
Sickle Nephropathy	2	2.7
Ocular Disease	2	2.7
Cardiac Disease/Pulmonary Hypertension	2	2.7
Acute Chest Syndrome	1	1.4
Stroke	0	0

*11 out of 34 males: 32.4% of males

Table 5: Comparison of BPC Rates Among Different Subgroups

VARIABLES	Frequency n=73	BPC rates Mean ± SEM	P values
AGE			0.652
15 – 19	7	3.43±1.79	
20 – 29	31	3.13±0.78	
30 – 39	23	1.70±0.46	
40 – 49	9	2.22±1.04	
≥50	3	2.67±2.67	
SEX			0.547
Males	34	2.85±0.69	
Females	39	2.33±0.53	
BMI			0.456
Underweight	14	2.86±1.04	
Normal	54	2.69±0.51	
Overweight	5	0.60±0.40	
Hb Phenotype			0.262
SS	68	2.71±0.45	
SC	5	0.80±0.49	
Hydroxyurea Use			0.094
Yes	33	3.36±0.76	
No	40	1.92±0.45	
Average duration of use (months) = 21.73 ± 4.11			
Water Intake			0.374
<3 L	43	2.26±0.45	
≥3L	30	3.03±0.82	
Routine Drugs			0.799
Regular	45	2.49±0.56	
Irregular	28	2.71±0.68	

Table 6: Association of BPC Rates With Haematologic Parameters

HAEMATOLOGIC PARAMETERS	BPC RATES PER YEAR	MEAN±SD	SEM	P-value
TOTAL LEUCOCYTE ($x10^3$)				0.139
	None	8.77±3.14	0.70	
	One or more	10.39±4.22	0.70	
GRANULOCYTE ($x10^3$)				0.138
	None	4.88±2.25	0.50	
	One or more	6.12±3.27	0.54	
LYMPHOCYTES ($x10^3$)				0.230
	None	2.71±1.21	0.27	
	One or more	3.14±1.28	0.21	
PLATELETS ($x10^3$)				0.399
	None	306.20±113.08	25.29	
	One or more	280.72±104.39	17.39	
HAEMATOCRIT				0.734
	None	26.45±5.54	1.24	
	One or more	25.88±6.24	1.04	
HAEMOGLOBIN(g/dl)				0.814
	None	8.52±1.90	0.43	
	One or more	8.39±1.92	0.32	

N = 56 (76.71% of total), None = 20, One or more = 36

V. Discussion

The modal age group among the study participants is 20 – 29 years, with a mean age of 30.14 ± 1.11years. In an earlier 10 year retrospective report among 350 Adult SCD subjects in Ilorin, Nigeria, Chijioke et al reported of 23 ± 6.6 years [16]. A gradual decline in the number of subjects was observed with increasing age. Only one subject in this cohort lived to the seventh decade. This could imply that there is a significant mortality associated with SCD and that survival reduces significantly after fourth decade. .

Females (53.4%) were slightly more compared to males. Some studies have suggested female survival advantage in Nigerian SCD [17]. Mean age at diagnosis of SCD in the cohort was observed to be about 8 years. This is disturbing and it connotes a lack or absence of routine neonatal, preschool and population screening systems. Routine antenatal, newborn and other forms of population screening should be established to facilitate early diagnosis and management. Though most sufferers are diagnosed during childhood, some cases of very mild SCD may be undiagnosed till adulthood when chronic complications set in.

Ninety-three percent of the subjects had SS disease phenotype. This is not unexpected as haemoglobin C has been shown to be less frequent in Benin City [6]. Though there is a relatively higher prevalence of C haemoglobin in the western part of the country, the prevalence of C variant of haemoglobin is low in the generality of the Nigerian populace. [6, 18, 19].

Adequate and regular hydration in excess of 3 liters per day of water/water based fluids except otherwise contra-indicated, is a widely accepted, preventive care measure among SCD authorities worldwide [20 – 22]. However, it was observed that less than half of our study participants regularly ingests at least 3 liters of water per day. Similarly, about forty percent of the subjects were not regular on routine medications which include folic acid, which are routinely prescribed as nutritional supplements to provide micronutrient for haemopoiesis; paludrine a prophylaxis for malaria and 75mg aspirin to facilitate vasodilation and anti-platelet activity [23].

About 67% experienced at least one episode of pain in the preceeding year. This finding is similar to a report of about 60% in the US by Platt et al [24]. While about a third experienced 3 or more BPC episodes. The mean BPC rate was observed to be 2.58 per annum. There is possibility for underreporting of BPC occurrences in the studied population due to the retrospective, memory dependent nature of the work. Most of their pain episodes were described (subjectively) as moderate intensity. About a quarter (23.3%) of the subjects experienced chronic pain, most were due to chronic morbidities such as osteo-necrosis of femoral/humeral heads and chronic leg ulcers. It was also observed that there was a high frequency (54.8%) of hospital admissions among the SCD subjects. Most (71.43%) of the hospitalizations/admissions were related to bone pain crisis. Comparatively, BPC accounts for 82% of acute hospital admissions in Britain and 34 - 65% in Nigeria from previous studies [25 – 27].

Sometimes, bone pain crisis are linked to certain known precipitants. The subjects reported physical stress, fever/malaria and cold as their most frequent precipitants. About 30% of BPC were spontaneous occurrences. Some of the subjects reported BPC episodes to be more frequent during cyesis. Though uncommon, 2 (2.74%) of the subjects reported physical inactivity as a trigger for BPC. Inactivity/sedentary lifestyle have not been reported to be a known precipitant. In a bid to getting pain relief, a fifth (20.5%) admits to self-opioid (pentazocine) use. Less than half (45.2%) have used hydroxyurea for a widely varying period of 1

to 96 months. Prophylactic hydroxyurea therapy has been shown to be associated with decreased incidence in the frequency and severity of BPC in SCD [28]. This could not be demonstrated in our study possibly due to the small sample size, non-compliance with therapy, suboptimal dosing and the retrospective nature of the study. However, 20 (60.60%) of 33 subject reported (subjectively) to have benefited from hydroxyurea therapy. There is a need for physicians to standardise hydroxyurea therapy in the management of SCD in Nigeria. Hydroxyurea use by many physicians in our environment is mainly restricted to patient with established severe disease status and not for the generality of SCD patients. This therapeutic approach may contribute to the lack of statistically significant benefit observed in the index study.

Lifetime prevalence of BPC was 98.6%, followed by chronic leg ulcers (31.5%), PUD/dyspepsia (31.5%) and avascular necrosis (23.3%). Priapism occurred in 32.4% of the male subjects. A similarly high prevalence rate has been observed among Nigerian subjects in other local studies [29].

Although the mean BPC rates were observed to be higher in the younger age groups and subjects with SS phenotype, there was no statistically significant relationship. This could be due to the relatively small sample size of the study. A larger cohort, prospective study would give a better reflection of the true picture. However, no significant association was found between BPC rates and other variables such as sex, BMI, compliance with routine drugs, water intake. Some studies have shown a higher steady state haemoglobin concentration level, low fetal haemoglobin level, leucocyte and platelet counts to positively correlate with higher BPC rates and a more severe phenotype [24, 30 - 33]. Similarly, some studies have found significant association between higher leucocyte/platelet count and SCD avascular necrosis [34, 35]. However, no such relationship was observed in this study.

VI. Conclusion

There is a significant burden of pain among Nigerian SCD patients. Conscientious approach as well as judicious use of both pharmacological and non pharmacological therapies is crucial to reducing pain burden and improving their quality of life. Clinical researches should be directed at evaluating the clinical utility of prophylactic hydroxyurea therapy among Nigerian sickle cell patients. This will help to provide standard local guideline on hydroxyurea therapy in SCD. Efforts should be directed at patient education during maintenance visits regarding avoidance of BPC triggers, adequate oral daily hydration, routine drugs and regular visits. In addition, greater efforts should be directed at prevention and control of sickle cell disease at all levels by relevant stakeholders.

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