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Pattern and Risk Factors for Musculoskeletal Complications of Sickle Cell Anaemia in South-East Nigeria: A Retrospective Study

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Authors' contributions

This work was carried out in collaboration between all authors. Author AND collected the data. Author AJM supervised the data collection. Author ACU did the data analysis. Authors KAM, AJM and ACU did the literature review. All the authors participated in writing the manuscript, read and approved the final manuscript.

Research Article

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ABSTRACT

Aims: To determine the pattern and associated risk factors for musculoskeletal complications among sickle cell anaemia patients in South-east Nigeria.
Methodology: A retrospective review of prospectively collected data. The study was conducted at the Sickle Cell Clinic of the University of Nigeria Teaching Hospital, Ituku/Ozalla, Enugu, Nigeria between December 31st 2004 and January 1st 2013. We included 163 eligible sickle cell anaemia patients (105 males and 58 females; age range 6-53 years). Clinical, haematological (haemoglobin, white cell count, platelet) and radiological evaluation of these patients were done. Data analysis was by SPSS version 19. Chi-square and Fisher's exact tests were used to test for significant association of the categorical variables while Mann Whitney U test was used to compare the mean ranks of the continuous variables and the dependent outcome.

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Results: The three most common musculoskeletal complications seen among our patients population were leg ulcer (29.4%), avascular necrosis (17.8%) and osteomyelitis (12.9%). Complications were significantly more in older patients (*P*=0.04) and those with higher platelet counts (*P*=0.04). Haemoglobin level and platelet count were significantly higher in patients with avascular necrosis (*P*=0.01) and osteomyelitis respectively (P=0.01).
Conclusion: Musculoskeletal complications of SCA are not uncommon among our patients. Age and higher steady state haemoglobin were risk factors for developing complications. Further controlled studies are required to evaluate the steady state hematological parameters and risk of complications among SCA patients.

Keywords: Sickle cell anemia; pattern; risk factors; south-east Nigeria.

1. INTRODUCTION

Sickle cell disease (SCD) is due to a point mutation in the β globin gene, resulting in the creation of abnormal hemoglobin molecules with a hydrophobic motif that is exposed in its deoxygenated state [1]. In sickle cell anaemia (SCA), an individual inherits the homozygous form of sickle cell gene (S). The prevalence of healthy carriers of the sickle cell gene (sickle cell trait) ranges between 1% and 40% across Africa [2]. Nigeria has an estimated carrier prevalence of 6-24% [3]. An estimated 150,000 children are born annually in Nigeria with SCD [4]. The country also contributes more than a fair share of about 1.2 million people to the SCD burden [5].

Most manifestations of SCD have genetic and environmental components [6]. It has been postulated that the processes of abnormal cellular adhesion, inflammation, coagulation, and vasoconstriction in SCD all have positive feedback loops that perpetuate the vaso-occlusive condition and promote cumulative damage to organs and tissues [7]. Musculoskeletal (MSS) complications of SCD include leg ulcer, avascular necrosis, chronic arthritis, osteoporosis, osteomyelitis and impaired growth [8,9]. Bone and joint complications are common in SCD in about 31% of patients [10]. Leg ulcers, particularly over bony prominences, are common and highly significant association with venous incompetence has been documented [11-13]. While the exact etiology of venous incompetence remains unknown, sluggish circulation, turbidity and impaired linear flow at venous valves, hypoxia-induced sickling, the rheological effects of high white cell counts, and activation of components of the coagulation system are thought to play some roles [13]. Bone infarction on the other hand, has been shown to be significant risk factors later in life for avascular necrosis (AVN) while a prior hospitalized vaso-occlusive sickle crisis in adults is significantly associated with the increased rate of AVN, leg ulcers, and early death [14,15]. Recent evidence suggests that patients with SCD and leg ulcers may also be at risk to develop other serious disease complications such as renal disease [16]. This highlights the need for renewed clinical research interests aimed at uncovering simple but preventive strategies against complications of SCD. The objective of this study therefore, is to identify the pattern and associated risk factors for musculoskeletal complications of SCA in Enugu, South-east Nigeria.

2. MATERIALS AND METHODS

2.1 Study Design

This was a retrospective study in which the prospectively collected data of patients who were seen at the Sickle Cell Clinic between December 31st 2004 and January 1st 2013 were reviewed.

2.2 Setting

This study was conducted at the Sickle Cell Clinic of the University of Nigeria Teaching Hospital, Ituku/Ozalla, Enugu, Nigeria.

2.3 Participants

Only patients with confirmed SCA using hemoglobin electrophoresis were included in the study. Data of one hundred and sixty-three patients who met the inclusion criteria were analyzed.

2.4 Materials

Musculoskeletal complications (leg ulcer, avascular necrosis, ankylosing spondylitis, osteoarthritis, and osteomyelitis) seen among the patients were documented using a proforma.

2.5 Diagnostic Methods

Diagnoses of leg ulcers were based on clinical evaluation while AVN, osteoarthritis and ankylosing spondylitis were diagnosed based on clinical suspicions and confirmed using radiographs. Diagnosis of osteomyelitis was by clinical (fever, bone pain and tenderness) and confirmed by characteristics radiological evidence of osteomyelitis in the affected bone. In our program, 5 patients were on chronic transfusion programs following cerebrovascular accident.

2.6 Data Analysis

The data were analyzed using SPSS version 19 (Chicago, IL). Chi square and Fisher's exact (where indicated) tests were used to test for statistically significant association of categorical variables with the outcome variables. The outcome variables were presence of leg ulcer, osteomyelitis or avascular necrosis. The Shapiro-Wilk test was used to verify data normality. The statistical significance of differences in risk factors between those with *vs* without complications was assessed by the Mann-Whitney's U test. All independent variables with *P*-value <0.15 as well as age and gender were fitted into a binary logistic model. A *P*-value < 0.05 was regarded as significant and all *P*-values reported are 2-sided.

2.7 Ethical Approval

Ethical approval was obtained from the Health Research and Ethics Committee of the University of Nigeria Teaching Hospital, Ituku/Ozalla, Enugu.

3. RESULTS

One hundred and sixty three patients (105 males and 58 females) were enrolled into the study. The median age at study entry was 23 years (range of 6 to 53) years. The age groups 10 to 19 years and 20 to 29 years respectively accounted for 26.5% and 49.1% of the study population.

Table 1. Musculo-skeletal system related complications of SCA

complications	No	(%)
Leg ulcers	48	29.4
Avascular necrosis	29	17.8
Osteomyelitis	21	12.9
Multiple complications	19	11.7
Septic arthritis	5	3.1
osteoarthritis	2	1.8
Ankylosing spondylitis	1	0.6

3.1 Musculoskeletal System Complications

Ninety-five (58.3%) of the 163 of the patients had at least a SCA related MSS complication. The three most common MSS complications were leg ulcers (29.4%), AVN (17.8%) and osteomyelitis (12.9%) as shown in Table 1. Leg ulcer was bilateral in 10 patients (20.8%). Seven of the 48 patients (14.6%) that had leg ulcers also had AVN. Thirty-five (34%) of 103 patients older than 20 years compared to 23.1% of those aged ≤ 20 years (12/52) had leg ulcers. This difference was not statistically significant (P=0.12). A slightly higher proportion of patients older than 20 years had AVN (18.4%) compared to 15.4% among those older than 20 years (P=0.82). Osteomyelitis was evenly distributed in 13.7% of each of the ≤ 20 years and > 20 years age groups (P=1). Seven of 51 patients (13.7%) ≤ 20 years had multiple complications compared to 11.7% (12/103) among those > 20 years and this difference was not statistically significant (P=0.8).

3.2 Risk Factors for Complications

The various risk factors analysed are shown in Table 2. The mean age of the patients that has MSS complication was 23.8 ± 1.4 compared to 27 ± 1.4 among the group without MSS complications. Patients without MSS complications also had a significant higher median age (27 years) compared to 23 years among those with complications (*P*=0.04, Mann Whitney U test).There was no statistically significant difference in the haemoglobin values (*P*=0.59, Mann Whitney U test), and white cell counts (*P*=0.34, Mann Whitney U test) of the group of patients that had MSS compared to those that did not develop any complications. However, the median (360 $X10^9$ vs 314 $X10^9$) platelet levels was significantly higher in the complication group than in the non-complication group (*P*=0.04). After multivariate adjustments, older age showed a trend that failed to attain statistical significance (*P*=0.08).

3.3 Leg Ulcer

The median frequency of vaso-occlusive crises was 3 in both groups of patients with and without leg ulcer (P=0.43, Mann Whitney U test). Although not statistically significant, 35 of 105 (33.3%) males compared to 13 of 58 females (22.4%) had leg ulcer (*P*=0.16).

3.4 Avascular Necrosis

The median haemoglobin level was higher in the group of patients that developed AVN (8.8 g/dl) compared to 7.7g/dl among those without AVN. This difference was statistically significant (*P*=0.01, Mann Whitney U test). Similarly, the median platelet count was higher in AVN patients (422 X 10^9/L) compared to 330 X 10^9/L in the non-AVN patients. This difference showed a trend that did not attain statistical significance (P=0.05, Mann Whitney U test). A slightly higher proportion of males (18.1%) than females (17.2%) had AVN (*P*=1). After a binary logistic regression only higher haemoglobin level remained a significant predictor of AVN (P=0.013).

3.5 Osteomyelitis

Thirteen of the 103 males (12.6%) had osteomyelitis compared to 8 of 58 (13.8%) of females (*P*=0.81). The median platelet counts (340.1x10^9/L) was significantly higher in patients with osteomyelitis (*P*=0.01, Mann Whitney U test).

Table 2. Risk factors for complications

Risk factors	Median		*P*-value
	Present	Absent	
Leg ulcer			
Age (years)	26	24	0.57
Frequency of VOC	3	3	0.43
Haemoglobin (g/dl)	7.7	7.8	0.34
WBC (10^9/L)	12	10.2	0.29
Platelet (10^9/L)	302	252	0.46
AVN			
Age (years)	24.7	25	0.59
Frequency of VOC	3	3	0.32
Haemoglobin (g/dl)	8.8	7.7	0.01*
WBC (10^9/L)	9.8	10.9	0.19
Platelet (10^9/L)	422	330	0.05
Osteomyelitis			
Age (years)	24.5	25	0.15
Frequency of VOC	2.5	3	0.91
Haemoglobin (g/dl)	8.3	7.8	0.87
WBC (10^9/L)	11.8	11.5	0.7
Platelet (10^9/L)	341.5	340.1	0.01*

VOC=Vaso-Occlusive Crises; WBC=White Blood Cell; AVN=Avascular Necrosis

4. DISCUSSION

We report a 58.3% prevalence of MSS complication among our population of SCA patients. The most common complications were leg ulcer (29.4%), AVN (17.8%) and osteomyelitis (12.9%). A previous study in Nigeria among 25 SCA patients that presented at a referral orthopaedic hospital also reported leg ulcer as the most common musculoskeletal complication of SCA and AVN, the next most common in keeping with current findings[17]. This however differs from the findings in Cameroun where AVN was the most common complication.[18] Among 457 SCD patients followed up over 10 years in France, the

prevalence of leg ulcers was 5.5% (which was lower than our reported prevalence); with 20% associated osteonecrosis of the hip [19] Seven out of the 48 patients (20%) that had leg ulcers in our study also had AVN which was slightly lower than the French study. In a US multi-center study, the prevalence of leg ulcer among 2, 075 SCA patients were 2.5% [20]. The study in France and USA documented lower rates of leg ulcer than the 29.4% in this current study. This may suggest that leg ulcers among SCA patients in developed countries are less common compared to their counterparts in developing countries. This can be explained by the higher risk factors for leg ulcer such as trauma, infection and anaemia in developing countries [16,21].

Our 17.8% prevalence rate for AVN was higher than 10.2% previously reported by Milner et al. [22] among 1785 SCA patients in US. It however compares to 15.9% prevalence rate reported by Akinyoola and colleagues [23] in a previous Nigerian study. Among 57 SCA patients with bone and joint involvement in Saudi Arabia, Bennett and Namnyak [24] reported that 29 (50.9%) of the patients had radiological evidence of AVN. Bahebeck et al. [18] in Cameroon examined the relative rates of musculoskeletal complications among 84 SCA patients with suspicion or evidence of any musculoskeletal disorder except acute episodes of pain; and reported 41.6% and 22.6% prevalence rates for aseptic osteonecrosis and malleolar ulcers respectively. Osteoarthritis was infrequent in their report just like in our current study. The higher prevalence of AVN in the Saudi Arabian and Cameroonian studies can be explained by selection bias of only patients with suspected or proven bone and joint involvement unlike our study that included all our SCA patients. Among 27 adult SCD patients in the UK that were examined for AVN using MRI and radiographs; the reported prevalence was 41% which contrasts with our 17.8% [25]. This highlights the greater sensitivity of higher resolution imaging techniques over conventional radiographs in early detection of AVN.

4.1 Risk Factors

Although not statistically significant, we documented that higher proportion of our male patients developed leg ulcers and AVN. Increased risk for musculoskeletal complications among male SCA patients is well documented in the literature [16,17,21,26-28]. Halabi-Tawil and colleagues [19] however, reported equal sex distribution of leg ulcer but their study was limited by a small sample size of 20. We theorize that males are more likely than females to engage in activities that predispose them to trauma, the latter being a known aetiology of sickle cell leg ulcers.

Overall, younger age significantly predicted MSS complication on univariete analysis and this still showed a trend after multivariate adjustments. Our patient population < 20 years significantly had more MSS complications than those ≥ 20 years. Specifically, the median age was lower in patients with AVN and osteomyelitis than those without these complications. Conversely, the median age was higher in patients with leg ulcers than in those without. Younger children have been reported to be prone to osteomyelitis [29-32]. In a prospective cohort study that evaluated the musculoskeletal disease burden among SCA patients, Balogun et al. [30], noted that osteomyelitis and septic arthritis were most commonly observed in children less than 10 years. A previous Nigerian study on acute osteomyelitis among SCD patients aged 9 months to 50 years also reported that 61.5% were under the age of 15 years [32]. This reason for the predilection among the younger patients is possibly due to a combination of expanded marrow together with high oxygen demand and sluggish circulation resulting in infarction that act as foci for infection [28]. It can be argued that the relatively higher prevalence of osteomyelitis among SCA patients in

developing nations could also be a reflection of it being a more common diagnosis in their general population. This highlights the need for further studies that compares prevalence of leg ulcers among SCA patients and controls without SCA.

The mean steady state haemoglobin was significantly higher in the AVN than the non-AVN patients in this study. This significance remained even after adjusting for possible confounding variables. The link between elevated haemoglobin levels and AVN is well documented [6] in the literature. The study by Akinyoola and colleagues [27] however differed by reporting no significant difference in the haematocrit values of SCD AVN group when compared with non AVN group although their study was limited by its small sample size of 25. Among 263 SCD patients, Taylor et al. [33] reported that patients with hyper-hemolysis had significantly less osteonecrosis (OR 0.32, 95% CI 0.19-0.54) [33]. This suggests that hyper hemolysis and therefore lower hemoglobin has a protective effect against developing osteonecrosis in SCA patients. Although not statistically significant, the median white cell counts were higher in patients with MSS, leg ulcers and osteomyelitis but lower among those with AVN. On univariate but not multivariate analysis, higher platelet count significantly predicted MSS and osteomyelitis, and showed a trend for AVN. This agrees with the findings by Akinyoola et al. [27] that there are no significant difference in the white cell and platelet counts of AVN and non AVN SCD patients.

Our results are limited by the retrospective design of the study; small sample size and lack of more specific tests such as radionuclide scan in making diagnosis of osteomyelitis which limits the generalizability of our findings. However, the inclusion of both paediatric and adult patients in the analysis may be considered hypothesis-generating strength of the study by allowing comparison of musculoskeletal complications of SCA among young and old patients in the same setting.

5. CONCLUSION

Musculoskeletal complications are not uncommon especially among our younger SCA patients. In line with previous studies, AVN was significantly associated with high steady state haemoglobin. Further controlled studies are required to evaluate the steady state haematological parameters and risk of complications among SCA patients.

CONSENT

Not applicable.

ETHICAL APPROVAL

Ethical approval was obtained from the University of Nigeria Health Research and Ethics Committee.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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