

Pattern and risk factors for musculoskeletal complications of sickle cell anaemia in South-east Nigeria: a retrospective study.

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ABSTRACT (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)

ABSTRACT:

Aims: To determine the pattern and associated risk factors for musculoskeletal complications among sickle cell anaemia patients in South-east Nigeria.

Study design: Retrospective review of prospectively collected data.

Place and Duration of Study: Sickle Cell Clinic of the University of Nigeria Teaching Hospital, Ituku/Ozalla, Enugu, Nigeria between December 31st 2004 and January 1st 2013.

Methodology: 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.

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%). The median age was significantly lower ($P=0.04$) and platelet count higher ($P=0.04$) in patients with complications than in those without complications. Haemoglobin level and platelet count were significantly higher in patients with avascular necrosis ($P=0.01$) and osteomyelitis respectively ($P=0.01$).

Conclusion: There is a high rate of musculoskeletal complications among our SCA patients. Higher steady state haemoglobin was still a risk factor for developing AVN after multivariate adjustments. Constant monitoring of the hemoglobin and evaluating for MSS complications among SCA patients is recommended.

Keywords: [sickle cell anemia, pattern, risk factors, south-east Nigeria]

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1. INTRODUCTION

Sickle cell disease (SCD) is due to a point mutation in the β^S globin gene, resulting in the creation of abnormal hemoglobin molecules with a hydrophobic motif that is exposed in its deoxygenated state¹. 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 10% and 40% across equatorial Africa and decreases to between 1% and 2% in northern Africa and less than 1% in Southern Africa². In West African countries such as Ghana and Nigeria, the frequency of the carrier state is 15% to 30% while in East African countries, it shows wide variations of up to 45% in some areas³. Nigeria has an estimated carrier prevalence of 24% and 20 per 1000 births are estimated to be affected by SCD resulting in 150,000 children with SCD born annually in Nigeria⁴. Nigeria accounts for one third of the approximately, 300,000 children born annually with SCD and contributes more than a fair share of about 1.2 million people to the SCD burden.⁵

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 tissues⁷. Musculoskeletal complications of SCD include leg ulcer, avascular necrosis, chronic arthritis, osteoporosis, osteomyelitis and impaired growth^{8,9}. These are associated with significant morbidity and mortality among population of SCD patients. Bone and joint complications are common in SCD in about 31% of patients.⁶ Leg ulcers, particularly over bony prominences, are also common as a result of venous stasis and tissue hypoxia^{10,11}. Bone infarction 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^{12,13}. Recent evidence suggests that patients with SCD and leg ulcers may also be at risk to develop other, much more serious disease complications like pulmonary hypertension, priapism and, possibly renal disease¹⁴. 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. MATERIAL AND METHODS

Study design: This was a retrospective study in which the medical charts of patients who were seen at the Sickle Cell Clinic between December 31st 2004 and January 1st 2013 were reviewed.

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

Participants: Only patients with confirmed SCA using hemoglobin electrophoresis were included in the study. One hundred and sixty-three patients who met the inclusion criteria were enrolled.

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

70 *Diagnostic methods:*

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

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

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

88

89 **3. RESULTS**

90 One hundred and sixty three patients (105 males and 58 females) were enrolled into study.
91 The mean and median ages at study entry were 24.2 and 23 years respectively, with a range
92 of 6 to 53 years. The age groups 10 to 19 years and 20 to 29 years respectively accounted
93 for 26.5% and 49.1% of the study population.

94 Table 1: Musculo-skeletal system related complications of SCA

complications	No	(%)
Musculoskeletal	95	58.3
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

95

96 *Musculo-skeletal system complications:*

97 Ninety-five (58.3%) of the 163 of the patients had at least a SCA related-musculoskeletal
 98 (MSS) complication. The three most common MSS complications were leg ulcers (29.4%),
 99 AVN (17.8%) and osteomyelitis (12.9%) as shown in Table 1. Leg ulcer was bilateral in 10
 100 patients (20.8%). Seven of the 48 patients (14.6%) that had leg ulcers also had AVN. Thirty-
 101 five (34%) of 103 patients older than 20 years compared to 23.1% of those aged ≤ 20 years
 102 (12/52) had leg ulcers. This difference was not statistically significant ($P=0.12$). A slightly
 103 higher proportion of patients older than 20 years had AVN (18.4%) compared to 15.4%
 104 among those older than 20 years ($P=0.82$). Osteomyelitis was evenly distributed in 13.7% of
 105 each of the ≤ 20 years and > 20 years age groups ($P=1$). Seven of 51 patients (13.7%) ≤ 20
 106 years had multiple complications compared to 11.7% (12/103) among those > 20 years and
 107 this difference was not statistically significant ($P=0.8$).

108

109 *Risk factors for complications:*

110 The various risk factors analysed are shown in Table 2. The mean age of the patients that
 111 had MSS complication was 23.8 ± 1.4 compared to 27 ± 1.4 among the group without MSS
 112 complications. Patients without MSS complications also had a significant higher median age
 113 (27 years) compared to 23 years among those with complications ($P=0.04$, Mann Whitney U
 114 test). There was no statistically significant difference in the haemoglobin values ($P=0.59$,
 115 Mann Whitney U test), and white cell count ($P=0.34$, Mann Whitney U test) of the group of
 116 patients that had MSS compared to those that did not develop any complications. However,
 117 both the mean ($384.1 \pm 28.5 \times 10^9$ vs $367.8 \pm 56.4 \times 10^9$) and median (360×10^9 vs 314×10^9)
 118 platelet levels were significantly higher in the complication group than in the non-
 119 complication group ($P=0.04$). After multivariate adjustments, age still showed a trend that
 120 failed to attain statistical significance ($P=0.08$).

121 *Leg ulcer:*

122 The median frequency of vaso-occlusive crises was 3 in both groups of patients with and
 123 without leg ulcer ($P=0.43$, Mann Whitney U test). Although not statistically significant, 35 of
 124 105 (33.3%) males compared to 13 of 58 females (22.4%) had leg ulcer ($P=0.16$).

125 *Avascular necrosis:*

126 The mean (8.5 ± 0.4 g/dl) and median (8.8 g/dl) haemoglobin levels were higher in the group
 127 of patients that developed AVN compared to 7.3 ± 0.3 g/dl and 7.7 g/dl respectively among
 128 those without AVN. This difference was statistically significant ($P=0.01$, Mann Whitney U
 129 test). Similarly, the mean ($459.1 \pm 51 \times 10^9$) and median (422×10^9) platelet count were
 130 higher in AVN patients compared to ($358.5 \pm 34.2 \times 10^9$) and 330×10^9 respectively in the
 131 non-AVN patients. This difference showed a trend that did not attain statistical significance
 132 ($P=0.5$, Mann Whitney U test). A slightly higher proportion of males (18.1%) than females
 133 (17.2%) had AVN ($P=1$). After a binary logistic regression only higher haemoglobin level
 134 remained a significant predictor of AVN ($P=0.013$).

135 *Osteomyelitis:*

136 Thirteen of the 103 males (12.6%) had osteomyelitis compared to 8 of 58 (13.8%) of females
 137 ($P=0.81$). The mean (394.7 ± 48.8 vs 374.1 ± 33.4) and median (340.1) platelet counts were
 138 significantly higher in patients with osteomyelitis ($P=0.1$, Mann Whitney U test).

139 Table 2: Risk factors for complications

Risk factors	Present		Absent		P-value
	Median	Mean (SEM)	Median	Mean (SEM)	
Musculoskeletal					
Age (years)	23	23.6 (1.4)	26	27 (1.4)	0.04*
Frequency of VOC	3	5.6 (1.5)	2	3.3 (0.6)	0.26
Haemoglobin (g/dl)	7.7	7.7 (0.3)	7.6	7.4 (0.4)	0.59
WBC (10 ⁹ /L)	11.2	11.6 (0.8)	10.7	11.4 (0.8)	0.34
Platelet (10 ⁹ /L)	360	384.1 (28.5)	314	367.8 (56.4)	0.04*
Leg ulcer					
Age (years)	26	27.5 (2.1)	24	24.3 (1.1)	0.57
Frequency of VOC	3	3.2 (0.7)	3	5 (1.1)	0.43
Haemoglobin (g/dl)	7.7	7 (0.5)	7.8	7.7 (0.3)	0.34
WBC (10 ⁹ /L)	12	12.9 (1.1)	10.2	11 (0.6)	0.29
Platelet (10 ⁹ /L)	302	325.2 (37.7)	252	394.6 (37.9)	0.46
AVN					
Age (years)	24.7	24.7 (1.8)	25	25.2 (1.2)	0.59
Frequency of VOC	3	6.8 (3.7)	3	4.1 (0.7)	0.32
Haemoglobin (g/dl)	8.8	8.5 (0.4)	7.7	7.3 (0.3)	0.01*
WBC (10 ⁹ /L)	9.8	10.9 (0.8)	10.9	11.6 (0.7)	0.19
Platelet (10 ⁹ /L)	422	459.1 (51.0)	330	358.5 (34.2)	0.05
Osteomyelitis					
Age (years)	24.5	24.7 (2.4)	25	25.2 (1.1)	0.15
Frequency of VOC	2.5	4.2 (1.7)	3	4.6 (1.0)	0.91
Haemoglobin (g/dl)	8.3	7.9 (0.6)	7.8	7.5 (0.3)	0.87
WBC (10 ⁹ /L)	11.8	13.1 (1.3)	11.5	13.6 (0.8)	0.7
Platelet (10 ⁹ /L)	341.5	394.7 (48.8)	340.1	374.1 (33.4)	0.01*

140 VOC=vaso-occlusive crises, WBC=white blood cell, AVN=avascular necrosis

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143 4. DISCUSSION

144 We report a 58.3% prevalence of MSS complication among our population of SCA patients.
 145 The most common complications were leg ulcer (29.4%), AVN (17.8%) and osteomyelitis
 146 (12.9%). A previous study in Nigeria among 25 SCA patients that presented at a referral
 147 orthopaedic hospital also reported leg ulcer as the most common musculoskeletal
 148 complication of SCA and AVN, the next most common in keeping with current findings¹⁵.
 149 This however differs from the findings in Cameroun where AVN was the most common
 150 complication¹⁶. Among 457 SCD patients followed up over 10 years in France, the
 151 prevalence of leg ulcers was 5.5% (which was lower than our reported prevalence); with
 152 20% associated osteonecrosis of the hip¹⁷. Seven out of the 48 patients (20%) that had leg
 153 ulcers in our study also had AVN which was slightly lower than the French study. In a US
 154 multi-center study, the prevalence of leg ulcer among 2, 075 SCA patients were 2.5%¹⁸. The
 155 study in France and USA documented lower rates of leg ulcer than the 29.4% in this current
 156 study. This may suggest that leg ulcers among SCA patients in developed countries are less
 157 common compared to their counterparts in developing countries. This can be explained by
 158 the higher risk factors for leg ulcer such as trauma, infection and anaemia^{14,19} in developing
 159 countries.

Our 17.8% prevalence rate for AVN was higher than 10.2% previously reported by Milner et al²⁰ among 1785 SCA patients in US. It however compares to 15.9% prevalence rate reported by Akinyoola and colleagues²¹ in a previous Nigerian study. Among 57 SCA patients with bone and joint involvement in Saudi Arabia, Bennett and Namnyak²² reported that 29 (50.9%) of the patients had radiological evidence of AVN. Bahebeck et al¹⁶ 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%. This highlights the greater sensitivity of higher resolution imaging techniques over conventional radiographs in early detection of AVN.

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.^{14, 15, 18, 24, 25} Halabi-Tawil and colleagues¹⁷ 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 to trauma, the latter being a known aetiology of sickle cell leg ulcers.

Overall younger age significantly predicted MSS complication on univariate 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 mean and median ages were lower in patients with AVN and osteomyelitis than those without. Conversely, the mean and median ages were higher in patients with leg ulcers than in those without. Younger children have been reported to be prone to osteomyelitis.^{26, 27} Studies done in Africa reported increased incidence of osteomyelitis in younger SCD patients^{15, 28, 29, 30}. In a prospective cohort study that evaluated the musculoskeletal disease burden among SCA patients, Balogun et al²⁸, noted that Osteomyelitis and septic arthritis were most commonly observed in children less than 10 years. A previous Nigerian study on acute osteomyelitis in the age group 9 months to 50 years also reported that 61.5% were under the age of 15 years. This reason 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.²⁷

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 documented⁶ in the literature. The study by Akinyoola and colleagues²⁵ 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 al³¹ reported that patients with hyper-hemolysis had significantly less osteonecrosis (OR 0.32, 95% CI 0.19-0.54)³¹. 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

209 significantly predicted MSS and osteomyelitis, and showed a trend for AVN. This agrees with
210 the findings by Akinyoola et al²⁵ that there are no significant difference in the white cell and
211 platelet counts of AVN and non AVN SCD patients.

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

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220 4. CONCLUSION

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222 There is a high rate of musculoskeletal complications among our SCA patients. The most
223 common complications were leg ulcers, AVN and osteomyelitis. Higher steady state
224 haemoglobin remained a risk factor for developing AVN even after multivariate adjustments.
225 SCA patients should be routinely evaluated for these common MSS complications and also
226 have regular monitoring of their hemoglobin.

227

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233 COMPETING INTERESTS

234

235 We have no competing interests

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237 AUTHORS' CONTRIBUTIONS

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239 AED collected the data. AJM supervised the data collection. ACU did the data analysis.
240 KAM, AJM and AC did the literature review. All the authors participated in writing the
241 manuscript, read and approved the final manuscript.

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245 ETHICAL APPROVAL (WHERE EVER APPLICABLE)

246

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

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