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A STUDY ON PREVALENCE OF AVN IN CHILDREN AND ADOLESCENTS HAVING SICKLE CELL DISEASE

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Abstract:

Background: Sickle cell disease (SCD) poses a significant public health challenge, particularly in sub-Saharan Africa (SSA), where it is prevalent and associated with high mortality rates, especially among children. Avascular necrosis (AVN) is one of the debilitating complications of SCD, yet its epidemiology and clinical correlates remain underexplored, especially in SSA settings. This study aimed to investigate the incidence of AVN among individuals with sickle cell anemia (SCA).

Methods: A cross-sectional analysis was conducted, enrolling stable SCA patients from the orthopedic department of the hospital. Demographic data, radiological diagnoses of AVN, frequency of pain crises and blood transfusions over the past year, and hematological parameters were collected and analyzed. Statistical analysis was performed using Microsoft Excel and appropriate statistical tests.

Results: Among 29 participants, 10.3% had AVN. The median age was 23 years, with a majority being female (69.0%). Individuals with AVN showed no significant differences in demographic or clinical variables compared to those without AVN. However, a trend towards older age and higher rates of blood transfusions and bone pain crises was observed in the AVN group. Hematocrit levels were lower, and platelet counts were higher in individuals with AVN.

Conclusion: AVN is a prevalent complication among SCA patients in Zaria, Nigeria, with potential associations with blood transfusions, bone pain crises, hematocrit levels, and platelet counts. Further research is warranted to elucidate the underlying mechanisms and optimize management strategies for AVN in SCD patients in SSA settings.

Key words: Avascular necrosis; sickle cell anaemia, sickle cell disease , adolescent

INTRODUCTION

The initial documentation of sickle cell disease (SCD) in Western literature can be attributed to James B. Herrick in 1910 [1]. He observed atypical red blood cells (RBCs) for which he did not have a specific diagnosis at that time. Herrick was informed of this unusual discovery

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by his 27-year-old intern, Ernest E. Irons, who, while working at Presbyterian Hospital, had noticed pear-shaped and elongated cells in the blood sample of a 20-year-old African American named Walter Clement Noel. Noel, whom Herrick regarded as "bright and intelligent," was studying dentistry at the Chicago College of Dental Surgery. Herrick and Irons conducted a thorough investigation to determine the diagnosis. They closely monitored Noel for a duration of 2.5 years following the first discovery, during which he experienced multiple serious illnesses. Noel passed away at the age of 32 due to pneumonia, nine years after his return to Grenada in the West Indies [1, 2]. Following this finding, scientists commenced the process of unraveling the molecular foundation and pathophysiological mechanisms of SCD. Prior to Herrick's discovery, Horton had already identified a clinical phenotype of SCD in tropical regions [3]. Sickle Cell Disease (SCD) was referred to by many names in West Africa, such as "Abiku," "Ogbanje," and "Sankara-jimi," and was managed using diverse traditional herbal remedies [4, 5]. In East Africa, SCD gained recognition among communities as early as the 18th century, being known as "Kagenge" and then "Nnalubiri" by the Baganda people in present-day Uganda. Traditional healers noted distinct symptoms including recurring bouts of fever and pain, inadequate growth in weight and height, persistent wounds, and premature mortality. Despite their efforts, they were unable to adequately treat the illness using extracts derived from certain tree leaves and bark [6]. The World Health Organization (WHO) acknowledged SCD as a public health priority in 2006 [7], and the United Nations (UN) followed suit in 2008 [8]. The United Nations designated June 19 as World Sickle Cell Day in 2009 to enhance public understanding and awareness of Sickle Cell Disease (SCD). Sickle cell disease (SCD) is most common among individuals of sub-Saharan African, Mediterranean, Middle Eastern, and Indian ancestry [10]. It has also spread worldwide due to population movement [11]. The present global number of individuals with SCD lacks reliable estimates, however, some writers approximate it to be within the range of 20 to 25 million [12]. Annually, over 312,000 newborns are diagnosed with sickle cell anemia (SCA), with 64 to 75% of these cases occurring in Sub-Saharan Africa (SSA). In this region, 50 to 90% of deaths attributable to the condition occur during infancy [13, 14]. Sickle Cell Disease (SCD) is the most common genetic illness in the sub-Saharan region of Africa, affecting around 1% to 3% of infants. The countries with the highest number of affected births include the Democratic Republic of Congo, Nigeria, Tanzania, and Uganda [13–18]. Projections indicate an increase in the number of newborns with Sickle Cell Disease (SCD). However, a significant proportion of SCD-related deaths in Africa happen before diagnosis, mostly because there is a lack of widespread newborn screening programs. Regrettably, in Sub-Saharan Africa (SSA), around 500 infants under the age of five perish daily as a result of complications connected to sickle cell disease (SCD) [20]. SCD-associated mortality contributes to nearly 9-16% of deaths among children under the age of five in countries with a high burden of the disease [21]. In contrast, almost 93% of individuals diagnosed with SCD in wealthy nations survive into adulthood [22], with a median age of survival ranging from 58 to 66 years [23].

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MATERIAL AND METHODS

This study was conducted as a cross-sectional analysis, where patients with sickle cell anemia (SCA) who were in a stable condition were enrolled consecutively from the orthopedic department of a tertiary care hospital. Information on gender, age, presence of radiologically diagnosed AVN (as determined by X-ray), number of pain crises, and blood transfusions over the past 12 months were collected and compiled. A complete blood count was performed and information on hematocrit (HCT), white blood cell (WBC), and platelet counts was gathered. The data were examined using Microsoft Excel and online free applications. Percentages were used to summarize qualitative factors. The distribution of quantitative data was evaluated by examining skewness and kurtosis. Means ± Standard Deviation (SD) were used to describe normally distributed variables, whereas medians [IQR (25th, 75th percentiles)] were used for non-normally distributed variables. The distribution of continuous variables across categories of qualitative variables was assessed using Mann Whitney U tests. A significance level of $\alpha = 0.05$ was established.

RESULTS

Table 1 summarizes the demographic characteristics of the study participants, indicating that out of a total of 29 participants, 69.0% were female. The median age of the participants was 23 years, with a range between 19.8 and 28.0 years. Additionally, 10.3% of the participants were identified as having avascular necrosis (AVN). This table provides essential insights into the gender distribution, median age, and prevalence of AVN within the studied population, offering a snapshot of the demographic profile of the cohort.

Table 1 distribution gender , **median age, AVN presence**

Variables	No. of participant [29]	Percentage
Females	20	(69.0%)
Median Age (years)	23 (19.8, 28.0)	
AVN Presence	3	(10.3%)

Table 2 provides a comprehensive summary of key variables in the study. The mean and median age of the participants are reported as 23.00 years, with a range between 19.8 and 28.0 years. The number of pain episodes experienced in the previous 12 months is characterized by a mean of 2.0, with a median of 1.0 and a range from 1.0 to 6.0 episodes. Additionally, the number of blood transfusions in the previous 12 months shows a mean of 0.0, with a median of 0.0 and a range from 0.0 to 0.3 transfusions. Hematocrit levels are reported as 23.0% with a standard deviation of 3.6, while white blood cell count is presented as 0.6±3.0 x 10^9/µL, and platelet count is noted as 456.7±146.1 x 10^9/µL. This table effectively encapsulates key quantitative information, providing a concise overview of the study's variables.

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Table 2. Summary of variables.

Variable	Mean (Median)
Age (years)	23.00 (19.8,28.0)
Number of pain episodes in previous 12 months	2.0 (1.0, 6.0)
Number of blood transfusions in previous 12 months	0.0 (0.0, 0.3)
Haematocrit (%)	23.0±3.6
White Blood Cell (x 109 /µL)	0.6±3.0
Platelets (x 109 /µL)	456.7±146.1

Table 3 presents the distribution of various variables across avascular necrosis (AVN) categories, indicating mean ranks, Mann-Whitney U statistics (MWU), and associated p-values. The variables examined include hematocrit levels, white blood cell counts, platelet counts, age, bone pains in the previous 12 months, and blood transfusions in the previous 12 months. Across all variables, there were no significant differences observed between the absence and presence of AVN, as indicated by p-values greater than 0.05. This table provides insights into the relationship between these variables and the occurrence of AVN, suggesting no substantial associations within this study cohort.

Table 3. Distribution of variables across avascular necrosis categories.

Variable	AVN	Mean Rank	MWU	p
Haematocrit (%)	Absent	30.13	123.500	0.414
	Present	24.08		
White Blood Cell counts (x 10^9/µL)	Absent	29.35	164.000	0.848
	Present	30.83		
Platelets (x 10^9/µL)	Absent	28.98	183.000	0.499
	Present	34.00		
Age (years)	Absent	29.45	158.500	0.959
	Present	29.92		
Bone pains in the previous 12 months	Absent	29.25	169.000	0.747
	Present	31.67		
Blood transfusions in the previous 12 months	Absent	29.05	179.500	0.433
	Present	33.42		

Table 4 provides effect sizes for the relationships between variables across categories of avascular necrosis (AVN), expressed as rank biserial correlations with corresponding 95% confidence intervals (CIs). The variables examined include age, pain experienced in the last 12 months, blood transfusions received in the last 12 months, hematocrit levels, white blood cell counts, and platelet counts. The rank biserial correlation values range from -0.208 to 0.173, indicating weak to moderate correlations between these variables and the presence of AVN. However, all confidence intervals include zero, suggesting that these correlations are not statistically significant at the 95% confidence level. This table highlights the degree of association between each variable and AVN, providing insight into their potential relationship within the study population.

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Table 4. Effect Sizes for Relationships of Variables Between Categories of Avascular Necrosis.

Variables	Rank Bi-serial Correlation	95% Confidence Interval	
		Lower	Upper
AGE (YEARS)	0.016	-0.443	0.468
Pain in last 12 months	0.083	-0.387	0.519
Blood transfusion in last 12 months	0.151	-0.328	0.568
Hematocrit (%)	-0.208	-0.607	0.274
White Blood Cell count ($x10^9$/L)	0.051	-0.414	0.496
Platelets ($x10^9$/L)	0.173	-0.307	0.583

DISCUSSION

The incidence of AVN in this study is similar to that documented by Akpan and Uboh (2018) among individuals with sickle cell anemia in Uyo, Nigeria.8 Nevertheless, our findings are comparatively lower than the reported rates from Ile-Ife, Nigeria (15.9%) and Saudi Arabia (21.7%), but higher than the reported rates from Enugu, Nigeria.[24,27,28] The observed discrepancies may be attributed to disparities in the methodologies employed. While the prior investigations were retrospective reviews, our study adopted a cross-sectional strategy. Unexplored disparities in genetic composition and environmental influences may also contribute to these discrepancies. This is due to the fact that there is a significant correlation between the number of alpha thalassemia genes and the rising prevalence of AVN. [29] The results of our study indicate that the median ages of individuals with and without AVN are similar. Nevertheless, our study design does not necessarily indicate the absence of any temporal difference in occurrence. Notably, the age box plots demonstrate that individuals with AVN have a greater proportion of older age compared to those without AVN. The highest occurrence of AVN has been documented to be in individuals between the ages of 21 and 30. [24]There may be a delay in diagnosing AVN, particularly in settings with limited resources that primarily use X-rays instead of MRI. MRI is more effective in early detection and staging of AVN .[30,31] Therefore, patients may undergo multiple treatments over an extended period of time for chronic hip pain before a conclusive diagnosis is evident through X-ray imaging.[32]We have analyzed our results by considering the interval estimates and effect sizes, rather than relying only on statistical significance. Various groups of statisticians have recently advocated for this method.[33,34] The confidence intervals for effect sizes in This study suggests that there may be significant disparities, varying from moderate to substantial, within the overall population. The secondary analyses in this study demonstrate a lack of power. It is crucial to emphasize that only multicenter trials can provide a substantial number of patients with AVN for accurate comparisons. Therefore, we support the need for larger future multicenter investigations in order to obtain larger sample numbers that can reveal more accurate connections.

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There is no correlation between gender and AVN in This study contradicts the anticipated outcome. Female SCD patients have higher levels of Nitric Oxide bioavailability and a more pronounced reaction compared to males.[35] Extensive research has been conducted on the associations between endothelial Nitric Oxide Synthase (eNOS) and AVN, specifically focusing on various genetic variations in the eNOS gene.[36-38] Although the point estimate indicates that being female may provide protection against AVN, our data also implies the potential for an increased prevalence of AVN among females. What remains uncertain is if our female SCA patient exhibits a similar level of NO expression as seen in this work, or if there are additional aspects that have not been examined yet that could account for our discovery.

The study found that individuals with AVN had comparatively lower levels of haematocrit and greater rates of bone pain crises, which aligns with the findings of Madu et al. in Enugu, Nigeria, among patients with sickle cell anemia (SCA). This condition is also observed in a specific group of individuals within the landmark Cooperative Study of Sickle Cell Disease cohort who also had alpha thalassaemia at the same time.[29]This brings up the question of whether it is necessary to identify the pattern of simultaneous alpha thalassemia and the potential impact it may have on our patients. This study also demonstrates a greater incidence of blood transfusion among individuals with AVN. The frequent and severe destruction of red blood cells, which requires blood transfusion, results in a decrease in the amount of available nitric oxide (NO) due to the absorption of cell-free hemoglobin and disruptions caused by the activity of arginase on arginine. The subsequent vasculopathy may contribute to the development of avascular necrosis (AVN). [39]

CONCLUSIONS

Avascular necrosis (AVN) is a prevalent condition among patients with sickle cell anemia (SCA) in Zaria. Patients with avascular necrosis (AVN) experience increased occurrences of blood transfusions and episodes of bone pain. Additionally, they exhibit lower levels of haematocrit and greater platelet counts compared to individuals without AVN.

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