Avascular necrosis in children with sickle cell disease: prevalence and pattern of presentation in Jos, Nigeria

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Abstract

Background: Avascular necrosis (AVN) is a common orthopaedic complication of sickle cell disease (SCD). Despite the previously reported childhood-onset of AVN, its actual prevalence among children with SCD in Nigeria is not known. Hence, we determined the prevalence and pattern of presentation of AVN in a homogenous paediatric population with SCD in Jos.

Methods: A cross-sectional study of children with SCD aged 5-17 years using a review of data from the SCD-registry of the Paediatric Haematology-oncology unit of Jos University Teaching Hospital from January 2016 to January 2021.

Results: Of the 589 children, 523(88.8%) had haemoglobin SS genotype while 59 (10%) and seven (1.2%) had haemoglobin SS+F and SC genotypes respectively. Thirty- eight children (20 males (52.6%) and 18 (47.4%) females) were diagnosed with AVN of the femoral head giving an overall prevalence of 6.5%. Five of the 38 children had a concomitant AVN of the shoulder giving a prevalence of 0.8%. Their ages at the time of diagnosis of AVN ranged from 7-17 years (mean: 13.6±3.2 years). The prevalence of AVN increased from 1.9% to17.3% among age groups 5-9 years and 15-17 years respectively. Majority of the children (75.8%) presented at the late stages of the disease.

Conclusion: Avascular necrosis of the hip is common among children with SCD and it could occur early in childhood. Most of the children presented at the late stages of the disease. Therefore, we recommend early and routine screening of children with SCD for AVN in Nigeria.

Keywords: Avascular necrosis, Sickle cell disease, children, prevalence, Nigeria

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Introduction

Avascular necrosis (AVN) is the cellular death of bone components due to interruption of the blood supply. [1,2] It is a common orthopaedic complication of sickle cell disease that is caused by repeated ischaemia-reperfusion injury of vulnerable articular surfaces.[1,2] Recurrent painful vaso-occlusive events in sickle cell disease result in impaired circulation to all joints thus increasing the likelihood of necrosis which mostly occurs at the distal portions of a bone near a joint where collateral circulation is insufficient and oxygenation level is severely compromised.[3] It is most commonly seen at the hip joint (involving the femoral head) but could also affect other joints such as the knee and shoulder.[3] Avascular necrosis of the femoral head causes chronic severe pain which is usually worse on ambulation, relieved by rest, and may be associated with significant limitation of motion when the patient bears weight on the affected leg.[4]

Avascular necrosis has been reported in children as young as five years of age. [5, 6] Its prevalence increases with age and the prevalence rates ranged from 3.2% to 39.4% in previous studies which were mostly conducted in populations comprising both children and adults with sickle cell disease.[6-13] Age, weight, frequent episodes of vasoocclusive crisis, acute chest syndrome, elevated haematocrit, low haemoglobin F and co-existence of alpha thalassemia trait have been documented to be associated with the development of AVN in patients with sickle cell disease.[5,8,10-13]

Considering the childhood-onset of AVN, it is imperative to determine the burden and understand the pattern of presentation of this debilitating condition in a paediatric population. Such data could be explored to design interventions that could help to mitigate the impact of the disease on the children. However, there are limited data on the prevalence and presentation of AVN in a homogenous paediatric population with SCD in Nigeria, hence the reason for this study.

Materials and Methods:

Study location

This study was conducted in Jos University Teaching Hospital using the data from the sickle cell disease (SCD)

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registry of the haematology-oncology unit of the department of Paediatrics. The registry which started in 2016 was partly supported by a National Institute of Health grant (D43 TW010130). The registry as of January 2021 has a total number of 913 children with SCD; and it archives all sickle cell-related events in the patients both at admissions and during clinic visits.

Study population

This study recruited children with SCD aged 5-17 years.

Study design

This was a cross-sectional study using a review of registry data to determine the prevalence and pattern of presentation of AVN in children with SCD. The inclusion criteria were all children with SCD aged 5-17 years whose data were captured on the registry between January 2016 and January 2021. Patients with AVN due to hip fracture, patients with septic arthritis of the hip, rheumatic joint diseases and those on corticosteroids as documented in the repository were excluded from the study. Also, data with missing or incomplete information were excluded.

Sample size determination

The sample size was determined using the formula for a cross-sectional study.[14]The parameters used included the prevalence of AVN in a previous similar study which was 26.7% (0.267),[12] the complementary probability (1 – p) of 0.73, the standard normal deviate at 95% confidence interval (1.96), the precision of the study set at 0.05 giving a minimum sample size of 300. However, since registry data was used, all units of elements in the repository who have met the inclusion criteria had their information extracted using a validated proforma developed for the study.

Sampling technique

A total population sampling method was used.

Data collection procedure

Two research assistants extracted the required data from the registry and this was validated by the lead researcher by comparing the extracted information with the data in the registry. The information extracted included the demographic characteristics of the subjects such as the age, age at diagnosis of AVN, sex, haemoglobin genotype and socioeconomic status. The clinical presentations including the stage of AVN at diagnosis were captured as well.

Grading of responses

Different age categorisation was used in this study. For those with AVN, age at diagnosis of AVN was used while for the others, age at the time of data abstraction (January 2021) was utilized. The primary outcome variable was whether AVN was present or absent. The diagnosis of AVN in the registry was based on clinical symptoms and signs such as local pain, limping, limitation of movement etc and was confirmed by plain radiograph which was reported by the Radiologists at the department of Radiology, Jos University Teaching Hospital following appropriate standard of practice. The staging of the AVN was done using the Ficat and Arlet classification.[15] The secondary outcome variable was the pattern of presentation which included the bone affected, site of AVN (unilateral or bilateral),number of limbs affected, stage at presentation etc. The socioeconomic status of the subjects was determined using the Olusanya et al index scoring method.[16]

Data analysis

This was carried out using SPSS version 23.0 for Windows (SPSS, Chicago, IL). Descriptive statistical analysis was carried out on qualitative variables such as sex, haemoglobin genotype, socioeconomic status and stage of AVN as well as the quantitative variables such as age, age at diagnosis of AVN etc. These were presented in the frequency table and expressed in frequencies and percentages. Mean and standard deviation was used as summary of indices for the age. Chi-square test was used to assess the relationship between the socio-demographic characteristics of the subjects and the prevalence of AVN. A p-value of <0.05 was considered statistically significant.

Ethical considerations

Ethical approval to conduct the study was obtained from the Health Research Ethics Committee of Jos University Teaching Hospital.

Results

Socio-demographic characteristics of the study population

Of the 913 children whose data were on the repository between January 2016 and January 2021, 70 children including two with the diagnosis of AVN were excluded on account of incomplete data while additional 254 records were excluded based on age-inclusion criteria.

Of the 589 children aged between 5 and 17 years whose records were analysed, 316(53.7%) were males, 523(88.8%) had haemoglobin SS genotype while only 7(1.2%) had haemoglobin-SC genotype. Thirty-eight children were diagnosed with AVN, of which 20(52.6%) were males and 18(47.4%) were females. Their ages at the time of diagnosis of AVN ranged from 7-17 years with a mean age of 13.6±3.2 years. Their haemoglobin genotypic characteristics were one (1.2%) haemoglobin SC, two (5.3%) haemoglobin SS+F and 35 (92.1%) haemoglobin SS (Table 1).

Table 1: Socio-demographic characteristics of children with sickle cell disease attending the Paediatric Outpatient Department

Variable	Frequency Total study population (%) n=589	AVN present (%) n=38
Age (years)		
5-9	265(45)	5(13.1)
10-14	220(37.3)	15(39.5)
>14 (15-17)	104 (17.7)	18(47.4)
Mean age	10.4±3.6	13.6± 3.2
Sex		
Male	316 (53.7)	20 (52.6)
Female	273(46.3)	18 (47.4)
Haemoglobin phenotype		
SS	523(88.8)	35(92.1)
SS+F	59(10.0)	2(5.3)
SC	7(1.2)	1(2.6)
Socioeconomic status		
High	174 (29.5)	7(18.4)
Middle	229 (38.9)	13(39.5)
Low	186 (31.6)	10(42.1)

AVN – Avascular necrosis

Table 2: Prevalence of avascular necrosis among children with sickle cell disease attending the Paediatric Outpatient Department

Variable	All N=589	AVN present Freq (%)	AVN absent Freq (%)	P- value
Age groups (years)				
5-9	265	5 (1.9)	260 (98.1)	<0.0001
10-14	220	15 (6.8)	205 (93.2)	
>14 (15-17)	104	18 (17.3)	86 (82.7)	
Mean age (years)	10.4±3.6	13.6± 3.2	10.8±3.5	
Overall prevalence		38(6.5)	551(93.5)	
Sex				
Male	316	20 (6.3)	296 (93.7)	0.618
Female	273	18(6.6)	255(93.4)	
Phenotype				
SS	523	35(6.7)	488(93.3)	0.344
SS+F	59	2(3.4)	57(96.6)	
SC	7	1(14.3)	6 (85.7)	
Type of bone affected				
Femur (hip)	589	38 (6.5)	-	
Humerus (shoulder)	589	5 (0.8)		

AVN- Avascular necrosis, Freq - frequency

Table 3: Pattern of presentation of avascular necrosis among children with sickle cell disease who developed the complication

Variable	Frequency (percent)	
Bones affected (n =38)		
Femur (Hip)	48	
Humerus (shoulder)	5	
Side affected	Hip (%)	Shoulder (%)
Right	20 (52.6)	3 (60)
Left	8 (21.1)	2 (40)
Both	10 (26.3)	0 (0)
Total[x]	48	5
Ficat staging[y] (n=33)		
1	0 (0.0)	0(0.0)
2	8 (24.2)	5(100.0)
3	9 (27.3)	0(0.0)
4	16 (48.5)	0(0.0)
Classification of stage of disease at presentation (n=33)		
Early(1 and 2)	8(24.2%)	5(100.0)
Late (3 and 4)	25(75.8)	0(0.0)
Clinical Presentation (n=38)	Present (%)	Absent (%)
Hip pain	30 (78.9)	8 (21.1)
Limping	30 (78.9)	8 (21.1)
Limitation of movement	26 (68.4)	12(31.6)
Shoulder pain	5 (13.2)	33(86.8)

[x]total number of affected limbs
[y]The higher stage was computed in those with bilateral lesion

Prevalence of avascular necrosis in the study population

Of the 589 subjects, 38 had a confirmed diagnosis of avascular necrosis of the femur giving an overall prevalence of 6.5%. When stratified by age, the prevalence of AVN of the femur increased with age from 1.9% among children in the age group of 5-9 years to 6.8% in children between ages 10-14 years and 17.3% among those in the age group of 15-17 years. Using Bonferroni's correction, the prevalence of femoral AVN was significantly higher among the age group 15-17 years compared to the other age groups (P <0.0001) Table 2. There was no statistically significant difference in the prevalence of femoral AVN based on gender (6.3% for males, 6.6% for females, P≤0.168).When stratified based on genotypes, the prevalence of AVN of the femur was higher among patients with haemoglobin SC (14.3%) than in those with haemoglobin SS (6.7%) and SS+F (3.4%), P≤0.344. Furthermore, five (one male, four females, all haemoglobin-SS genotype, age group 10-

14years) of our subjects also had a co-existing AVN of the humerus giving a total prevalence of 0.8%.

Pattern of presentation of avascular necrosis in the study population

Thirty-eight children presented with avascular necrosis of the femur of which 10 were bilateral giving 48 affected hips, and five of them had a concomitant AVN of the shoulder. The right side was more involved in both the hips 20(52.6%) and the shoulders 3(60%). Sixteen (48.5%) of the patients with AVN of the hip presented with stage 4 disease while none was diagnosed in stage 1. None of the children with humeral AVN presented with an isolated disease and they were all diagnosed in stage 2. Table 3. Cumulatively, 25 (75.8%) of the subjects with AVN presented in the late stages of the disease.

Regarding the clinical presentation, hip pain (78.9%) and limping (78.9%) were the common presenting symptoms. Either hip pain or limping was absent in eight (21.1%) patients each at the time of diagnosis (Table 3).

Discussion

Avascular necrosis is one of the debilitating chronic complications of sickle cell disease that is associated with chronic pain and disability as well as poor quality of life among those affected.[17]

The overall prevalence of avascular necrosis of the hip in our study (6.5%) is higher than the rate reported in Zaria, Nigeria (3.2%) among 899 SCD patients comprising adults and children over the age of five years but lower than the rates reported in Kuwait (26.7%) among 30 Kuwaiti children aged 6-17 years and by a study in Israel (15.6%) among a cohort of 32 children with sickle cell disease.[6, 7, 12] Higher prevalence rates than in our study of 10.3%, 13.1% and 15.9% have also been reported by other studies in Zaria, Enugu and Ile-Ife, Nigeria respectively among a homogenous adult populations or heterogenous paediatric and adult populations.[9, 10, 18] This discrepancy in the prevalence rates could be due to several factors such as the differences in the study population, study design, method of diagnosis of the AVN and genetic factor. Whereas the study in Kuwait was conducted in children with a similar age group as our study, the prospective study utilised a magnetic resonance imaging (MRI) test, a more sensitive investigation than the plain radiograph used in our study for the diagnosis of AVN.[12,19] Moreover, unlike in our study, more than a third of the population in the Kuwaiti study had a coexistent alpha-thalassemia trait, a factor that has been reported to increase the risk for the development of AVN. The other Nigerian studies had adults in their study populations which could have been responsible for the increased prevalence since the prevalence of AVN increases with age.[5, 13, 20]

Our study also corroborated the fact that the prevalence of AVN increases with age.[5,12,13,20] The prevalence of AVN of the hip in our study population more than tripled from age nine to 14 years and more than doubled between the ages of 14 and 17 years. The outcome of our study also indicated that AVN could occur early in childhood as two of our patients developed AVN of the hip as early as seven years of age and this is comparable to the reports in Israel and Brazil where AVN was reported at 5 and 8 years respectively.[6, 13] This finding implies that such children could likely have a very poor quality of life having to live with pain for the most time of their life. In addition, this also underscores the need to begin screening for AVN at a young age as early as five to seven years to ensure early detection and prompt intervention which could translate into reduced morbidity and better quality of life for the affected children.

Avascular necrosis was previously considered as mainly a complication of sickle cell disease in adults, with peak age incidences of 21-30 years reported by some Nigerian studies.[9,10]However, our study documented a peak age incidence of 15 -17 years with a prevalence rate among this age group (17.3%) that was higher than the rates in some Nigerian studies which comprised mainly adult populations.[9, 10] The reason for this change in the trend could be as a result of existing paucity of data in the paediatric population and may also be due to other factors that need to be explored.

There was no difference in the prevalence of AVN based on gender in our study. This finding is similar to the report by some studies where no significant gender differences was found.[7, 18]

In our study, there was a trend, though not significant, of higher prevalence of femoral AVN among patients with haemoglobin-SC compared to haemoglobin-SS, an observation that was also made in a Nigerian study (17.1% SC versus 15.6% SS).[9] Other studies have, however, found a higher prevalence of femoral AVN in patients with haemoglobin-SS compared to SC subjects.[5, 7] Our observation may be due to the fewer numbers of patients with haemoglobin-SC in our cohort. Nevertheless, a prospective longitudinal study involving a large cohort of patients with haemoglobin-SC will be needed to unravel this.

It is worthy of note that five of our subjects (one male, four females, all haemoglobin-SS phenotype) also had a coexisting humeral AVN. There are fewer studies that have reported the prevalence of AVN of the shoulder compared to the AVN of the hip because the latter is by far commoner.[21,22] The prevalence of AVN of the shoulder in our study is lower than the finding in the study by Milner et al among 2524 SCD patients (5.6%) where radiographic evidence was also used.[21]The reason for the lower prevalence in our study is unclear but may be related to the few number of cases reported. A high

index of suspicion will be needed subsequently to ensure that some cases are not missed.

In our study, no patient was diagnosed in stage 1 of the disease while over three-quarter of our study participants were diagnosed at the late stages of the disease. This is similar to the findings of the study conducted in Ile-Ife where 81.8% of the study participants presented in Ficat and Arlet Stages 3 and 4 but contrasted a Brazilian study where 30% of the patients with AVN were diagnosed in stage 1.[9,23] The reason for this observation may be due to the methods of diagnosis. Plain radiography which is the most widely available investigation for the diagnosis of AVN may be normal in the early stage of AVN (stage 1) and therefore unable to detect the condition. Conversely, the magnetic resonance imaging tests which are capable of detecting early lesion in AVN are mostly inaccessible in most facilities in the developing countries (unlike in the developed world) thus limiting the ability to diagnose AVN at a very early stage.

Early diagnosis could afford the opportunity for some interventions such as core decompression which could help delay the progression to joint destruction and the need for hip replacement surgery.[24]

Limitations

This study being a review of registry data did not capture some data that could help in answering some pertinent questions such as the interval between the onset of hip or shoulder pain and diagnosis of AVN which could help to objectively quantify the extent of delay in presentation. Similarly, data on the severity of pain experienced was not documented. The contribution of the alpha-thalassemia trait to the prevalence of AVN could also not be ascertained since the facility to screen for this was unavailable.

Conclusion

This study demonstrated that the prevalence of AVN of the hip is high among children with SCD in Jos and the condition could occur early in childhood. The prevalence of AVN of the hip increases with age and the majority of the patients presented at late stages of the disease. We therefore, recommend early and routine screening of children with SCD for AVN in Nigeria as early as seven years of age to ensure timely detection and prompt intervention which could translate into reduced morbidity and better quality of life for the affected children.

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