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Screening for Avascular Necrosis of Hip Joint in Sickle Cell Pediatric Patients and Comparison between X-Ray and Magnetic Resonance Imaging in Diagnosis

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Dr. Israa Mustafa Almusawi[1], DR. Mustafa Rafiq Zair Ali[2], Dr. Lina Muhsen[3]

1. C.A.B.P. Asst. Prof. Hereditary Blood Diseases Center, Karbala, Iraq

2. M.B.Ch.B, Karbala Teaching Hospital for Children, Karbala, Iraq

3. DMRD, Radiologist in Allmam Alhussan Teaching Hospital, Karbala, Iraq

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ABSTRACT

Background: Orthopedic complications of sickle cell disease include vaso-occlusive bone pain, osteonecrosis, and infections (osteomyelitis and septic arthritis). Avascular necrosis is one of the complications of sickle cell anemia characterized by death of bone tissue, which is believed to be caused by a disruption in blood supply. It most commonly affects the femoral or humeral heads. X-ray is usually the first imagining test performed when avascular necrosis is suspected, as it can help differentiate avascular necrosis from other causes of bone pain, like fracture. **Aim of study:** To determine the prevalence of avascular necrosis in patients with sickle cell disease age between five and twenty years old and to evaluate the rule of X-ray finding in the diagnosis of avascular necrosis. **Methods:** A cross-sectional study that conducted in Karbala Teaching Hospital for Children and Al-Hussain Teaching Hospital during a period of 18 months from 1st of November 2021 to 1st of May 2023. It included initially 59 children (118 hip joints) who were known cases of sickle cell disease. Eleven patients were excluded from this study (Two died, seven refused MRI study, and two didn't attend MRI examination date), so the total number of children included in this study was 48 (96 hip joints). Their hips were evaluated with x-ray and MRI studies for detection of any hip pathology including presence of avascular necrosis. **Results:** In this study, 22 patients (45.9%) had avascular necrosis of the hip while the remaining 26 (54.1%) didn't. There is a statistically significant association between clinical presentation and the MRI diagnosis, as 11 patients (91.7%) who presented with hip pain had avascular necrosis. X-ray was 75% sensitive, 92.6% specific, and 87.5% accurate in diagnosis of avascular necrosis of the hip joints. **Conclusion:** The prevalence of avascular necrosis among patients with sickle cell anemia is relatively high. X-ray examination is considered as the first line approach especially in later stages of avascular necrosis which can reveal bone changes but due to limited sensitivity in early stage, MRI is indicated.

INTRODUCTION

Definition of CSA

Sickle cell anemia is defined as an inherited disorder develop in the sixth amino acid locus in the β-chain of the hemoglobin molecule. As a result, neither hemoglobin molecule nor RBC form sickle cell erythrocytes, take the form of a crescent. When they develop, during childhood and adolescence, they have increased susceptibility to infection, and multi-organ problems [(1)].

Pathophysiology of CSA

The loss of RBC elasticity is essential to the pathophysiology of SCD. Normal RBC are elastic and have a biconcave disc shape, which permit them to deform to pass through capillaries. In CSD, low oxygen tension promotes RBC sickling and repeated episodes of sickling damage their cell membrane and decrease their elasticity. These cells fail to return to normal shape when normal tension is restored. As a consequence, these rigid RBC are unable to deform as they pass through narrow capillaries, causing vessel occlusion and ischemia [(2)].

Clinical presentations

1 .Pain crisis

Pain crises represent the most distinguishing clinical feature of SCD and are the leading cause of emergency department visits and hospitalizations. It begins suddenly and last several hours to several days and relived as fast as it began. The pain can affect any body part and involves the abdomen, bones, joints, and soft tissue [(3)].

2 .Anemia.

Anemia is universally present. It is chronic and hemolytic in nature and usually very well tolerated. The SCA develop as the sickle cells destructed easily and die. RBCs usually live for about 120 days before they need to be replaced. But sickle cells typically die in 10 to 20 days, leaving a shortage of red blood cells (anemia). Without enough RBCs, the body can't get enough oxygen and this causes fatigue [(4)].

3 .Frequent infections.

Patients are especially susceptible to infections with encapsulated organisms because of their functional asplenia, as well as because of functionally immunocompromised state (increased bone marrow turnover and altered complement activation). Infants and children with SCA commonly receive vaccinations and antibiotics to prevent potentially life-threatening infections, such as pneumonia [5].

4 .Delayed growth or puberty

The RBC provide body with the oxygen and nutrients necessary for growth. A shortage of healthy RBC can slow growth in infants and children and delay puberty in teenagers [6].

Avascular Necrosis of Joints (AVN).

Definition

Avascular necrosis is a condition in which ischemia of bone tissue developed, causing an infarction. AVN can result from trauma as femoral neck fracture, also a number of atraumatic etiologies, such as systemic lupus erythematosus (SLE), radiation therapy, coagulopathy as factor-V leiden, glucocorticoid use, and Sickle Cell anemia [7].

Clinical presentations

The clinical presentations of AVN is differ according to the age of patients, as [8,9]:

AVN typically is asymptomatic until late-stage disease, and once symptomatic, there is rapid progression to collapse, especially in AVN secondary to SCD.

Pain: mechanical of variable onset and severity in hip and groin region.

Limited range of motion.

Abnormal gait.

Limb-length discrepancy in children and adolescents.

Soreness on palpation, and discomfort during abduction and internal rotation of the hip area are some physical exam findings suggestive of femoral head osteonecrosis.

Diagnosis of AVN

Along with a medical history and physical exam, the work may include doing x-ray**,** Magnetic resonance imaging (MRI) and some times need bone biopsy or angiography [(10)].

Staging system

The Steinberg staging system is the most often utilized. It includes:

Table 1.1: Steinberg staging system [(11)].

Stage	Features
0	Normal radiograph, bone scan, and MRI
I	Normal radiograph, abnormal bone scan, and or magnetic resonance imaging IA Mild (involves less than 15% of the femoral head). IB Moderate (involves 15–30% of the femoral head) IC Severe (affects over 30% of the femoral head)
II	Cystic and sclerotic change of the femoral head IIA Mild (involves less than 15% of the femoral head) IIB Moderate (affects 15–30% of the femoral head) IIC Severe (affects more than 30% of the femoral head)
III	Subchondral collapse (crescent sign) without flattening of the femoral head IIIA Mild (involves under 15% of the femoral head) IIIB Moderate (affects 15–30% of the femoral head) IIIC Severe (affects over 30% of the femoral head)
IV	Flattening of the femoral head/femoral head collapse IVA Mild (involves under 15% of the femoral head) IVB Moderate (involves 15–30% of the femoral head) IVC Severe (affects more significant than 30% of the femoral head)
V	Joint space narrowing and acetabular changes VA Mild VB Moderate VC Severe
VI	Advanced degenerative joint disease

Table 1.2: Ficat and Arlet classification of AVN of femoral head, which include five stages[12]

Stage	Radiographic signs
Early: stage 0. preclinical	None marrow necrosis may be present histologically
Early: stage 1. pre-radiographic	None abnormal MRI with marrow and bone necrosis
Early: stage 2. Before flattening of head or sequestrum formation	Diffuse porosis, seclerosis or cyst
Transition	Femoral head flattening Crescent sign
Late: stage 3. collapse	Broken contour of head Sequestrum Joint space normal
Late: stage 4. Osteoarithritis	Flattened contour Decreased joint space Collapse of head

Aim of study

To determine the prevalence of AVN in patients with SCD aged between five and twenty years old.

To evaluate the rule of X-ray finding in the diagnosis 0f AVN.

PATIENTS AND METHODS

Study design, setting and data collection time

This was a comparative study that conducted in Karbala Teaching Hospital for Children and Al-Hussain Teaching Hospital during a period of 18 months from 1st of November 2021 to 1st of May 2023.

Study population and sample size

The study included initially 59 children (118 hip joints) who were known cases of sickle cell disease attended the hospital. Eleven patients were excluded from this study (Two died, seven refused MRI study, and two didn't attend MRI examination date). So the total number of children included in this study was 48 (96 hip joints). Their hips were evaluated with x-ray and MRI studies for detection of any hip pathology including presence of AVN.

Exclusion criteria

Past history of hip AVN.

Signs or symptoms of suspected vaso-occlusive crisis / AVN.

Patients whose parents refused to be part from this study.

Data collection tools

The data had been collected through distribution of well-designed questionnaire including the following:

Age and sex.

Diagnosis of hematological disease.

Clinical presentation.

Complications of sickle cell disease.

Imaging study workup

X-ray imaging study : It was performed in Karbala Teaching Hospital for Children for 59 patients by SHIMADZU device.

MRI study : It was performed in Al-Hussain Teaching Hospital for 48 patients by MAGNETOM Avanto device.

Ethical considerations and official approvals

Verbal permission was obtained from each parent prior to collecting data, and information were anonymous. Names were removed and replaced by identification codes. All information

kept confidential in a password secured laptop and data used exclusively for the research purposes.

Statistical analysis

The data was analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. The significance of difference of different percentages (qualitative data) were tested using Pearson Chi-square test (X^2-test) with application of Yate's correction or Fisher Exact test whenever applicable. Sensitivity, specificity, accuracy, positive and negative predictive values of X-ray in diagnosis of avascular necrosis of the hip, were calculated. A level of P – value less than 0.05 was considered significant.

RESULTS

This study included a total of 48 patients who were screened for avascular necrosis of the hip.

1.1. Sociodemographic and clinical characteristics

The age range of studied patients was 5 - 20 years with a mean of 12.89 ± 3.91 years. The highest proportion of patients aged ≥ 15 years, 20 patients (41.7%) (Figure 1.1).

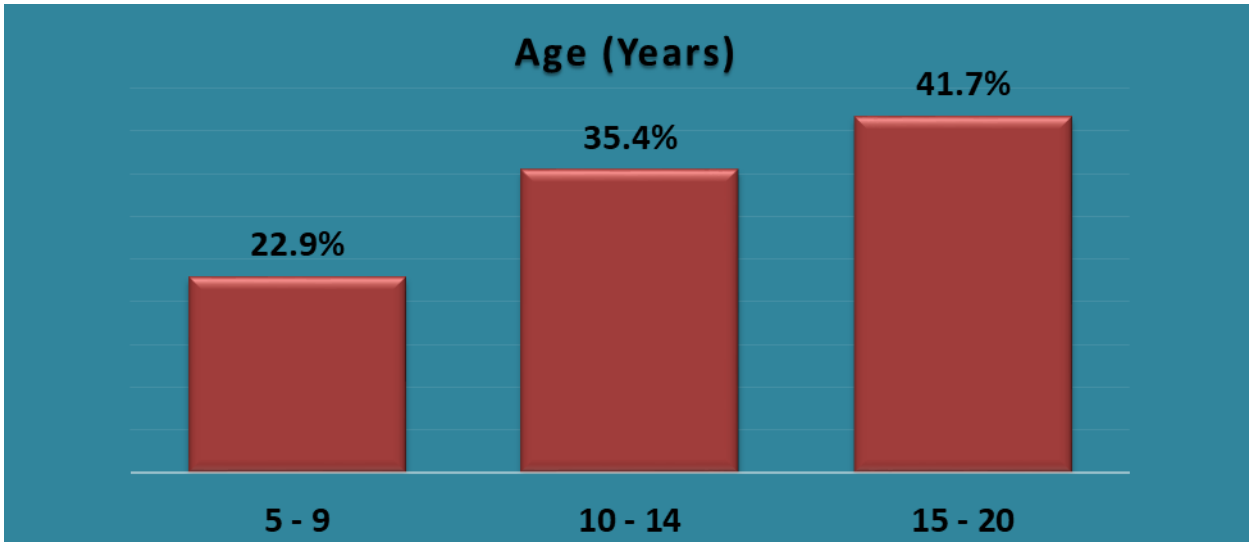

Figure1.1: Distribution of the studied children according to age

Regarding gender, there were 27 males (56.3%) versus 21 females (43.7%) with a ratio of 1.28:1. Thirty-five patients (72.9%) had sickle cell anemia while 13 (27.1%) had sickle-

βThalassemia. Concerning clinical presentation, hip pain was reported in 12 patients (25%) while the remaining 36 patients (75%) were with a symptomatic lesion. (Table 1.3).

Table 1.3: Distribution of the study group according to baseline characteristics

Patients' characteristics	No. (n= 48)	Percentage (%)
Sex		
Male	27	56.3
Female	21	43.7
Diagnosis		
Sickle Cell Anemia	35	72.9
Sickle-βThalassemia	13	27.1
Clinical Presentation		
Hip Pain	12	25.0
A symptomatic	36	75.0

The complications were as follows: painful crisis in all patients (100%), splenic sequestration in 12 patients (25%), ACS in 8 patients (16.7%), priapisim in 2 patients (4.2%), each hemolytic and a plastic crisis in 1 patient (2.1%) (Figure 1.2).

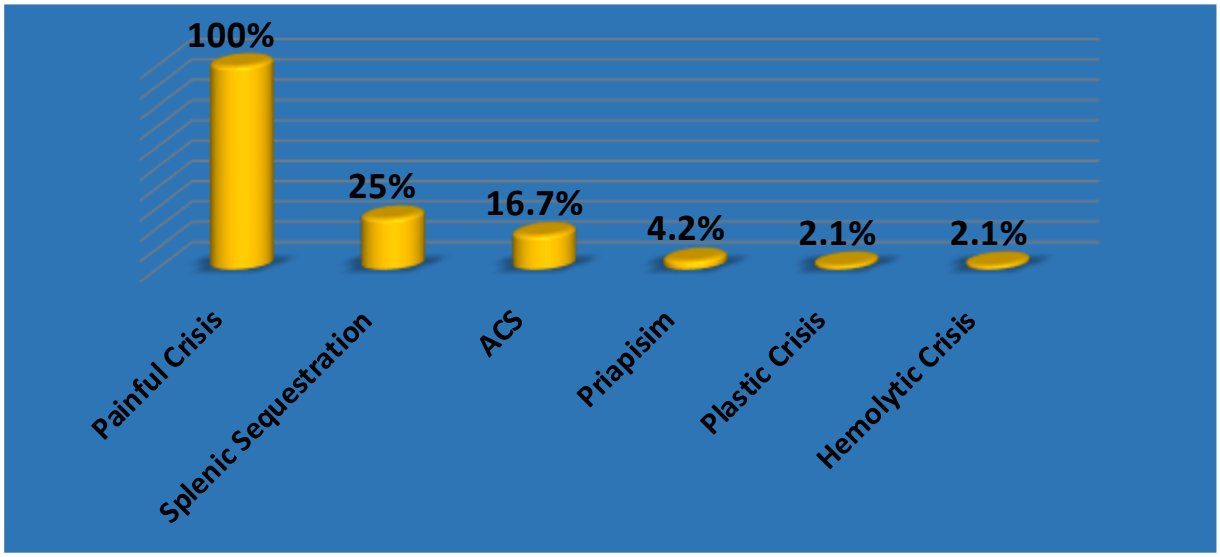

Figure 1.2: Distribution of the studied children according to complications

1.2. MRI diagnosis

MRI of the hips was done for the 48 studied patients. According to FICAT and Alert classification of avascular necrosis, 26 patients (54.1%) had stage 0, 9 patients (18.7%) had stage I, 6 patients (12.5%) had stage II, 3 patients (6.3%) stage III, and 4 patients (8.3%) were at stage IV (Figure 1.3).

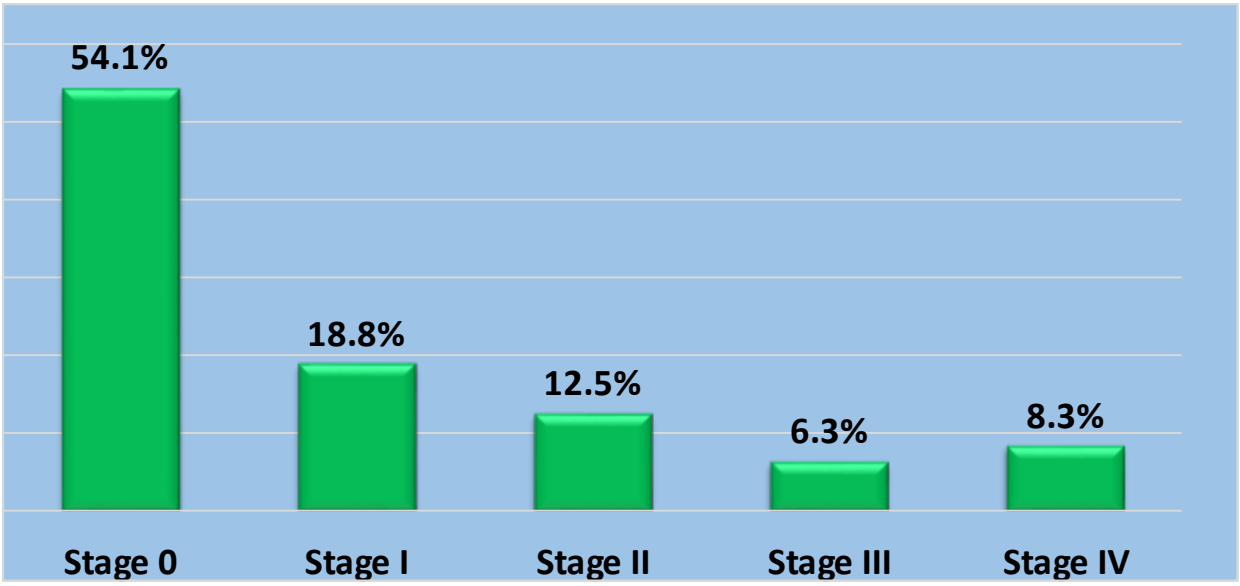

Figure 1.3: Distribution of the studied children according to results of MRI

The final diagnosis of MRI was as follows; 22 patients (40.9%) had avascular necrosis of the hip while the remaining 26 (59.1%) didn't (Figure 1.4).

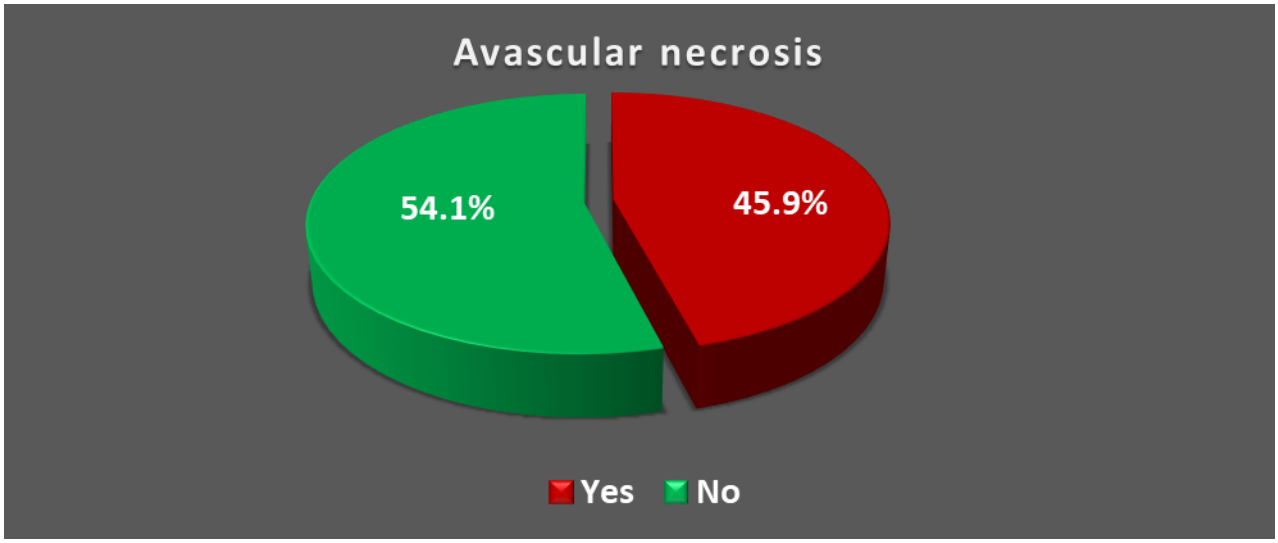

Figure 1.4: Distribution of the study patients according to final diagnosis of MRI

Among the 22 patients with avascular necrosis, there were 28 affected hip joints; right side in 9 patients (40.9%), left side in 7 patients (31.8%), and bilateral in 6 patients (27.3%) (Figure 1.5).

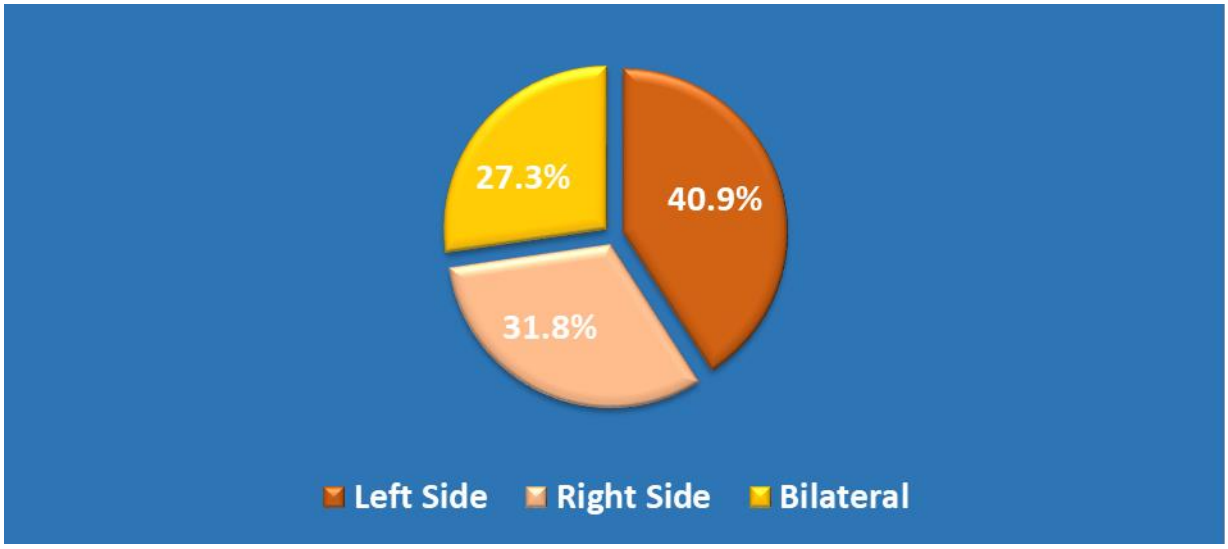

Figure 1.5: Distribution of the avascular necrosis cases according to side of the affected hip joint1

The distribution of study patients by MRI diagnosis and sociodemographic and clinical characteristics revealed a statistically significant association ($P < 0.05$) between clinical presentation and the MRI diagnosis, as 8 patients (88.9%) who presented with hip pain had avascular necrosis. Other variables were not significantly associated ($P \geq 0.05$) with development of avascular necrosis (Table 1.4).

Table 1.4: Distribution of study patients by clinical characteristics and MRI diagnosis

Patients' characteristics	**Avascular Necrosis**		**Total (%) n= 44**	**P- Value**
	Yes (%) n= 22	**No (%) n= 26**		
Age (Years)				
5 - 9	4 (36.4)	7 (63.6)	11 (25.0)	**0.586**
10 - 14	5 (33.3)	10 (66.7)	15 (34.1)	
15 - 20	9 (50.0)	9 (50.0)	18 (40.9)	
Sex				
Male	10 (29.4)	24 (70.6)	34 (63)	**0.911**
Female	8 (40.0)	12 (60.0)	20 (37.0)	
Diagnosis				
Sickle Cell Anemia	15 (46.9)	17 (53.1)	32 (72.7)	**0.189**
Sickle-βThalassemia	3 (25.0)	9 (75.0)	12 (27.3)	
Clinical Presentation				
Hip Pain	8 (88.9)	1 (11.1)	9 (16.7)	**0.001**
A symptomatic	10 (22.2)	35 (77.8)	45 (83.3)	

1.3. Diagnostic performances of X-ray

According to X-ray radiological findings, X-ray was 75% sensitive, 92.6% specific, and 87.5% accurate in diagnosis of avascular necrosis of the hip joints, with positive predictive value of 80.7% and negative predictive value of 90% (Table 1.5).

Table 1.5: Sensitivity, specificity, and accuracy of X-ray in diagnosis of avascular necrosis of the hip

X-ray Diagnosis	Avascular necrosis by MRI		Total
	Yes	No	
Abnormal	**21**	**5**	**26**
Normal	**7**	**63**	**70**
Total	**28**	**68**	**96**

* Total number of hip joints that were screened with MRI and X-ray was 96 (48 patients).

DISCUSSION

In the present study, The final diagnosis of MRI was; 40.9% of patients had AVN of the hip while the remaining 59.1% didn't, which was higher than that published in Adekile et al study, as reported that MRI evidence of AVN in more than 25% of thirty patients with AVN secondary to SCA [13]. In the same concern, and according to FICAT and Alert classification of AVN applied in Elalfy et al study whose enrolled 68 children, with SCD and AVN in their study; 22 patients had stage-0 (38%), two patients had stage-I (2.9%), 13 patients had stage II (19.1%), 14 had stage III (20.8%) and 17 patients were at stage IV (25%); 64% had stage II and above at diagnosis [14]. In Mallet et al study, a total of 25 hips in 17 patients were included, in which MRI was performed to confirm the diagnosis of AVN and evaluate femoral head acetabular cartilage coverage, initial severity of the disease classified according to the FICAT system, reported two patients presented with stage-I (8%), nine patients with stage-II (36%), 13 patients with stage-III (52%) and one patients presented with FICAT stage-IV (4%) [15].

The present work revealed a significant association between clinical presentation and the MRI diagnosis, as 88.9% of patients with hip pain had AVN ($P<0.05$). Age, gender and diagnosis hadn't significant associations with AVN ($P \geq 0.05$). These results agreed to that published in Boeisa et al study, in which results revealed that no significant relation between diagnosis of AVN and the gender of participants ($P>0.05$) [15].

Sociodemographic characteristics In the present work, age range of studied patients was 4 – 18 years with a mean of 12.89 ± 3.91 years. The highest proportion aged ≥ 15 years (41.7%). Regarding gender, there were a slight male predominance observed (56.3%) with a ratio of 1.28:1.

In Boeisa et al study, 322 children with sickle cell disease were screened and referred to pediatric orthopedics. Age of all children groups was ranging between 4-14 years. The mean age and standard deviation of the participants was 8.54 ± 2.2 years. A slight male predominance reported among them, as male group constituted 56.5%, with male to female ratio was 1.51:1 [15]. In comparison to other studies, a case-control study was conducted by Musowoya and colleagues. In which, 57 cases and 114 controls were obtained by systematic sampling method. They observed that median age for cases was nine and half years (as the age of participants ranged between seven and nine years old), differently a female predominance reported, as they formed 57% of the enrolled patients with female to male ratio was 1.37:1 [16]. Differently, Almeida-Matos et al study enrolled 33 patients with SCA underwent evaluation for AVN. The mean and SD of age was 17±37.3 years. On the other hand, a slight male predominance reported among participants, as they constituted 53% of them with male to female ratio was 1.16:1 [17].

In the same concern, Elalfy and other co-authors enrolled Sixty-eight children, adolescents and young adults with SCD and AVN in their study. They found that Thirty-seven of the participants (54%), were males with male to female ratio was 1.2:1. Also found that mean age of them was 16 years, aged between 8-22 years [14].

Such difference in the age at presentation may be as the result of the difference in the socioeconomic status of the different populations which differs markedly from the affluent nations that report earlier ages of presentation. It may also be the result of early exposures to pathogens in the less affluent societies which are not as clean or the increased mortality that may have occurred among the younger age groups.

Clinical characteristics

In the present study, 72.9%of patients had hemoglobin SS disease while 27.1% had Sickle-β Thalassemia. Concerning clinical presentation, hip pain reported in 25% of patients, while the remaining 75% were with asymptomatic lesion.

Regarding the type of SCD among 70 patients enrolled in Lage et al study, the majority, 67 patients were homozygous for the HbS (95.7%). Only one case of Hemoglobin SC (1.4%), Hb Sβ+-Thalassemia (1.4%), Hb Sβ0-Thalassemia (1.4%) were identified[18] .

As compared to other studies, a different results published in Musowoya et al study, in which the vast majority of patients had hemoglobin SS disease (98.2%), while 1.8% had other types of genotypes of the SCA. Also, the commonest presentation was chronic osteomyelitis (29.8%), followed by acute osteomyelitis (21.1%), AVN of the femoral head (14.0%), and septic arthritis (10.5%). Other manifestations included: Leg ulcer, pathological fractures, vertebral collapse, and dactylitis. [16]. Another different results published in Elalfy et al study, as reported that 29.4% of the participants had hemoglobin SS while 70.6% had Sickle-βThalassemia [14]. On the other hand, a total of 25 hips (17 patients) were retrospectively included in Mallet et al study, in which observed that a total of 14 patients (82%) had a SS-haemoglobin disease. The remaining participants had the other SC-haemoglobin disease (18%) [15].

Regarding complications in the current study, painful crisis observed in all patients (100%), splenic sequestration in 25% of patients, ACS in 16.7% of patients, priapism in 4.2% of patients, each hematologic and a plastic crisis in 2.1% of patient. These results were a close to that published in Hazzazzi et al study, in which 91 patients with SCA were participated. Almost all sickle patients (83 patients) had VOC as a complication of SCA (91.2%), and more than half of them had ACS 58.2%, cholecystitis developed in 25.3% and splenomegaly in 17.6% [19]. Another close results observed in Saidi et al study, when 124 participants with SCA were enrolled. They reported that the most prevalent complication of SCA was a VOC episode, which had been diagnosed in 121 patients (97.6%). ACS had been diagnosed in 83 patients (66.9%), and stroke had been diagnosed in 21 participants (16.9%) [20].

Differently, From the 70 children enrolled in Lage et al study, 64% had at least one VOC. Of which, 49.2% children presented with trunk pain crises versus 46% with limb pain. About a third of t VOCs (32.3%) were associated with fever or an infectious [18].

A variety of factors determined the difference observed above, represented by the different study design or different sample size. Also may related to severity of the disease, type of management received, presence of co-morbid conditions exacerbates the complication, in addition to genetic (having multiple family members with the same disease is expected to increase awareness of symptoms and prompt higher quality care for subsequent children),

socioeconomic (represented by programs for explanation of the disease and its stages of progression, and poor community awareness about the early symptoms of sickle cell disease) and educational factors [21]

Conclusion

The prevalence of AVN among patients with SCA is relatively high.

2 X-ray examination is considered as the first line approach especially in later stages of avascular necrosis which can reveal bone changes but due to limited sensitivity in early stage, MRI is indicated.

5.2. Recommendation

We recommend evaluation of all SCD patients (25 years) for AVN, even if they are asymptomatic by doing X-ray and MRI of hips (if available) annually. 2. Management of AVN by analgesia and consult orthopedics for assessment and

follow up.

Further researches needed with larger sample of SCD patients to confirm its effect on occurrence of AVN.

Studying the effect of treatment mainly hyroxyurea in those patients.

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