Acta Biomed 2023; Vol. 94, N. 5 e2023198 DOI: 10.23750/abm.v94i5.14603 © Mattioli 1885

Original article

Clinical and epidemiological features and therapeutic options of avascular necrosis in patients with sickle cell disease (SCD): A cross-sectional study

Awni Alshurafa[1], Ashraf T Soliman[2], Vincenzo De Sanctis[3], Omar Ismail[1], Mohammad Abu-Tineh[1], Mohammad Khair Eddin Hemadneh[4], Farah Rahat Rashid[4], Hana Qasim[1], Khadra Yassin[1], Abdulqadir Jeprel Nashwan[5], Mohamed A Yassin[1]

[1]Hematology department, Hamad Medical Corporation, Doha, Qatar; [2]Pediatric Endocrinology Division, Hamad General Hospital, Doha, Qatar; [3]Pediatric and Adolescent Outpatient Clinic, Quisisana Hospital, Ferrara, Italy; [4]Department of Internal Medicine, Hamad Medical Corporation; [5]Department of Nursing, Hazm Mebaireek General Hospital, Hamad Medical Corporation, Doha, Qatar

Abstract. *Background:* Avascular necrosis (AVN) is a debilitating complication in sickle cell disease (SCD) patients, and its management is usually challenging. This study aims to evaluate the clinical and epidemiological features and therapeutic options of AVN in sickle cell patients in Qatar. *Patients and methods:* A cross-sectional study was conducted on a 49 SCD patients who were diagnosed with AVN and attended the hematology clinic at the National Center for Cancer Care & Research, Hamad Medical Corporation, Qatar between Jan-2011 to Jan2021. *Results:* Forty-nine adult patients with SCD who were diagnosed with AVN were studied. The median age of the study population is 32 years, and the median age at the first AVN diagnosis was 26 years (range: 11-44 yr.). 37 (75.5%) patients suffered from multiple joints AVN while 12 (24.5%) had single joint involvement. 31 (63.3%) patients had bilateral hip AVN and 18 (36.7%) had shoulder involvement. 30 patients (61%) were on hydroxyurea treatment. Based on Ficat and Arlet classification of AVN, 57 % of patients had stage III and above at first diagnosis. 20 (40.8%) were managed with a conservative approach, 11 (22.4%) received hyperbaric oxygen with good response, 6 (12.2%) underwent hip core decompression and 12 (24.5%) underwent hip replacement surgery. *Conclusion:* In SCD patients, AVN occurred more during the 3rd and 4th decades of life. The majority of AVN represented with advanced stage and had multiple joint involvements. We recommend adopting a low threshold of joint imaging for early detection and prevention of further complications. (www.actabiomedica.it)

Key words: sickle cell disease, avascular necrosis, osteonecrosis, hemolysis, hyperbaric oxygen

Introduction

Sickle cell disease (SCD) is a group of inherited disorders characterized by chronic hemolysis and intermittent vaso-occlusive episodes which can cause pain, tissue ischemia, and various end-organ damage (1). SCD affects millions of people with an estimated incidence of 300,000 new cases worldwide each year (2). The SCD prevalence ranged from 0.24%-5.8% across the Gulf Cooperation Council (GCC) and the sickle cell trait from 1.02%-45.8% (3).

Avascular necrosis (AVN) is an incapacitating complication in SCD patients, and its management is usually challenging and demanding. Pretreatment staging and early involvement of an orthopedic surgeon are critical for getting better outcomes. Treatment options are conservative and surgical, including core decompression, bone grafts, and arthroplasty (4).

Risk factors for AVN include Age, HbSS and concomitant alpha thalassemia, male sex, smoking, low bone mineral density, joint trauma, recurrent vaso-occlusive pain, and acute chest syndrome episodes. Around 50% of the cases were discovered radiologically but clinically they are asymptomatic. Femoral and humeral heads are the most affected when symptomatic. A careful history and physical examination are essential as asymptomatic involvement of other joints is also possible (5).

AVN in SCD has not been studied in detail before in the GCC population and there is limited worldwide literature about the variability of severity among patients and about optimal time of surgical intervention. This study aimed at collecting data about the clinical and epidemiological features and outcomes of avascular necrosis in sickle cell patients who were treated at the National Center for Cancer care & research (NCCCR), HMC, Qatar between 1- 2011 and 1- 2021.

Patients and methods

A cross-sectional study was conducted in a group of 49 AVN cases out of 500 SCD patients who were attending the hematology clinic at National center for Cancer Care & Research hospital (NCCCR), Hamad Medical Corporation (HMC), Qatar from Jan-2011 to Jan-2021. Clinical and epidemiological features, laboratory values, and management details were reviewed and recoded. The study is of a descriptive nature with descriptive analysis.

Data obtained included demographic characteristics, risk factors, Clinical presentation, age at first AVN diagnosis, hemoglobin S level, affected joints, hydroxyurea treatment and compliance, stage at diagnosis, and management options which included conservative physiotherapy, hyperbaric oxygen, core decompression, and hip replacement. AVN was diagnosed by MRI scans in all patients, and it was staged according to Ficat and Arlet classification of AVN.

Results

Forty-nine adult patients with SCD complicated by AVN were reviewed (Table 1). The median age of the study population was 32 years (range: 18-64) and the median age at first AVN diagnosis was 26 years (range: 11-44). 25 patients (51 %) were males. 41 patients (83.6%) had hemoglobin SS, 3 (6.1%) with hemoglobin S/D (double heterozygosity), 3 (6.1%) hemoglobin C/S, 1 (2.1%) with hemoglobin S/E, and 1 (2.1%) with sickle/thalassemia.

37 (75.5%) patients suffered from multiple joints AVN while 12 (24.5%) had single joint involvement. 31 (63.3%) patients had bilateral hip AVN and 18 (36.7%) had shoulder involvement. Most of the patients (79%) were symptomatic. Joint pain and a limited range of motion were the most common symptoms. 30 patients (61%) of the recruited

Table 1. Characteristics of 49 patients with avascular necrosis included in the retrospective survey.

Gender	
Male	25 (51%)
Female	24 (49%)
Ethnicity	
Asian	13 (26.5%)
Black/African	10 (20.4%)
White	3 (6.1%)
Others (Arabs & others)	23 (47%)
Age at diagnosis, years, median, range	26 (11-44)
Sickle cell disease types	
hemoglobin SS	41 (83.6%)
hemoglobin S/D	3 (6.1%)
hemoglobin C/S	3 (6.1%)
hemoglobin S/E	1 (2.1%)
sickle/thalassemia	1 (2.1%)
Affected joints	
Unilateral hip AVN	6 (12.2%)
Bilateral hip AVN	31 (63.3%)
Unilateral shoulder AVN	10 (20.4%)
Bilateral shoulder AVN	8 (16.3%)
AVN Stage at diagnosis	
Stage I	8 (16.3%)
Stage II	13 (26.5%)
Stage III	9 (18.4%)
Stage IV	13 (26.5%)
Stage V	6 (12.3%)
Management	
Conservative	20 (40.8%)
Hyperbaric oxygen	11 (22.5%)
Core decompression	6 (12.2%)
Joint replacement	12 (24.5 %)

population were on Hydroxyurea; six of them (20%) were non-compliant.

Based on Ficat and Alert classification of AVN, 8 (16.3%) patients had stage I, 13 (26.5%) had stage II, 9 (18.4%) had stage III, 13 (26.5%) patients had stage IV; and 6 (12.3%) patients had stage V. 57 % of patients had stage III and above at diagnosis.

20 (40.8%) patients were managed with a conservative approach including (pain killers, hydration, blood transfusion and physiotherapy), 11 (22.4%) received hyperbaric oxygen with good response, 6 (12.2%) underwent hip core decompression and 12 (24.5%) underwent a hip replacement surgery.

Discussion

SCD patients are at risk to develop different forms of bone and joint complications. It includes vaso-occlusive bone pain, AVN, osteomyelitis, and septic arthritis. AVN or osteonecrosis is a common complication of vaso-occlusive phenomena that affects around 10 % of SCD patients. The long bones epiphyses are the most common areas of AVN involvement due to limited collateral blood circulations and the femoral head is the most commonly affected joint (6,7).

Our study showed that the prevalence of AVN was (45/500) 9% and overall incidence 9 in 1000 /yr. and that it is more common in the 3rd decade of life. In a large SCD cohort from the state of California, 1356 (22 percent) out of 6237 SCD individuals developed symptomatic hip osteonecrosis at a median age of 27 years with an overall incidence rate of 1.79 cases per 100 person-years (8).

The data about the clinical features, prevalence, and outcome of AVN in the Arabic population and Gulf area are limited. Our study showed that 57 % of patients had stage III and above at diagnosis, 75.5% patients suffered from multiple joints involvement, and 63.3% had bilateral hip affection (prevalence = 5.7% of SCD patients), while 36.7% had shoulder involvement. A cross-sectional study done in Oman showed that the prevalence of femoral osteonecrosis is 2.8 % among SCD Omani children and young adults with 82% of the cases having grade III and above at diagnosis(9)). In another cross-sectional study carried out among Egyptian and Omani pediatric and young adults individuals with SCD, 64% of patients presented with AVN stage II or above at diagnosis with median age of 16 years at diagnosis (10). In our cohort, the median age of AVN diagnosis was later (26 yrs.).

AVN often affects more than one joint at diagnosis. 63% of our patients had bilateral hip AVN at diagnosis. Similar to our findings, Milner et al.(11). reported that bilateral femoral osteonecrosis was bilateral in 54% of their patients. These observations may support the practice of bilateral hip evaluation when managing patients with femoral AVN.

There is no consensus about the optimal timing of surgical intervention for AVN in SCD patients.

Strong recommendations are available to support conservative management as initial measures, especially for early stages of AVN. These include good analgesia, hydration, physical therapy, and using a weight-bearing crutch. However, it is not clear when to switch from conservative to surgical management (12). Surgical options mainly are core decompression and joint replacement. Surgical intervention is usually a joint decision between the patient, orthopedic surgeon and hematologist; however, randomized trials would help to know the optimal approach and timing for surgical intervention of AVN in SCD patients.

While 23% of the patients with ONFH in the California study underwent hip replacement surgery, around 37% of our study population underwent surgical intervention with core decompression and arthroplasty as they deteriorated on conservative management, or they had advanced disease at diagnosis (8).

Hyperbaric oxygen (HBO) may improve AVN by increasing oxygen supply to the ischemic area and ameliorating oxidative and inflammatory changes. Currently, the main rule of HBO in AVN is an adjunctive conservative modality to reduce pain and improve range of joint movement (13,14). 22.5 % of our cohort received hyperbaric oxygen and they have significant improvement; however radiological impact wasn't studied. Few studies showed that there was a significant continuous radiological improvement of AVN with HBO on short and long-term follow-up (15–17). However, further large-scale studies are needed to study the radiological changes before and

after giving HBO. Currently, there is a lack of data on the effectiveness of novel treatments for AVN in patients with SCD.

The study has several limitations, the small sample size restricts the generalizability of the findings, and selection bias may be present due to the reliance on medical records. Moreover, retrospective studies rely on patients' or caregivers' ability to recall past events, leading to recall bias, where memories may be imperfect or biased. Lastly, due to the study's design, it may be challenging to thoroughly analyze the complex causality between sickle cell disease and avascular necrosis, as factors such as comorbidities, medications, and lifestyle choices might not be adequately accounted for or controlled. Therefore, careful interpretation and further research are necessary to fully understand the implications of the study's findings.

In conclusion, most AVN patients in the study had multiple joint involvements and an advanced stage of the condition at diagnosis, highlighting the need for early detection through a low threshold of joint imaging.

Declaration: Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Ethical Disclosure: The case approved by Hamad Medical Corporation Medical Research center, MRC-01-21-974, on 15/11/2021, and the patient signed a written informed consent for the publication of any potentially identifiable images or data included in this article.

Funding: The publication of manuscript was supported by the academic health system, Hamad Medical Corporation.

Authorship Contributions: Conceptualization: AA, ATS, VDS, MAY. Data curation and analysis: MKEH, FRR, KY, AJN. Methodology: HQ, MAT, OI. Writing original draft preparation: AA, MAY, VDS, OI, MAT, HQ, MKEH, FRR, KY, AJN. Revision of manuscript for important intellectual content and editing: AA, MAY, ATS. All authors have read and approved the final version of the manuscript.

Data Availability Statement: All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Correspondence:
Received: 17 April 2023
Accepted: 7 June 2023
Dr. Awni Alshurafa, MD
Hematology fellow
Hamad Medical Corporation, Doha, Qatar
E-mail: dr.a.shurafa@gmail.com