ORIGINAL RESEARCH

Symptomatic Avascular Necrosis in Patients with Sickle Cell Disease: Need for Acute Care Utilization, a Retrospective Study

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ABSTRACT

Objectives: Sickle Cell Disease is a disabling disease which causes Symptomatic Avascular Necrosis (AVN) of the Femur Head, causes multiple visits along with prolonged stay in hospital and finally complete damage of the major weight bearing joint of the body: The Hip Joint. Properly early diagnosis and treatment can improve quality of life. Apart from vaso - occulsion and osteonecrosis, which occurs secondary to sickling, predisposing to infection. The disease also attacks the humerus head which in its final stage causes collapse of the head and arthritis of the joint. Thus it requires careful monitoring by imaging, and timely intervention by surgical or non-surgical methods. Aim of this article is to go through the different imaging techniques and to clarify whether AVN predicts acute care utilization in adults with Sickle Cell Disease and to identify characteristics that predict higher utilization in those with AVN.

Methodology: We reviewed medical records of 37 symptomatic AVN patients of SCD and compared acute care utilization and clinical characteristics with 37 sex- and age-matched patients without symptomatic AVN of SCD. Patients with ≥2 years of follow-up were included. Outcomes were compared using multivariate regression.

Results: our study included 564 follow-up years, with a median of 2 years per patient. The group with AVN had greater median rates of urgent care visits (3.6/year vs 1.6/year; P = 0.0095), admissions (1.5/year vs 0.6/year; P = 0.0042), and admission days (6.1 days/year vs 2.8 days/year; P = 0.0057). History of acute chest syndrome (Odds Ratio 3.72; P = 0.025), pneumonia (Odds Ratio 2.20; P = 0.003), hydroxyurea therapy (Odds Ratio 2.63; P = 0.046), and long-term transfusion (Odds Ratio3.33; P = 0.064) were associated with AVN. In a median regression model, pneumonia, acute chest syndrome, and AVN were independently associated with greater urgent care visits and admissions.

Conclusions: In patients with sickle cell disease, Symptomatic AVN was found to be a risk factor for acute care utilization. As it is a potentially modifiable factor, further studies are needed to determine whether Avascular necrosis prevention/early treatment interventions will improve outcomes for patients with Sickle Cell Disease.

Keywords: Avascular necrosis, Osteonecrosis, Sickle Cell Disease.

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INTRODUCTION

Sickle Cell Disease is a disabling disease which causes Symptomatic Avascular Necrosis (AVN) of the Femur Head, causes multiple visits along with prolonged stay in hospital and finally complete damage of the major weight bearing joint of the body: The Hip Joint. It causes High Health care utilization.[1]Proper early diagnosis and treatment can improve quality of life. Apart from vaso-occulsion and osteonecrosis, which occurs secondary to sickling, predisposing to infection is also a concern. This disease also attacks the humerus head which in its final stage causes collapse of the head and arthritis of the joint. Thus it requires careful monitoring by imaging, and timely intervention by surgical or non-surgical methods. Studies of patients with SCD with varying hemoglobinopathies report humeral / femoral AVN prevalence in ranges from 5% to 32%, based on imaging and clinical diagnoses.[6-12]Actual Prevalence is Higher, It has been reported that 42% of patients had silent AVN of at least one hip when evaluated by radiography and magnetic resonance imaging.[12] AVN has been associated with a higher number of hospitalized sickle cell pain crises, irreversible organ damage, and mortality.[2,5]AVN is typically asymptomatic until late-stage disease, and so once

symptomatic, there is rapid progression to collapse[7,13–15] . Hence Surgical intervention is one of the few treatment options available for AVN.[13,16] By comparing utilization rates of hospitalization and the clinical characteristics of patients with SCD with and without AVN, our goals is to clarify whether AVN is an independent risk factor for utilization and to identify characteristics of those with AVN that predict higher acute care utilization.

METHODS

Data Collection: We retrospectively reviewed medical records at the GAYATRI VIDYA PARISHAD HOSPITAL Sickle Cell Center for Adults (SCCA) to identify all patients with SCD diagnosed as having symptomatic AVN. These patients were then individually sex and age matched (±5 years) with patients with SCD without symptomatic AVN, resulting in a total sample of 74 patients (37 patients with SCD with symptomatic AVN, and 37 patients with SCD without symptomatic AVN). Patients with chronic joint pain (femoral or humeral head) with confirmation of AVN by available imaging records (CT SCAN or MRI SCAN), were Symptomatic AVN . Cases in the study were included based on hematologist notes confirming the review of prior medical records and medical/surgical history of AVN. For controls, imaging was not consistently done but was reviewed where possible to verify that AVN was not present. . All of the patients were 18 years old or older as of January 31, 2023. For those with AVN, baseline was defined as the date of AVN diagnosis or the date of established hospital visit at the SCCA. For those without AVN, baseline was defined as the date of established visit at the SCCA. All of the patients had ≥2 years of follow-up. Data collected was on the frequency of hospital admissions and urgent care visits. Also Laboratory &clinical markers that were associated with AVN and/or high hospital utilization were recorded. Laboratory markers included hemoglobin and absolute reticulocyte count. Clinical markers included latest weight; tricuspid regurgitation peak velocity; transfusion history; hydroxyurea use; and history of cholecystectomy, pulmonary embolism, pneumonia (PNA), cerebrovascular accident, psychiatric illness, deep vein thrombosis, leg ulcer, retinopathy, substance use, chronic kidney disease and acute chest syndrome (ACS).

STATISTICAL METHODS

STATA version 13.1 (StataCorp) was used for all of the analyses. Utilization rates: total urgent care visits divided by years of follow-up and total admissions divided by years of follow-up. Wilcoxon signed rank tests, Student t tests and Pooled odds ratios (ORs) were used for bivariate analyses of cases (AVN) and controls (no AVN). Variables from significant bivariate tests ($P \leq 0.05$) and traditional AVN comorbidities were then used in a median regression risk factor model for urgent care utilization rates.

RESULTS

Data for sample characteristics of cases and controls are shown in Table 1. The sample was 59.7% female patients, with a mean age of 41 years (range 24–71 years). The study included564 follow-up years, with a median of 2 years per patient (interquartile range 1–4 years).Thirteen (18%) patients had at least 1 year without JHH encounters, which was then excluded from the respective number of follow-up years per patient. Patients with HbSS or HbSβ0 thalassemia (SS) constituted 72.5% of the sample and had a lower mean age of 36 years compared with 44 years for patients with other SCD genotypes (P = 0.0069). No other significant differences were found between cohorts regarding SCD genotype, age or sex, and follow-up period distributions also were comparable for both cohorts.

Table 1: Sample characteristics of cases (AVN) and controls (no AVN)

Variable	Total, N = 74	AVN, n = 37	No AVN, n = 37
Female sex (%)	44 (59.7)	22 (59.2)	22 (59.8)
Mean (range) years olda			
Start age	32 ± 12 (7–68)	32 ± 12 (7–61)	33 ± 12 (18–68)
End age	41 ± 11 (24–71)	41 ± 12 (24–68)	41 ± 11 (24–71)
SS genotype (%)	54(72.5)	28 (75.8)	26 (69.2)
Total follow-up years	561	279	280
Median (IQR) follow-up years per patient	2	2	2

The data for bivariate analysis of patient characteristics are shown in Tables 2 and 3.

Table: 2 Bivariate analysis of binary variables and association with AVN

Variable	OR	95% CI
SS genotype	1.44	0.71–2.83
High utilizer (≥4 visits/y)	4.27***	1.87–9.76
Cholecystectomy	1.87	0.96–3.56
ACS	3.13***	1.40–6.93
Pneumonia	3.21*	1.16–8.73

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CVA	0.81	0.31–2.03
Pulmonary embolism	1.01	0.34–2.85
Leg ulcer	1.87	0.73–4.65
DVT	2.12	0.95–4.67
Retinopathy	1.48	0.78–2.72
Chronic kidney disease	0.60	0.26–1.28
Ever used hydroxyurea	2.24*	1.15–4.29
Ever received long-term transfusion	2.34*	1.18–4.60
Psychiatric illness	1.44	0.71–2.83
Substance use	0.95	0.48–1.83

ACS, acute chest syndrome; AVN, avascular necrosis; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; OR, odds ratio; SS, Sβ0 thalassemia.
*P ≤ 0.05;
**P ≤ 0.01;
***P ≤ 0.005.

Table 3: Bivariate analysis of continuous variables and association with AVN

Variable	AVN	No AVN	*P*
Urgent care visits/y/patient	3.2 (1.1–8.1)	1.3 (0.5–3.4)	0.016
Admissions/y/patient	1.3 (0.5–2.1)	0.4 (0.1–1.2)	0.000
Admission d/y/patient	5.1 (2.3–11.9)	1.8 (0.3–5.7)	0.0007
Hemoglobin, g/dL	9.4 (8.0–10.8)	9.1 (8.1–10.5)	0.913
Absolute reticulocyte count (K/mm3)	230.7 (165.6–324.6)	255.1 (150.0–326.4)	0.988
Tricuspid regurgitation peak velocity (m/s)	2.44 (2.26–2.73)	2.32 (2.06–2.62)	0.198

There are greater rates of urgent care visits and admissions and admission days per year/per patient in the AVN cohort (Table 3, Fig.). In addition, AVN cohort has a history of high utilization (mean acute care visits per year ≥4), 2 ACS, Retinopathy, PNA, hydroxyurea therapy, and chronic transfusions (Table 2). When limiting this analysis to SS patients, not receiving long-term transfusion therapy, higher hemoglobin levels were significantly associated with AVN of Femoral Head(AVN cohort mean hemoglobin 9.4 g/dL, 95% confidence interval [CI] 8.3–9.0; no AVN cohort mean hemoglobin 9.1 g/dL, 95% CI 7.5–8.6; P = 0.043). In a regression model controlling for comorbidities and genotype, ACS, AVN and PNA were independently associated with a greater number of urgent care visits and admissions per year (Table 4). Within the AVN cohort, the mean age at symptomatic AVN diagnosis was lower for SS patients than for those with other genotypes, 27 years old as compared with 38 years old, respectively. Of 44 individuals in the cohort, 12 (28%) individuals had symptomatic femoral head AVN only, 7 (17%) individuals had symptomatic humeral head AVN only, and 24 (55%) individuals had both symptomatic femoral and humeral head AVN. The median number of affected joints was three. Twenty-Four (55%) individuals had at least one surgical intervention for AVN, and 31 (30%) had more than one operation. We did not find a statistically significant association between number of affected joints, rates of utilization and type of affected joint, nor history of surgical intervention respectively. In addition, type of affected joint was not associated with Sickle cell Disease genotype. Of those who underwent surgical correction, 37 (77%) were operated upon during the follow-up period. When comparing history of hydroxyurea therapy, patients with AVN who had used it had greater mean urgent care visits per year (4.8/year vs 1.8/year; P < 0.0001) and greater mean admissions per year (1.7/year vs 0.48/year; P < 0.0001) than those who never used hydroxyurea. When the analysis was limited to SS patients (hydroxyurea is primarily indicated for patients with SS disease), showing an association between AVN and using hydroxyurea (OR 2.5, 95% CI 0.970–6.443; P = 0.058).

DISCUSSION

Increased findings that AVN is the single main orthopaedic cause for acute care utilization among sickle cell disease patients, has raised many questions regarding the current prevention, diagnosis, and treatment of AVN in patients with SCD. Based on our knowledge, this is one of the prime studies to specifically examine AVN as a predictor of acute healthcare utilization events. Although there are vast number of studies which have broadly examined rising SCD healthcare utilization and costs, only few have evaluated specific predictors of utilization among these patients, especially of adults and the subset identified as high users.[2–5,17–23] A bivariate analysis of 25 patients with SCD with femoral head AVN who were age and sex matched with 26 patients with SCD without AVN, for 1 year duration, found a significantly higher mean number of admissions, for patients diagnosed as having femoral head AVN.[7] Our analysis expands upon these findings by affirming the presence of AVN (humeral or femoral)

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as an independent predictor of acute care utilization in a larger cohort, with a longer follow-up period. Regarding acute complications, the finding that ACS and PNA independently predict greater utilization rates also affirms previous findings.[5]The association found between ACS/PNA and AVN suggests that AVN may be a marker of more severe disease. The findings that AVN cohort patients who, ever used hydroxyurea therapy and/or chronic transfusions were more prevalent and that patients with AVN who had ever used hydroxyurea had greater acute care utilization rates than those with AVN without hydroxyurea history, supports this hypothesis. When comparing utilization rates of the AVN cohort to thos e without AVN, our average rates appear to be lower than previously reported.[3] A 1-year study specifically comparing patients with SCD with AVN to those without AVN reported even higher admission rates for both the AVN and no-AVN cohorts.[6] It is possible that our average rates are due to a different study population or due to some other factors which needs further research. The utility of SCD genotype as a predictor of AVN requires further investigation.[24] Although we did not find differences in AVN prevalence among SCD genotypes, AVN tends to develop later in life for other genotypes.[8,11] These data support the need for early intervention options in children and young adults. Hematological markers are also important clinical predictors of AVN. Regarding hemoglobin and hematocrit, studies report varying degree of associations with AVN. Some studies report associations between higher hematocrit and/or hemoglobin for SS patients and femoral head AVN.[8,25] A smaller study also examining age- and sex-matched AVN and no-AVN cohorts did not find any difference in hematocrit levels.[6] Similarly, in our study sample we did not find meaningful differences in hemoglobin levels between those with and without AVN. Although we used rigorous criteria, for determining steady-state values, sample size and the retrospective design made it difficult to control for possible effects from and hydroxyurea therapy, transfusions and comorbid chronic kidney disease. Although our study supports the need for early predictors of AVN in SCD, to improve prevention and early diagnosis. The paucity of data on interventions, that effectively slow progression, limits pote ntial benefits of early monitoring. A full discussion of management options is outside the scope of this study, but our findings underscore the importance of further investigation of optimal management strategies for AVN in SCD. The treatment of AVN in SCD is not standardized.[16] Operative and no operative treatments have been described with variable success rates.[26] Savage et al highlighted major evidence gaps in AVN management longitudinal studies to determine predictors of AVN at a younger age, randomized controlled trials to evaluate safety and efficacy of physical therapy versus surgical intervention at different stages of AVN, and comparative studies of the incidence and prevalence of AVN among different types of SCD.[24] Regarding operative treatment, more than half of the AVN group had at least one surgical intervention indicated for AVN, because surgery remains one of the few treatment options. Unfortunately, AVN with SCD as the underlying etiology, is associated with worstTHR outcomes and has higher revision rates than all-cause revision rates.[16,26–28] The interpretation of these results were challenging because of the sample size, the unknown effects of surgery on utilization, the variation in the number of years with data before and following the year of surgery per patient, the variation in type of surgery (eg, core decompression, arthroplasty), prior treatments, and other unknown influences on utilization from comorbidities or a history of multiple AVN-indicated surgeries. More research is needed to prospectively evaluate utilization outcomes after surgery as well as optimal timing for surgical intervention. There are several limitations to our study like underestimate of admissions and acute visits because we missed visits that occurred outside our study center. The retrospective nature of our study limited our ability to standardize the characterization of AVN in our inclusion criteria. For example, because we do not routinely screen asymptomatic patients in our center, negative imaging was not available for all of the controls. We mean, that some control patients may have AVN that has not yet been clinically detected and/or diagnosed, so our analysis and conclusions are limited to symptomatic AVN. Lastly pain is another important factor associated with SCD, AVN and utilization, As such because of the retrospective nature of our study, we could not directly examine associations among pain, AVN, and utilization. Despite these limitations, we collected available data on different types of affected joints, number of affected joints and AVN-specific surgical interventions in an attempt to characterize features of SCD and AVN that may be associated with higher utilization. Though we could not determine meaningful associations between these characteristics and acute care utilization rates, our analyses raised important questions concerning the definition and use of AVN as a marker for acute care utilization in SCD patients. Prospective studies should specifically examine AVN severity, features of AVN itself, or treatments that may modulate acute care utilization in SCD patients. The cost of treating or not treating AVN is high, and our study raises the question of how we can better prevent AVN in SCD and support those living with this chronic, debilitating complication.[21] To improve long-term outcomes, including acute care utilization, efficacious measures for preventing and/or slowing AVN progression in SCD must be identified.

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CONCLUSIONS

In patients with sickle cell disease, Symptomatic AVN was found to be a risk factor for acute care utilization. As it is a potentially modifiable factor, further studies are needed to determine whether vascular necrosis prevention/early treatment interventions will improve outcomes for patients with Sickle Cell Disease.

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