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Trends in Sickle-Cell-Disease-Related Priapism in U.S. Children's Hospitals

Hsin-Hsiao Scott Wang, MD, MPH¹, Katherine W. Herbst, MS², Jennifer A. Rothman, MD³, Nirmish R. Shah, MD^{3,4}, John S. Wiener, MD^{1,3}, and Jonathan C. Routh, MD, MPH^{1,3}

¹Department of Surgery, Duke University Medical Center, Durham, NC

²Department of Urology, Connecticut Children's Medical Center, Hartford, CT

³Department of Pediatrics, Duke University Medical Center, Durham, NC

⁴Department of Medicine, Duke University Medical Center, Durham, NC

Abstract

Objective—To define rates of priapism diagnosis and inpatient admission among males with SCD.

Methods—We retrospectively reviewed the Pediatric Health Information System database for males aged <21 years treated 2004–2012. We identified patients with SCD and priapism based on ICD-9-CM diagnosis codes. Logistic regression and generalized estimating equation models were used to control for confounding and to adjust for within-hospital clustering of similar patients.

Results—We identified 17,186 males who were admitted 137,710 times during the study period. Of these, 362 (2.1%) were diagnosed with priapism on 748 admissions. There was a significant decrease in the number of priapism admissions among patients with SCD over time (0.81% in 2004 to 0.44% in 2012, $p < 0.001$). The number of patients diagnosed with SCD-related priapism varied over time without a statistically significant trend (2.3% in 2004, 2.69% in 2008, 1.01% in 2012, $p = 0.34$). Rates of priapism admissions (0–4.4%) varied widely between hospitals. Older patient age was associated with an increased likelihood of a priapism admission in the multivariate logistic regression model after adjusting for treatment year, hospital region, and for hospital-level clustering of similar patients.

Conclusions—From 2004–2012, the number of admissions for SCD-related priapism declined while the number of individual patients diagnosed with SCD-related priapism did not. Rates of priapism-related admissions in males with SCD vary widely among PHIS hospitals.

Keywords

Sickle Cell Disease; Priapism; Epidemiology; Urology; Clinical Care Variation

Corresponding Author: Jonathan C. Routh, MD, MPH, Division of Urologic Surgery, Duke University Medical Center, DUMC 3831, Durham, NC 27710, (919) 684-6694, FAX (919) 681-5507, jon.routh@duke.edu.

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INTRODUCTION

Priapism is a common urologic complication of sickle cell disease (SCD) and is often anecdotally cited as one of the more difficult clinical problems encountered by pediatric urologists. SCD is estimated to account for up to 65% of all priapism episodes occurring in children,^{1, 2} and up to 89% of men with SCD report experiencing at least one priapism episode before age 20 years.³ The exact pathophysiology of priapism in SCD is unclear. However, the most likely etiology is dysfunction within the nitric oxide pathway that leads to hypoxia with sickling of erythrocytes and eventual sludging of blood within the corpora cavernosa.^{1, 4} Importantly, a significant portion of male patients with SCD will experience stuttering priapism at some point during their lifetime;^{3, 5} these children are at high risk of long-term morbidity, particularly erectile dysfunction.^{6, 7}

The aim of this study was thus to describe temporal trends in the diagnosis and treatment of priapism in males with SCD in United States children's hospitals.

PATIENTS AND METHODS

Data Source

Data for this study was obtained from the Pediatric Health Information system (PHIS) database, an administrative database that contains inpatient, emergency department, ambulatory surgery, and observation encounter-level data from over 44 not-for-profit, tertiary care pediatric hospitals in the United States. These hospitals are affiliated with the Children's Hospital Association (Overland Park, KS). Data quality and reliability are assured through a joint effort between the Children's Hospital Association and participating hospitals. Portions of the data submission and data quality processes for the PHIS database are managed by Truven Health Analytics (Ann Arbor, MI). Data are de-identified at the time of data submission, and data are subjected to a number of reliability and validity checks before being included in the database. We excluded hospitals without complete billing and pharmacy data throughout the entire course of the study; 10 hospitals were excluded for this reason. In total, complete data from 34 hospitals were included in this study.

Patients and Outcomes

We identified all inpatient hospital encounters occurring between January 2004 and December 2012 (inclusive) for males under 21 years of age with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code for sickle cell disease (282.41, 282.42, 282.5, 282.60-282.69). Priapism was defined in 2 different ways in this analysis:

- 1) Patient-level analysis. Patients who had a diagnosis code for priapism (607.3) during the study period were defined as having a history of priapism beginning with their index admission with priapism at a PHIS hospital. For patients without a history of priapism, the index admission was defined as the first SCD admission at a PHIS hospital.
- 2) Admission-level analysis. Because priapism is a dynamic state, priapism admissions were defined as occurring if the patient had a diagnosis code for

priapism during that admission only. These data were then used to generate analyze temporal trends in priapism diagnoses among patients with SCD.

Approximate resource utilization was estimated based on hospital billing records. Of note, PHIS data include hospital charges only; physician reimbursements (both within the hospital and within the clinic) are not necessarily captured. Pharmacy data was obtained via review of pharmacy billing codes based on use during inpatient admissions, ambulatory medical or surgical short-stay visits, or emergency department visits, but not during routine outpatient clinic visits.

Statistical Methods

Initial bivariate tests of association were performed using Fisher's exact, Cochran-Armitage trend, or Wilcoxon rank-sum tests as appropriate based on data characteristics and distribution. These were performed on both a per-patient and per-admission basis. Based on these results, logistic (priapism episodes) and negative binomial (charge and length of stay) regression models were constructed to further examine trends after adjusting for possible confounding effects. Model covariates were chosen based on biological plausibility and/or a bivariate p-value of 0.2 or less on initial bivariate analysis. Other covariates entered into our final model included patient age, year of admission, U.S. census region, and the individual hospital at which a patient was treated. Model diagnostics revealed no significant violations of regression assumptions. Generalized estimating equations were used to adjust for hospital- and patient-level clustering. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). All tests were two-sided and p-values of less than 0.05 were considered significant.

This study was deemed exempt from review by our institutional review board, and administrative approval was obtained from PHIS prior to data collection or analysis.

RESULTS

Cohort Demographics

We identified 17,186 males with SCD who were admitted to 34 PHIS hospitals a total of 137,710 times between 2004 and 2012 (median 9 admissions to PHIS hospitals per patient, range 1-180). Ten hospitals were excluded for incomplete billing data during the study period. The mean (SD) age at first SCD admission to a PHIS hospital was 7.9 ($\pm$ 6.1) years. Table 1 shows the demographic characteristics of the cohort, by priapism history.

Trends in Priapism Diagnosis

Among the study cohort, 362 patients (2.1% of all patients with SCD) were admitted with priapism at least once. These patients were admitted 748 times over the study period (median 2, range 1-32 admissions per patient, Table 2). Patients with a diagnosis of priapism at/during admission were older than those without priapism (10.2 versus 7.9 years, $p<0.001$). Patients with a history of priapism were more likely to receive hydroxyurea during any inpatient stay (41% versus 16%, $p<0.001$). On multivariable analysis based on SCD admissions, a diagnosis of priapism was associated with increased patient age ($p<0.001$) and hydroxyurea use ($p<0.001$) after adjusting for hospital- and patient-level clustering.

There was a significant decrease in the proportion of priapism admissions to PHIS hospitals among patients with SCD over time (0.81% in 2004 to 0.44% in 2012, $p<0.001$, Figure 1). The number of patients admitted with SCD-related priapism varied over time without a statistically significant trend (2.3% in 2004, 2.69% in 2008, 1.01% in 2012, $p=0.34$, Figure 1). Rates of priapism admission (0-4.4%) varied widely among hospitals (Figure 2).

Economic Impact of Sickle-Cell Related Priapism

The median length of stay of patients with a history of priapism (regardless of priapism diagnosis during a given hospitalization) was 2 days (interquartile range, 1-4 days). In the multivariate model, earlier treatment year ($RR=0.96$ per year, $p<0.005$), older age ($RR=1.02$ per year, $p<0.001$), and hospital location in the western United States (versus Midwest, $RR=1.94$, $p<0.001$) were associated with longer hospital stays.

After adjusting for treatment year, age, hospital region, and hospital clustering, the median inpatient hospital charge per hospitalization among patients with a history of priapism was higher than those who had never been diagnosed with priapism (\$8,397 versus \$6,358, $p<0.001$). Total billed charges were not significantly different for patients with priapism as compared to patients who did not have priapism ($p=0.49$).

DISCUSSION

Our review of PHIS hospital data found that, although there was significant variation in the number of patients with SCD diagnosed with priapism over the study period, there was an interesting decline in admissions for priapism. Furthermore, we found increased use of hydroxyurea, longer admissions, and higher associated cost in patients with SCD and a history of priapism.

In our cohort of males with SCD, admissions more often occurred for teenagers aged 12-18 years (44.6%), similar to previous reports.^{3, 8} Interestingly, we found that there was a significant decline in the number of admissions for SCD-related priapism (0.8% to 0.4%, $p<0.001$ for trend), but not for the number of individual patients diagnosed with SCD-related priapism (~2% throughout the study period, $p=0.34$ for trend). Rates of priapism diagnoses and admissions in males with SCD varied widely among PHIS hospitals.

Thus in recent years, males with SCD are not necessarily more or less likely to develop priapism, but they are less likely to be admitted to the hospital for priapism. This would seem to imply that outpatient management strategies may be increasingly effective or increasingly implemented among patients with SCD. These could include preventative outpatient medication regimens and/or clinic interventions not requiring admission. Likewise, the wide variation among PHIS hospitals in rates of priapism admissions would seem to imply that some centers are being more effective at implementing these strategies than others.

Interestingly, we observed an association between rates of SCD-related priapism and inpatient hydroxyurea use. However, it is important to note that the PHIS database does not capture outpatient pharmacy data; as such, the inpatient hydroxyurea use we capture may or

may not be associated with outpatient use or adherence prior to or after priapism diagnosis or treatment. Although we were unable to identify if patients were taking hydroxyurea before or after admission, based on the available literature it seems unlikely that increased hydroxyurea use leads to increased priapism. We therefore hypothesize that while the effectiveness of hydroxyurea on preventing priapism may be minimal, hydroxyurea may have been more frequently initiated by clinicians in males with SCD who were admitted for priapism. Given the likely reticence of practitioners to intervene operatively for SCD-related priapism in children and that priapism has been associated with other SCD sequelae, it is logical that maximum medical therapy would be initiated in priapic patients with a history of SCD.⁹⁻¹¹

Perhaps unsurprisingly, the treatment-related costs of males with SCD who had a history of priapism were higher than those who never had priapism (\$8,397 versus \$6,358, $p<0.001$). Interestingly, this increased cost persisted regardless of whether patients had a priapism diagnosis during a specific hospitalization. Whether this persistence is related to increased disease severity, noncompliance, or some other factor is unclear.

This study's results should be interpreted in light of its limitations. The PHIS database is derived from not-for-profit, tertiary-care children's hospitals; thus our patient population may not be typical of patients or treatment patterns seen at other hospital types. Likewise, there are no data available on presentation of patients to non-PHIS hospitals, nor are there data on outpatient management or pharmacy use. As such, it is unclear whether our results are generalizable to the wider community. Additionally, PHIS does not capture data from ambulatory clinics, nor does it capture treatment rendered before patients are referred to a PHIS hospital. Therefore, it seems likely that at least some of our included priapism patients who were only treated in ER may not have been captured. However, PHIS does capture data from PHIS hospital satellite and ambulatory surgical centers, which may better represent non-hospital-based ambulatory settings.

Our analysis relies on the accuracy of the diagnostic and procedure codes included in PHIS; while the accuracy level of PHIS is high for an administrative database, it is possible that at least some portion of our cohort may be incorrectly coded. However, the PHIS database is rigorously monitored and audited for coding accuracy and, therefore, represents a reasonably reliable panorama of the characteristics of its patients. Lastly, we had limited knowledge of the clinical details of any particular patient in terms of their outpatient treatments and outcomes. This lack of temporal specificity restricted our ability to evaluate the diagnosis and management of priapism in males with SCD.

There are likely to be unmeasured confounders influencing our results. Informal sensitivity analyses were performed to estimate the influence of specific confounders, either measured or unmeasured. We are reassured by the lack of significant changes in the effect estimates in the model after adjusting for other associated variables. This finding implies that, although residual confounding may yet be present, it is unlikely to have a substantial effect on our reported results.

CONCLUSIONS

From 2004 to 2012, there was a significant decline in the total number of PHIS hospital admissions for SCD-related priapism but not in the number of individual patients admitted with SCD-related priapism. Rates of priapism-related admissions in males with SCD vary widely among PHIS hospitals, although this clinical variation does not appear to influence the likelihood of patients being admitted or treated for priapism.

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Figure 1.
Rate of priapism diagnosis admissions across PHIS hospitals, 2004-2012

Figure 2.
Rate of priapism diagnoses among all SCD admissions across PHIS hospitals

Table 1

Patient Demographics

Characteristics	Priapism	No Priapism	p value
Number of patients	362	16,824	
Age in years (mean, SD)	10.2 (5.3)	7.9 (6.1)	<0.001 ^a
Patient Age, By Category			<0.001 ^b
0-1 years	7(2%)	1,592(9%)	
1-3 years	12(3%)	2,123(13%)	
3-6 years	25(7%)	2,420(14%)	
6-12 years	89(25%)	4,268(25%)	
12-18 years	158(44%)	4,664(28%)	
18-21 years	71(20%)	1,757(10%)	
Treatment year			0.21 ^b
2004-2007	76(21%)	4,014(24%)	
2008-2011	286(79%)	12,810(76%)	
Hospital region			0.01 ^b
Northeast	41(11%)	1,799(11%)	
Midwest	125(35%)	4,629(28%)	
South	168(46%)	9,130(54%)	
West	28(8%)	1,265(8%)	
Length of Stay (median, IQR)	2 (1-4)	1 (1-3)	<0.001 ^c
Charges (median, IQR in US dollars)	8,397 (3,323-2,2804)	6,358 (2,122-15,067)	<0.001 ^c

Abbreviations:

^a p-value from t-test^b p-value from chi-square test^c p-value from Wilcoxon rank-sum test

Table 2

Average SCD admission and patient priapism diagnoses by year

Year	2004	2005	2006	2007	2008	2009	2010	2011	2012
SCD admissions	9,880	11,020	10,836	15,434	15,694	18,705	17,907	18,409	19,824
Mean SCD admissions/hospital	291	324	319	454	462	550	527	541	583
Priapism admissions	80	86	75	55	89	69	101	106	87
Mean priapism admissions/hospital	0.81%	0.78%	0.69%	0.36%	0.57%	0.37%	0.56%	0.58%	0.44%