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Overactive Bladder in Adults with Sickle Cell Disease

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Abstract

Aims—To characterize the prevalence and impact of nocturnal enuresis and overactive bladder (OAB) symptomatology in the adult sickle-cell disease (SCD) population.

Methods—We performed a single-center, cross-sectional study of adult SCD patients from October 2012 to February 2014, using the validated Pfizer OAB short form questionnaire and brief voiding history surveys. Patient responses and scores were compared to that of controls having normal or sickle cell trait hemoglobin genotypes.

Results—A group of 239 SCD patients (116 males, 123 females) were compared with 104 normal and 57 sickle cell trait patients. Seven of 239 (2.9%) SCD patients compared to none of the 161 patients without SCD ($p = 0.04$) reported current nocturnal enuresis. The median age of nocturnal enuresis cessation was higher in SCD patients (12.0, IQR 9.0–15.0 yrs) compared to that of both normal (7.5, IQR 6.0–9.8 yrs) and sickle cell trait (7.5, IQR 6.0–8.8) groups ($p < 0.0001$). Ninety-three of 239 (38.9%) SCD patients compared to 17 of 104 (16.3%) normal and 11 of 57 (19.3%) sickle cell trait had scores indicating OAB symptomatology ($p < 0.0001$). Patients with SCD had higher OAB symptom severity and lower Health-Related Quality of Life scores compared to the normal and sickle cell trait groups ($p < 0.0001$ and $p < 0.0001$, respectively).

Conclusions—We demonstrate an elevated rate of nocturnal enuresis and OAB symptoms in the adult SCD population. An OAB phenotype may be an under-recognized complication of SCD irrespective of age.

Keywords

prevalence; nocturnal enuresis; epidemiology; quality of life; population-based

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INTRODUCTION

Urinary symptoms such as nocturnal enuresis and overactive bladder (OAB) symptoms (i.e. nocturia, urinary frequency, urgency and urinary incontinence) have been clinically observed in the pediatric population with sickle cell disease (SCD).¹⁻¹² Nocturnal enuresis, defined as bedwetting during sleep more frequently than twice weekly for at least 3 months in individuals older than 5 years of age,¹³ is recognized in the pediatric SCD population. Prevalence rates between 20–69% have been estimated in this population, far exceeding rates observed in children without SCD.^{1, 3, 5-8, 14} Nocturia, frequent voiding at nighttime, also occurs commonly in children with SCD, with rates of this condition noted to be as high as 68%.¹ Although these conditions have been estimated to lessen in frequency as patients with SCD enter young adulthood¹⁴, their prevalence rates are still estimated to exceed that of the non-SCD population at comparable ages.^{2, 11}

Perspectives on urinary symptoms in the pediatric SCD population have recently been broadened with a revelation that this population manifests an OAB phenotype. In a sample of children and adolescents up to 17 years of age with SCD, urinary frequency and urgency were reported in 32% and 34% of individuals, respectively, more than 3-fold higher than the rate of a control group.¹¹ In this same report, daytime urinary incontinence was observed in 23% of patients with SCD, exceeding the control group rate by more than 2-fold.¹¹

Despite the emergence of the OAB phenotype as an important clinical problem in the pediatric SCD population, little is known regarding the extent of this problem and its correlates in the adult SCD population. We hypothesized that adult patients with SCD manifest dysfunctional voiding similar to that seen in the pediatric SCD population. Here, we present the first characterization of nocturnal enuresis and OAB in a large group of adult SCD patients.

METHODS

Study Design

We performed a cross-sectional study of adult patients presenting to the Sickle Cell Unit, an outpatient center, University of the West Indies, Kingston, Jamaica from October 2012 to February 2014. The study group included patients ≥ 17 years of age with a diagnosis of SCD (SS, SC, S β^0 , SO Arab hemoglobinopathy). Patients were compared to a convenience sample of similarly-aged controls recruited from the University of the West Indies campus population. Control groups were separately patients with normal (AA) and sickle cell trait (AS) hemoglobin genotypes. Individuals in the study and control groups were enrolled without specification regarding presence or absence of urinary symptoms. Patients with active genitourinary tract infections or malignancy or overt neurological disorder were excluded.

Patients completed the self-administered, validated Pfizer Overactive Bladder short form questionnaire (OAB-q SF)^{15, 16} along with voiding and SCD history surveys (Fig. S1). Those scoring ≥ 12 were classified as potentially having OAB symptomatology. Symptom severity and health-related quality of life (HRQL) scores were transformed to a 0 to 100-

point scale. Higher symptom severity scores are indicative of greater symptom severity or bother while higher HRQL scores are indicative of greater HRQL. Current enuresis was defined as bedwetting during sleep more frequently than twice weekly for at least 3 months.¹³

Ethical approval was granted by the Ethics Committee at the University of the West Indies, Kingston, Jamaica (ethics approval number ECP 71, 13/14).

Statistical Analysis

Demographics, characteristics, and scores of the SCD group were compared to those of the sickle cell trait and normal groups. Means $\pm$ standard deviations along with median and interquartile ranges (IQR) were determined. Categorical data were compared using the Chi Square test or Fisher's Exact test where appropriate. Quantitative data were evaluated using the Kruskal-Wallis nonparametric test to compare all three groups. Multiple comparisons between specific groups were performed using the Wilcoxon rank sum test with application of Bonferroni's correction to control for type 1 error. Odds ratios were determined using multivariable logistic regression analysis and presented with corresponding 95% confidence intervals (CI). Data were analyzed using Stata 11 (StataCorp, College Station, Texas, USA) and GraphPad Prism 5 (GraphPad Software, Inc, La Jolla, CA, USA). A *P*value < 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Of the 400 patients enrolled, 239 (59.8%) had SCD (median age 31.0, IQR 24.0–38.0 years) while 104 (26%) normal (median age 23.0, IQR 21.0–38.0 years) and 57 (14.3%) sickle cell trait (median age 32.0, IQR 28.0–38.0 years) comprised the control groups. The majority of the 239 SCD patients were hemoglobin SS genotype (78.7%), followed by hemoglobin SC (13.8%), hemoglobin S β^0 (6.7%), and hemoglobin SO Arab (0.8%) genotypes. Additional demographic information and SCD complication histories are described in Table I. Multiple comparisons between specific groups are available in Table SI.

Nocturnal Enuresis

Current nocturnal enuresis was reported by a significantly greater proportion of SCD patients (all having SS hemoglobinopathy) compared to patients without SCD ($p = 0.04$) (Table I). Subgroup age analysis of SCD patients showed that 4 of 23 (17.4%) aged 17–20, 1 of 52 (1.9%) aged 21–25, 1 of 39 (2.6%) aged 26–30, and 1 of 48 (2.1%) aged 31–35 reported current enuresis. There was no difference in reported past nocturnal enuresis when specifically comparing the SCD and normal patient groups ($p = 0.82$). Among those reporting a past history of enuresis, the median age of nocturnal enuresis cessation was higher in SCD patients (12.0, IQR 9.0–15.0 years) compared to that of both normal (7.5, IQR 6.0–9.8 years) and sickle cell trait (7.5, IQR 6.0–8.8 years) groups ($p < 0.0001$).

OAB Symptomatology, Symptom Severity, and HRQL

SCD patients had a nearly two-fold higher rate of having OAB symptomatology compared to both the normal and sickle cell trait groups ($p < 0.0001$) (Table I). The median OAB symptom severity score was also higher in SCD patients (13.3, IQR 3.3–30.0) compared to both the normal (6.7, IQR 0–13.3) and sickle cell trait (3.3, IQR 0–13.3) groups ($p < 0.0001$). Finally, the median OAB HRQL score was significantly lower in SCD patients than that of the other groups ($p < 0.0001$) (Table I).

SCD Complications and OAB

The relationship between several SCD complications and OAB symptomatology was also studied. An association was demonstrated between a history of priapism and the presence of OAB as significantly more SCD patients with OAB reported a history of priapism than those without OAB ($p = 0.0405$). No other significant associations were found regarding other complications (Table II).

Logistic regression analysis demonstrated that the SCD group had an odds ratio of 3.13 for having OAB (Table IIIA). Among patients with SCD, those who were female, or had vaso-occlusive or priapic complications had a nearly 2-fold or greater risk of having OAB symptomatology (Table IIIB).

DISCUSSION

Urinary symptoms, specifically nocturnal enuresis, are well-investigated in the pediatric SCD population. However, investigations of voiding disturbances in adults with SCD are lacking. Here, we present the first study examining the prevalence and severity of several aspects of these dysfunctions in an exclusively adult SCD population. We found that adult SCD patients had a higher rate of nocturnal enuresis and older age of its cessation in those reporting past nocturnal enuresis compared to control groups without SCD. Additionally, the rate, severity, and risk of OAB symptomatology were greater and HRQL was worse among SCD patients than those without SCD.

Nearly 3% of all adult patients with SCD reported current nocturnal enuresis, higher than previously estimated 0.5% for a comparably-aged adult population.¹⁷ Given the expected decrease in nocturnal enuresis from a high prevalence in childhood to near absence in adulthood in the general population,¹⁸ it is remarkable to find that these symptoms exist with high prevalence in the SCD compared to the non-SCD adult population. Interestingly, all of these SCD patients had hemoglobin SS genotypes. Readett et al. found a significantly higher rate of nocturnal enuresis among patients with homozygous SS compared to either hemoglobin SC and normal genotypes, which we also found. Based on this understanding, the pathophysiology of OAB and nocturnal enuresis generally in the SCD population may be related to the homozygous SS variant. However, our sample size of patients with homozygous SC variant was small. Further investigation may better establish the correlations between nocturnal enuresis and SCD subtypes.

Although there was no appreciable difference in the reported history of past nocturnal enuresis between groups, there was an age-related difference in the cessation of this

symptom, with SCD patients having a substantially higher mean age than that of other groups. This notable finding coincides with the persistently increased prevalence rates of nocturnal enuresis described among later age-groups of children with SCD compared to those without SCD.¹⁴ Our finding of current nocturnal enuresis in 17% of SCD patients aged 17–20 is nearly identical with the reported nocturnal enuresis rate in a similar age group (age 16–20 years) in a systematic review by Wolf et al.¹⁴ Additionally, we provide new data demonstrating a current nocturnal enuresis rate of approximately 2% in multiple age groups beyond age 20, suggesting that a basal rate persists into middle adulthood.

The prevalence rates of OAB based on identified OAB symptomatology in the non-SCD groups (16.3% and 19.3%) are similar to previously described estimates in the general population.^{19–21} Nearly 40% of patients with SCD were identified as having OAB or some component thereof, indicating the alarming frequency of this condition. As we demonstrated, patients with SCD demonstrated over a 3-fold higher risk of OAB symptomatology than the normal and sickle cell trait groups. Additionally, we demonstrated female gender to be a risk factor for OAB in our study sample. Although it has not been generally described as so in previous OAB studies, we confirmed it to be an independent risk factor in a separate analysis of the normal patient group (not shown). Notably, age was not a significant risk factor, likely because of the lack of younger and older study patients, age groups that tend to manifest these symptoms. Although the median ages were statistically significantly different between the study groups, logistic regression analysis demonstrated that this study variable was not an independent risk factor for OAB symptomatology in these observed groups.

The etiopathogenesis of OAB and nocturnal enuresis in SCD is unknown. Current proposed theories regarding SCD-associated nocturnal enuresis include low kidney concentrating ability, low functional bladder capacity or high nocturnal bladder over-activity, high sensory arousal thresholds, and sleep-disordered breathing.¹⁴ Recent investigations in a mouse model of SCD suggest aberrations in nitric oxide (NO) regulatory signaling as a common pathophysiologic mechanism for these derangements of the lower genitourinary tract (Anele and Burnett, unpublished). This theory would be supported by our findings of a nearly 3-fold higher risk of OAB among SCD patients with priapism, for which NO dysregulation is understood to be a principal molecular mechanism.^{22, 23} The significantly decreased NO bioavailability,²⁴ and thus dysregulation, found in SCD may also offer a mechanism for the increased OAB symptomatology identified in the SCD compared to non-SCD groups. The 2-fold higher risk of OAB found among SCD patients with vaso-occlusive crises may also be demonstrative of this NO dysfunction. Associations have been shown between the compensatory vaso-dilatory mechanisms involving both initially increased NO demand and eventual arginine (an NO precursor) depletion and the vaso-occlusive crises in patients with SCD compared to both normal patients and SCD patients without vaso-occlusive crises.^{25–28} Further investigations may serve to clarify the pathophysiologic mechanism of this disorder.

Urinary symptoms, specifically OAB, in the SCD adult population is likely clinically under-recognized. Often these issues, if addressed at all, are given low priority in relation to the multitude of other complications associated with SCD.²⁹ Additionally, patient embarrassment or acclimation to urinary symptoms ongoing from childhood may contribute

to the failure to address these issues during clinical encounters. Given this deficiency and the poorly understood etiology of these dysfunctions, these issues can be left undermanaged. However, they clearly affect the quality of life of patients with SCD as demonstrated by their decreased range of HRQL scores compared to that of the non-SCD groups. We must note that the statistically significant differences found between groups may not represent clinical significance. The magnitude of the difference in symptom severity scores between SCD and non-SCD groups was found to be greater than that of the HRQL scores. While symptom severity can inversely influence quality of life, the two are not necessarily linearly related. Notably, patients with chronic diseases, specifically SCD, may report a worse health status yet similar well-being compared to the general population when not actively experiencing high levels of pain or disease complications.³⁰⁻³³ It is hoped that this investigation promotes clinician awareness and, accordingly, heightens efforts to improve study and management of these conditions.

We acknowledge certain limitations of this study. Although we excluded patients reporting absence of active genitourinary tract infections or malignancy, we did not perform further screening procedures such as urinalysis or urinary cytology. Patient recall may contribute bias regarding the reported extent of past nocturnal enuresis and the age of its cessation. We realize the OAB-q SF is primarily used as a measure of symptom severity rather than a screening tool for OAB.^{15, 16} However, its use in our evaluation of OAB symptomatology is meant to highlight the relative, rather than absolute, differences between observed groups. The use of voiding diaries along with a clinical evaluation of symptomatology and diagnosis of OAB may have established more detailed findings, specifically regarding the nature of the symptoms comprising OAB. Finally, we acknowledge the role of medical co-morbidities such as obesity and diabetes as possibly confounding risk factors associated with OAB that were not adjusted for in our logistic regression analysis.³⁴

This report represents the first characterization of OAB and nocturnal enuresis in a large sample of adults with SCD. Our findings indicate that the rate of nocturnal enuresis is elevated in the adult SCD population compared to those without SCD. Additionally, OAB symptomatology appears to be quite common and is manifest with relatively high severity in adult patients with SCD. Adult patients with SCD have an over 3-fold higher risk of OAB symptomatology compared to those without SCD. Our data are also suggestive of an association between priapism history and OAB. This finding lends support for a more generalized lower genitourinary system dysfunction, possibly mediated by NO dysregulation, in the SCD population that extends beyond erection disorders. OAB may be an under-recognized complication of SCD that exists irrespective of age.²⁹

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I

Demographic and voiding variables among all patient groups

Characteristic	SCD (n=239)	SCt (n=57)	Normal (n=104)	P-Value*
Median Age, yrs (IQR)	31.0 (24.0–38.0)	32.0 (28.0–38.0)	23.0 (21.0–38.0)	0.0031
Gender, n (%)				
Male	116 (48.5)	13 (22.8)	49 (47.1)	0.0017
Female	123 (51.5)	44 (77.2)	55 (52.9)	
Past Enuresis, n (%)	95 (39.7)	9 (15.8)	40 (38.5)	0.0027
Current Enuresis, n (%)	7 (2.9)	0 (0)	0 (0)	0.0449 [†]
Median Age of Enuresis Cessation, yrs (IQR) [‡]	12.0 (9.0–15.0)	7.5 (6.0–8.8)	7.5 (6.0–9.8)	<0.0001
OAB, n (%)	93 (38.9)	11 (19.3)	17 (16.3)	<0.0001
Median Age, yrs (IQR)	31.0 (24.0–40.0)	35.0 (27.0–39.0)	22.0 (21.0–26.5)	0.0041
Gender, n (%)				
Male	37 (39.8)	3 (27.3)	4 (23.5)	0.3546
Female	56 (60.2)	8 (72.7)	13 (76.5)	
OAB Symptom Severity, median (IQR)	13.3 (3.3–30.0)	3.3 (0.0–13.3)	6.7 (0.0–13.3)	<0.0001
OAB HRQL, median (IQR)	95.4 (86.2–96.9)	96.9 (92.3–100.0)	98.5 (95.4–100.0)	<0.0001

SCD = sickle cell disease, SCt = sickle cell trait, n = number, yrs = years, IQR = interquartile range OAB = overactive bladder, HRQL = health-related quality of life,

[†] compared SCD to all non-SCD patients

[‡] responses not reported by 7 SCD and 1 SCt patients,

* represents comparison of all 3 groups

Table II

Association of OAB with SCD complications

SCD Complication	Patients with OAB	Patients without OAB	P-Value
	n = 93	n = 146	
Vaso-occlusive crisis, n (%)	70 (75.3)	99 (67.8)	0.2166
	n = 93	n = 146	
Leg Ulcer, n (%)	21 (22.6)	22 (15.1)	0.1405
	n = 93	n = 146	
Necrosis, n (%)	4 (4.3)	1 (0.7)	0.0768
	n = 37	n = 79	
Priapism [†] , n (%)	23 (62.2)	33 (41.8)	0.0405
	n = 93	n = 146	
Stroke, n (%)	2 (2.2)	2 (1.4)	0.6436

SCD = sickle cell disease, n = number, OAB = overactive bladder,

[†] males only

Table III**A Logistic regression analysis for odds of having OAB among all groups**

	OR (95% CI)	P-Value
Years in Age	1.01 (0.99–1.03)	0.478
Female Gender [†]	1.97 (1.23–3.14)	0.005
Sickle Cell Trait [‡]	1.13 (0.48–2.66)	0.785
Sickle Cell Disease [‡]	3.13 (1.73–5.66)	0.000
Current Enuresis	4.28 (0.77–23.75)	0.096
Past Enuresis	1.44 (0.89–2.32)	0.134

B Logistic regression analysis for odds of having OAB among SCD group

	OR (95% CI)	P-Value
Years in Age	1.01 (0.99–1.03)	0.314
Female Gender [†]	1.93 (1.20–3.10)	0.007
Current Enuresis	5.80 (0.98–34.38)	0.053
Past Enuresis	1.46 (0.90–2.36)	0.125
Complications		
Vaso-Occlusive Crisis	2.40 (1.52–3.79)	0.000
Leg Ulcer	1.94 (0.95–3.94)	0.068
Stroke	2.78 (0.35–22.00)	0.334
Necrosis	5.88 (0.60–57.72)	0.128
Priapism [*]	2.62 (1.10–6.26)	0.030

OAB = overactive bladder, SCD = sickle cell disease OR = odds ratio,

[†]referenced to males,

[‡]referenced to normal group

^{*} separate analysis performed including only males