Published in final edited form as:

Urology. 2008 July ; 72(1): 81–84. doi:10.1016/j.urology.2008.02.006.

Enuresis Is a Common and Persistent Problem Among Children and Young Adults with Sickle Cell Anemia

Joshua J. Field, Paul F. Austin, Ping An, Yan Yan, and Michael R. DeBaun

Department of Internal Medicine; Division of Urology, Department of Surgery; Division of Statistical Genomics; Department of Genetics; and Departments of Pediatrics, Biostatistics, and Neurology, Washington University School of Medicine, St. Louis, Missouri

Abstract

OBJECTIVES—Enuresis and nocturia are common among children with sickle cell anemia (SCA). The objectives of this study were to describe the prevalence of enuresis and nocturia among children and young adults with SCA and determine the relationship, if any, between these symptoms and SCA-related morbidity.

METHODS—A prospective infant cohort of African-American children with SCA was previously established from the Cooperative Study for Sickle Cell Disease. Included in this cohort were children with SCA enrolled before 6 months of age for whom questions about enuresis and nocturia had been completed.

RESULTS—A total of 213 participants were included in this analysis. Sixty-nine individuals (33%) experienced enuresis over the course of the study. No children under 6 years of age were asked about enuresis. Thereafter, enuresis was most prevalent between the ages of 6 and 8 years (42%) and continued to be common in young adults ages 18 to 20 years (9%). Seventy-nine percent of individuals reported a history of nocturia. There was no association between enuresis or nocturia and an increased rate of pain or acute chest syndrome (ACS) episodes.

CONCLUSIONS—Enuresis and nocturia are common in children with SCA. Among adults with SCA, enuresis and nocturia are more persistent compared with adults in the general population. Enuresis and nocturia are not associated with an increased rate of pain or ACS.

Enuresis and nocturia are common problems for individuals with sickle cell anemia (SCA).^{1,2} Prevalence estimates of enuresis in children with SCA range from 20% to 69%,^{1–7} whereas nocturia has been described in up to 68% of children with SCA.¹ Among the general pediatric population, the prevalence of enuresis at age 5 years is 15%,⁸ and the prevalence of nocturia is 40% in children ages 6 to 11 years.⁹ The prevalence of enuresis and nocturia decreases with age in the general population, and in young adults enuresis and nocturia are present in 1% to 2% and 3%, respectively.^{10,11} The reason why enuresis and nocturia are more common in SCA is not well defined. Multiple factors may contribute to the underlying mechanism of enuresis and nocturia among individuals with SCA including a decreased ability to concentrate urine and a low maximum functional bladder capacity.^{1,12}

Sickle cell anemia is one of the most common genetic diseases in the United States, affecting 1 in 600 African-American births.¹³ Vaso-occlusion due to rigid sickle erythrocytes causes many of the complications associated with SCA. SCA-related morbidities attributable to vasoocclusion include pain and acute chest syndrome (ACS)

episodes. Many authors postulate that vaso-occlusion may be important in the development of enuresis and nocturia among children with SCA; however, the relationship between enuresis and nocturia and vaso-occlusive complications has not been firmly established.^{1,5}

Several studies have reported the prevalence of enuresis and nocturia among children with SCA; however, few data exist describing how the prevalence of enuresis and nocturia changes as children become young adults. In a cross-sectional study of 987 children with SCA, Mabiala Babela *et al.* reported a 59% prevalence of enuresis in children ages 5 to 10 years, which decreased to 16% at 16 years of age.⁵ Few studies have reported the prevalence of enuresis among young adults with SCA. Furthermore, the relationship between enuresis and SCA-related complications such as pain and ACS is not well defined. A prospective cohort study of children with SCA (n = 281) noted more visits for illness from males with enuresis ($P = 0.03$), but not females.⁶ However, these data have not been validated in other cohorts.

The objective of this study was to describe the prevalence of enuresis and nocturia in children and young adults with SCA, and, if present, whether these abnormalities are associated with an increased rate of vaso-occlusive complications (pain and ACS episodes).

MATERIAL AND METHODS

The Cooperative Study for Sickle Cell Disease (CSSCD) was a prospective, multi-center study conducted from 1978 to 1998 to determine the natural history of SCA.¹⁴ CSSCD was conducted in three phases. Phase 1 of the study was the enrollment phase; 4085 newborns, children, adolescents, and adults were enrolled. Baseline demographic data including past medical history, physical examination, and laboratory values were obtained. Phase 2 and 3 were designed to follow the participants in phase 1 for up to 10 years. Thereafter, CSSCD participants were monitored on an annual basis with a physical examination and a standardized history form that included questions about enuresis and nocturia. Guidelines of human subject committees at participating clinical centers, including Washington University, were followed when obtaining consent and assent.

We identified infants enrolled in the follow-up phase of CSSCD before 6 months of age. This cohort was selected to increase the length of follow-up and thus provide more reliable morbidity data. All subjects were African American with hemoglobin SS, referred to as SCA. From this cohort of 408 children, 213 children and young adults (52%) answered questions about enuresis and nocturia (Fig. 1). The CSSCD did not provide explanations for those who did not complete the questionnaire. Categorical responses (yes or no) to these questions were used for the analysis. The questions were as follows. Does the patient currently have a problem with enuresis (bedwetting)? Does the patient get up during the night to urinate?

We determined prevalence data from a cross-sectional analysis of the number of children and young adults with SCA reporting symptoms of enuresis or nocturia at a particular age.

Definitions

We defined enuresis as a current problem with bedwetting, and nocturia as symptoms of increased urination at night. We defined a painful episode as pain in the extremities, back, abdomen, chest, or head for which no other explanation other than SCA could be found, lasting for at least 2 hours and leading to a clinic visit.¹⁵ ACS was defined as a new pulmonary infiltrate demonstrable on chest radiograph or perfusion lung scan, or pleuritic chest pain with an abnormal perfusion lung scan.¹⁶

Data Analysis

We entered data into a database and analyzed them. We compared the counts of pain and ACS episodes among individuals with and without enuresis and in those with and without nocturia by the Poisson regression. We analyzed pain and ACS episodes that occurred after parents responded to the enuresis or nocturia questions. Then we used the corresponding follow-up times as the offset, adjusting for age, white blood cell count, percent fetal hemoglobin, and hemoglobin. Overdispersion was accounted for by using negative binomial distribution. To avoid any distributional assumption of data, we also used the model Pearson Chi-square divided by its degree of freedom as the overdispersion parameter estimate. We used SAS software V 9.1 (Cary, NC) for data analysis.

RESULTS

Baseline Characteristics

From this infant cohort composed of 408 children, 213 children with SCA answered sleep-related questions on the yearly CSSCD history form (Fig. 1). The cohort was composed of 54% males. Questions were first asked at a mean age of 11.4 ± 2.8 years. The mean follow-up after the questions were asked was 2.8 years.

Prevalence of Enuresis and Nocturia Among Children and Young Adults with Sickle Cell Anemia

The overall prevalence of enuresis in our cohort was 33%. Enuresis became less common with age, but was still prevalent in young adults (Fig. 2). A total of 42% of children between 6 and 8 years of age reported enuresis. The prevalence fell to 36% in children between 8 and 10 years of age, 30% between the ages of 10 and 12 years, 25% between the ages of 12 and 14 years, 18% between the ages of 14 and 16 years, 11% between the ages of 16 and 18 years, and 9% between the ages of 18 and 20 years. Difficulties with nocturia persisted into adulthood to a greater degree than enuresis. Seventy-nine percent of individuals in the cohort reported a history of nocturia. Nocturia was reported by 64% of children between the ages of 6 and 8 years, 71% between the ages of 8 and 10 years, 69% between the ages of 10 to 12 years, 71% between the ages of 12 and 14 years, 69% between the ages of 14 and 16 years, 68% between the ages of 16 and 18 years, and 61% between the ages of 18 and 20 years.

Frequency of Enuresis and Nocturia Episodes Among Children and Young Adults with Sickle Cell Anemia and Enuresis

Among children and young adults with SCA who reported episodes of enuresis or nocturia, the events occurred frequently (Table 1). For those participants with enuresis, only 10% reported less than 1 episode of enuresis per month, whereas 35% reported more than 21 episodes per month. In participants with nocturia, only 3% reported less than 1 episode per month, whereas 49% reported more than 21 episodes per month. We determined frequency of enuresis and nocturia from first report of symptoms.

Enuresis and Nocturia and Sickle Cell Anemia–Related Morbidity

When individuals who reported enuresis were compared with those who did not report enuresis, there was no difference in the rate of pain ($P = 0.83$) or ACS ($P = 0.44$). Similarly, the rate of pain or ACS in individuals who reported nocturia did not differ from those who did not report nocturia: $P = 0.35$ and $P = 0.52$, respectively (Table 2). When adjusted for established covariates associated with pain and ACS (age, white blood cell count, hemoglobin, and percent fetal hemoglobin), there was no difference in the rate of pain between individuals with and without enuresis ($P = 0.79$) or nocturia ($P = 0.20$). The

adjusted rate for ACS also did not achieve statistical significance when we compared individuals with and without enuresis ($P = 0.73$) or nocturia ($P = 0.77$).

COMMENT

The natural history of enuresis and nocturia in children and young adults with SCA and the relationship of these complications to morbidity are poorly defined. Our study supports previous reports of the higher prevalence of enuresis and nocturia among children and young adults with SCA compared with the general population. We also found that the prevalence of enuresis declines throughout childhood, but continues to be a persistent problem for many young adults with SCA. Unlike enuresis, the prevalence of nocturia remains relatively constant throughout childhood and young adulthood (Fig. 2).

The mechanism underlying the increased rate of enuresis among children with SCA is not clearly delineated. Previously, repetitive infarcts to the renal medulla were thought to be responsible for the high prevalence of enuresis in children with SCA. These infarcts purportedly affected the ability of the kidney to concentrate urine, resulting in a form of nephrogenic diabetes insipidus and subsequent high urine volumes.¹ However, when Readett *et al.* compared the urine osmolality of enuretic children with SCA with those without enuresis, they did not find a significant difference in urine osmolality after a water deprivation test. Instead, the authors reported that children with SCA and enuresis had a lower maximum functional bladder capacity compared with phenotype-, age-, and gender-matched controls.¹² Furthermore, other factors may contribute to enuresis among children with SCA, such as social and environmental factors and decreased arousal during sleep.¹²

Few studies have examined therapeutic interventions for enuresis or nocturia in children with SCA. Figueroa *et al.* studied desmopressin acetate in a group of 10 children with SCA and enuresis.⁷ Enuretic episodes resolved in 4 participants and improved in 2 more children. Although the results suggest a benefit for desmopressin acetate, no definitive conclusions can be drawn from this small observational study. Further studies are needed to elucidate more carefully the pathogenesis of enuresis and nocturia in SCA, and afterward, therapeutic studies aimed at potential targets can be conducted.

In our study, we examined one potential etiology of enuresis and nocturia among individuals with SCA, vasoocclusion–related morbidity. Previous studies have not rigorously examined the relationships among SCA-related morbidity, such as pain and ACS episodes, and enuresis and nocturia. Participants in our cohort were observed for an average of 2.8 years after enuresis was reported and we did not find an increased rate of pain or ACS episodes in children or young adults with enuresis or nocturia compared with those without enuresis or nocturia. Despite these negative findings, enuresis and nocturia may still be due to SCA-related factors. Other morbidities common in individuals with SCA, such as pulmonary hypertension, leg ulcers, and priapism, are not clearly associated with pain and ACS episodes.^{17,18}

As expected in a cohort study that was not designed specifically to address the prevalence of enuresis, there are limitations to our study. Although the International Children's Continence Society broadly defines enuresis as intermittent incontinence while sleeping, enuresis is typically categorized as monosymptomatic (no history of lower urinary tract symptoms, excluding nocturia, and without a history of bladder dysfunction) and non-monosymptomatic enuresis (often due to bladder overactivity).¹⁹ Owing to our study design, we could not determine whether lower urinary tract symptoms were present in our study population. The ability to classify enuresis into monosymptomatic and non-monosymptomatic is important for understanding the mechanism of enuresis in this

population. Another limitation of our study is that many children who were eligible for our cohort did not complete the questions related to enuresis and nocturia on the annual history form, and thus selection bias may have influenced our results. The CSSCD was an observational, natural history study and individuals who did not complete all study-related activities were still included in the analysis. Finally, our prevalence data were determined with a cross-sectional as opposed to longitudinal design. Cross-sectional prevalence data may reflect differences between individuals in the cohort instead of changes within an individual over time. In this study, we did not perform a longitudinal analysis because there were too few individuals with repeated responses to the questionnaire. Despite these limitations, our study provides evidence suggesting that enuresis and nocturia are a problem not only for children with SCA, but also for adults.

CONCLUSIONS

Enuresis is prevalent among children with SCA, and continues to be prevalent throughout early adulthood. Although we did not find evidence that enuresis was associated with SCA-related morbidity, the impact of enuresis on the quality of life for adolescents and young adults could be significant. Given the high prevalence of enuresis in this population, more formal studies are required to address the etiology of enuresis and potential targets for therapeutic interventions.

Acknowledgments

Sponsored by National Heart, Lung, and Blood Institute Grants HL079937 (MRD) and K12 HL08710 (JIF).

References

1. Noll JB, Newman AJ, Gross S. Enuresis and nocturia in sickle cell disease. *J Pediatr*. 1967; 70:965–967. [PubMed: 6026121]
2. Kwak KJ, Scott RB, Ferguson AD. Studies in sickle-cell anemia. XXXIV. Observations on enuresis in childhood and nocturia in adults. *Clin Pediatr (Phila)*. 1969; 8:344–346. [PubMed: 5770267]
3. Barakat LP, Smith-Whitley K, Schulman S, et al. Nocturnal enuresis in pediatric sickle cell disease. *J Dev Behav Pediatr*. 2001; 22:300–305. [PubMed: 11718233]
4. Suster G, Oski FA. Enuresis in sickle cell anemia. *Am J Dis Child*. 1967; 113:311. [PubMed: 6019449]
5. Mabiala Babela JR, Loumingou R, Pemba-Loufoua A, et al. Enuresis in children with sickle cell disease. *Arch Pediatr*. 2004; 11:1168–1172. [PubMed: 15475271]
6. Readett DR, Morris JS, Serjeant GR. Nocturnal enuresis in sickle cell haemoglobinopathies. *Arch Dis Child*. 1990; 65:290–293. [PubMed: 2334206]
7. Figueroa TE, Benaim E, Griggs ST, et al. Enuresis in sickle cell disease. *J Urol*. 1995; 153:1987–1989. [PubMed: 7752379]
8. Forsythe WI, Redmond A. Enuresis and spontaneous cure rate: study of 1129 enuretics. *Arch Dis Child*. 1974; 49:259–263. [PubMed: 4830115]
9. Neveus T, Cnattingius S, Olsson U, et al. Sleep habits and sleep problems among a community sample of schoolchildren. *Acta Paediatr*. 2001; 90:1450–1455. [PubMed: 11853345]
10. Jalkut MW, Lerman SE, Churchill BM. Enuresis. *Pediatr Clin North Am*. 2001; 48:1461–1468. [PubMed: 11732125]
11. Schatzl G, Temml C, Schmidbauer J, et al. Cross-sectional study of nocturia in both sexes: analysis of a voluntary health screening project. *Urology*. 2000; 56:71–75. [PubMed: 10869627]
12. Readett DR, Morris J, Serjeant GR. Determinants of nocturnal enuresis in homozygous sickle cell disease. *Arch Dis Child*. 1990; 65:615–618. [PubMed: 2378519]
13. Motulsky AG. Frequency of sickling disorders in U.S. blacks. *N Eng J Med*. 1973; 288:31–33.

14. Gaston M, Rosse WF. The cooperative study of sickle cell disease: review of study design and objectives. *Am J Pediatr Hematol Oncol.* 1982; 4:197–201. [PubMed: 7114401]
15. Platt OS, Thorington BD, Brambilla DJ, et al. Pain in sickle cell disease: rates and risk factors. *N Engl J Med.* 1991; 325:11–16. [PubMed: 1710777]
16. Castro O, Brambilla DJ, Thorington B, et al. The acute chest syndrome in sickle cell disease: incidence and risk factors. The Cooperative Study of Sickle Cell Disease. *Blood.* 1994; 84:643–649. [PubMed: 7517723]
17. Gladwin MT, Sachdev V, Jison ML, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. *N Engl J Med.* 2004; 350:886–895. [PubMed: 14985486]
18. Kato GJ, McGowan V, Machado RF, et al. Lactate dehydrogenase as a biomarker of hemolysis-associated nitric oxide resistance, priapism, leg ulceration, pulmonary hypertension, and death in patients with sickle cell disease. *Blood.* 2006; 107:2279–2285. [PubMed: 16291595]
19. Neveus T, von Gontard A, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. *J Urol.* 2006; 176:314–324. [PubMed: 16753432]

Figure 1.
Enrollment in the sickle cell anemia cohort and eligibility for study cohort.

Figure 2.
Prevalence of enuresis and nocturia among children and young adults with sickle cell anemia, from ages 6 to 20 years.

Table 1

Frequency of enuresis and nocturia among children and young adults with sickle cell anemia

Patients	213
Patients with enuresis (%) *	143 (67)
<1 episode/month (%)	14 (10)
1–7 episodes/month (%)	43 (30)
8–14 episodes/month (%)	16 (11)
15–21 episodes/month (%)	20 (14)
>21 episodes/month (%)	50 (35)
Patients with nocturia (%) *	168 (79)
<1 episode/month (%)	5 (3)
1–7 episodes/month (%)	35 (21)
8–14 episodes/month (%)	32 (19)
15–21 episodes/month (%)	14 (8)
>21 episodes/month (%)	82 (49)

* Participants who reported a history of enuresis or nocturia at any time during the study.

Table 2

Rate of pain and acute chest syndrome episodes among children and young adults with sickle cell anemia with and without the symptoms of enuresis and nocturia

Morbidity/ symptom	Pain episodes/year			ACS episodes/year		
	Yes	No	Significance	Yes	No	Significance
Enuresis	0.79	0.83	0.83	0.18	0.13	0.44
Nocturia	0.81	0.61	0.35	0.15	0.11	0.52