Enuresis and Hyperfiltration in Children with Sickle Cell Disease

Rima Zahr[1], Juan Ding[2], Guolian Kang[3], Winfred Wang[2], Jane Hankins[2], Kenneth Ataga[4], Jeffrey Lebensburger[5], and Jerlym Porter[2]

[1]The University of Tennessee Health Science Center
[2]St Jude Children's Research Hospital
[3]St.Jude Children's Research Hospital
[4]University of Tennessee Health Science Center
[5]University of Alabama-Birmingham

January 31, 2024

Abstract

Background Nocturnal enuresis is a common symptom in children with sickle cell disease (SCD). Risk factors for development of enuresis are currently unknown. An early manifestation of SCD-associated kidney damage is glomerular hyperfiltration. We test the hypothesis that in a pediatric SCD cohort, individuals with hyperfiltration are more likely to have nocturnal enuresis when compared to children without hyperfiltration. Procedures To assess the relationship between nocturnal enuresis and hyperfiltration, we retrospectively evaluated children with SCD enrolled in the Evaluation of Nocturnal Enuresis and Barriers to Treatment among Pediatric Patients with SCD study (PEESC; NCT01959958) and prospectively identified children who reported nocturnal enuresis and were enrolled in the longitudinal cohort study Sickle Cell Clinical Research and Intervention Program (SCCRIP, NCT02098863). Results Nocturnal enuresis occurred in 46.5% of PEESC participants and was more frequent in participants with HbSS/HbSβ0-thalassemia and in male participants. We did not identify an association between hyperfiltration from three to five years of age with the later development of enuresis. Hyposthenuria was not associated with enuresis. Conclusions Severe SCD genotypes and male sex were associated with nocturnal enuresis after age 5 years. However, we could not identify additional renal or hematologic predictors associated with the diagnosis of nocturnal enuresis. Future studies should incorporate non-renal risk factors into studies that predict development of enuresis.

Enuresis and Hyperfiltration in Children with Sickle Cell Disease

Rima S. Zahr, DO[1], Juan Ding, Ph.D[2], Guolian Kang, Ph.D[2], Winfred C. Wang, MD[3],

Jane S. Hankins, MD[3], Kenneth I. Attaga, MD[4], Jeffrey D. Lebensburger, DO[5]and Jerlym S. Porter, Ph.D[6].

[1]Division of Pediatric Nephrology and Hypertension, University of Tennessee Health Science Center, Memphis, TN,

[2]Department of Biostatistics, St. Jude Children's Research Hospital, Memphis, TN

[3]Department of Hematology, St. Jude Children's Research Hospital, Memphis, TN

[4]Center for Sickle Cell Disease, University of Tennessee Health Science Center, Memphis, TN

[5]Division of Pediatric Hematology and Oncology, University of Alabama at Birmingham, Birmingham, AL

[6]Department of Psychology, St. Jude Children's Research Hospital, Memphis, TN

Correspondence:

Rima S. Zahr, 49 N. Dunlap Street, Suite 321 Memphis, TN 38105.

Email: rzahr@uthsc.edu

Phone (901) 287-7814

Word Count: 2360

Main Text: 2360

Tables: 1

Figures: 2

Running Title: Enuresis in Children with Sickle Cell Disease

Key Words : Sickle Cell Disease, Hyperfiltration, Enuresis

Abbreviation	Full Term
SCD	Sickle cell disease
GFR	Glomerular filtration rate
eGFR	Estimated glomerular filtration rate
GEE	Generalized estimating equation
LDH	Lactose dehydrogenase
SCCRIP	Sickle Cell Clinical Research and Intervention Program
PEESC	The Evaluation of Nocturnal Enuresis and Barriers to Treatment among Pediatric Patients with Sickle Ce

Abstract

Background

Nocturnal enuresis is a common symptom in children with sickle cell disease (SCD). Risk factors for development of enuresis are currently unknown. An early manifestation of SCD-associated kidney damage is glomerular hyperfiltration. We test the hypothesis that in a pediatric SCD cohort, individuals with hyperfiltration are more likely to have nocturnal enuresis when compared to children without hyperfiltration.

Procedures

To assess the relationship between nocturnal enuresis and hyperfiltration, we retrospectively evaluated children with SCD enrolled in the Evaluation of Nocturnal Enuresis and Barriers to Treatment among Pediatric Patients with SCD study (PEESC; NCT01959958) and prospectively identified children who reported nocturnal enuresis and were enrolled in the longitudinal cohort study Sickle Cell Clinical Research and Intervention Program (SCCRIP, NCT02098863).

Results

Nocturnal enuresis occurred in 46.5% of PEESC participants and was more frequent in participants with HbSS/HbSβ^0-thalassemia and in male participants. We did not identify an association between hyperfiltration from three to five years of age with the later development of enuresis. Hyposthenuria was not associated with enuresis.

Conclusions

Severe SCD genotypes and male sex were associated with nocturnal enuresis after age 5 years. However, we could not identify additional renal or hematologic predictors associated with the diagnosis of nocturnal enuresis. Future studies should incorporate non-renal risk factors into studies that predict development of enuresis.

Introduction

In children without sickle cell disease (SCD), nocturnal enuresis, defined as discrete episodes of urinary incontinence during sleep occurring at age five years or older[1], occurs more frequently in males[2], in children with a family history of nocturnal enuresis, in children with abnormal sleep patterns, and in children with a low socioeconomic status[3]. Prior studies have demonstrated that nocturnal enuresis is a common comorbidity for children and adolescents with SCD, affecting 20-58% of this population[4-6].

Glomerular hyperfiltration and hyposthenuria are two early manifestations of SCD kidney disease, but it is unclear if they are associated with the later development of enuresis[7-9]. Hyperfiltration refers to a supraphysiologic elevation in the glomerular filtration rate (GFR); hyposthenuria is defined by the inability to concentrate urine to >500 mOsmoles during overnight water deprivation[8, 10, 11]. A previous clinical trial, BABY HUG, which randomized young children (mean age 13 months) with sickle cell anemia (HbSS/HbSβ^0-thalassemia) to receive either placebo or a fixed dose of hydroxyurea (20 mg/kg/day) for two years, established normative values of measured GFR for the 75$^{\text{th}}$ and 95$^{\text{th}}$ percentiles in a young cohort and demonstrated that 50-70% of young children with sickle cell anemia experience hyposthenuria[10].

Prior cross-sectional studies have evaluated laboratory markers of kidney disease at the time nocturnal enuresis was reported. However, the pathology that contributes to the development of nocturnal enuresis likely occurs over time rather than at a single time point. Therefore, we suggest that it is biologically plausible that nocturnal enuresis diagnosed at age 5 years and above may result from clinical and subclinical kidney injury which occurs earlier in childhood. We hypothesized that young children who experience hyperfiltration or hyposthenuria between three to five years of age would be more likely to be diagnosed with nocturnal enuresis after age five years. To test this hypothesis, we performed a longitudinal analysis of laboratory evaluations from patients who were enrolled in two studies at St. Jude Children's Research Hospital. In addition, because no studies have evaluated the impact of nocturnal enuresis on future kidney disease, we performed a secondary longitudinal analysis to determine if patients with and without nocturnal enuresis had different trajectories in eGFR after five years of age.

Methods

Study Population : We identified children and adolescents with SCD enrolled in two cohort studies at St. Jude Children's Research Hospital: The Evaluation of Nocturnal Enuresis and Barriers to Treatment among Pediatric Patients with Sickle Cell Disease (PEESC; NCT01959958) and the Sickle Cell Clinical Research and Intervention Program (SCCRIP, NCT02098863)[12]. PEESC is a single center study of the epidemiologic, psychosocial, medical, and sociodemographic determinants of nocturnal enuresis and barriers to successful intervention among children and adolescents with SCD aged 6-17 years. SCCRIP is a longitudinal clinical cohort study of sickle cell patients which collects data to determine the incidence, prevalence, and severity of SCD complications and adverse health conditions within SCD[12]. The SCCRIP study does not collect data on nocturnal enuresis but does prospectively collect laboratory data of kidney function. The PEESC study identified patients with nocturnal enuresis and SCCRIP provided longitudinal follow-up on laboratory data before and after nocturnal enuresis was diagnosed.

Participants provided informed consent for these two studies, both of which were approved by the Institutional Review Board at St. Jude Children's Research Hospital. Eligibility criteria for PEESC enrollment were a diagnosis of SCD and age 6-17 years.

Definitions: For our primary outcome measure, we identified patients enrolled in PEESC who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for nocturnal enuresis[1]. We analyzed patients according to two groups: 1) "Lifetime Enuresis" if either caregiver or patient reported the patient having nocturnal enuresis in the past and/or currently and 2) "Current Enuresis" (a subset of Lifetime Enuresis) if the caregiver or patient reported the patient having nocturnal enuresis at the time of enrollment. We categorized participants as having or not having nocturnal enuresis in each of these groups.

For our predictor variables, we obtained patient age, sickle cell disease type, and exposure to sickle cell modifying therapy (hydroxyurea and chronic transfusion therapies) prior to age 3 years. We collected the mean values of height, weight, and laboratory results from annual visits between three and five years of age.

We determined mean white blood cell count, hemoglobin, platelet count, absolute reticulocyte count, lactose dehydrogenase (LDH) and serum creatinine from these visits. The eGFR was determined by the mean eGFR measured at 3.0-4.9 years old using the Schwartz formula[13]. We defined hyperfiltration as a mean eGFR >75thpercentile in this cohort[10]; which resulted in an eGFR threshold of > 133 cc/min/1.73m^2 for eGFR. Hyposthenuria was defined by a random urine specific gravity < 1.010[9, 14]. For our longitudinal analysis, we abstracted calculated eGFR, urine specific gravity, and hemoglobin from every annual visit.

Statistical analysis: The descriptive statistics of this study were summarized using frequencies for categorical variables and mean and standard deviation (SD) for continuous variables. Normality of data was evaluated by the Shapiro-Wilk test. Continuous data were compared by either two-sample t-tests or the Wilcoxon rank sum tests and categorical data were compared between the two groups by the Fisher exact test. Univariate and multivariate logistic regression models were used to assess the associations between covariates and lifetime enuresis or current enuresis. The generalized estimating equation (GEE) was used to assess the association of hyperfiltration and hyposthenuria with current enuresis for repeated data analysis. For the 45 patients with current enuresis, we included age, sex, and SCD type in the GEE model. For all analyses, p <0.05 was considered statistically significant.

Results

Study Population :

We identified 217 pediatric patients with SCD enrolled in both the SCCRIP and PEESC studies (Table 1); 151 (70%) had sickle cell anemia (HbSS, HbSβ^0 thalassemia) and 109 (50%) participants were female.

Risk factors associated with a diagnosis of Lifetime Enuresis:

One hundred and one (46.5%) children reported nocturnal enuresis after age five. Male participants had a higher risk of enuresis after age five (Odds Ratio (OR): 2.1, Confidence Interval (CI): 1.2-3.6, p=0.008). Neither the means of eGFR or mean urine specific gravity collected from ages three to five were associated with a subsequent diagnosis of nocturnal enuresis after age five years. Among laboratory values, a higher mean hemoglobin value between the ages of three to five (OR: 0.73, 95% CI: 0.55-0.95, p=0.02) was a protective factor and remained a protective factor (OR: 0.75, 95% CI: 0.56-0.99, p=0.042) when adjusted for sex. Mean WBC, platelet count, mean corpuscular volume, absolute reticulocyte count, LDH, and total bilirubin between the ages of three to five age were not associated with nocturnal enuresis. No association was observed between nocturnal enuresis and chronic transfusion prior to age 3 (p= 0.11) or hydroxyurea treatment prior to age 3 (p= 0.33)

Risk factors associated with a diagnosis of Current Enuresis :

In participants with current enuresis, a subset of lifetime enuresis group, 45 (21%) children continued to have recurrent symptoms of nocturnal enuresis. The prevalence of nocturnal enuresis decreased with age. We identified 30% of 6–8-year-olds, 21% of 9–12-year-olds and 19% of 13–15-year-olds as currently having nocturnal enuresis (Figure 1). In univariate analyses, currently having nocturnal enuresis was associated with sickle cell anemia (HbSS, HbSβ^0thalassemia) (OR 2.33, 95% CI 1.07-5.69, p=0.04), age (OR 0.88, 95%CI, 0.79-0.97, p=0.011), and HbF (OR, 1.09, 95% CI 1.03-1.16, p=0.006). Children with hyposthenuria had lower odds of currently having nocturnal enuresis (OR 0.34, 95% CI 0.11-0.89, p=0.04). After adjusting for age and sickle cell type, hyposthenuria remained associated with current enuresis (OR 0.27, 95% CI 0.08-0.75, p=0.019).

Impact of Current Enuresis on long term outcomes:

We performed repeated data analysis to determine the impact of currently having enuresis on longitudinal kidney outcomes using a GEE approach. In a univariate analysis, children with current enuresis had increased odds of having sickle cell anemia (OR: 2.33 95% CI: 1.02-5.34, p=0.045). Children with current enuresis were identified with higher odds of having higher eGFR values (OR 1.07, CI 1.1-1.12, p=0.014) and categorized as having hyperfiltration (OR 1.01, CI 1.0-1.02, p=0.038) (Figure 2) when adjusted for age and sex in the

model. When SCD type was added to the model of age and sex, the association between current enuresis and either eGFR or hyperfiltration (eGFR: OR: 1.05, 95% CI: 0.99-1.10, p=0.085; hyperfiltration: OR: 1.01, 95%CI: 1.00-1.02, p=0.11) was no longer statistically significant. Children with current enuresis maintained an average lower hemoglobin and an average higher LDH over time (OR: 0.92, CI: 0.85-0.98, p=0.016 and OR 1.03, CI: 1.01-1.06, p=0.0017), which remained significant after adjusting for age and sex (OR:0.91, CI: 0.84-0.99, p=0.027 and OR 1.03, CI:1.01-1.06, p=0.0048, respectively). Again, when including SCD type in the GEE model, this association was no longer significant.

Discussion

This study confirms prior epidemiologic reports that nocturnal enuresis defined by DSM criteria is highly prevalent in children with SCD and occurs more commonly in males.[4, 5, 15-17] We currently have a poor understanding of why nocturnal enuresis occurs with high prevalence in patients with sickle cell anemia or what the potential risk factors for nocturnal enuresis are and if they might lead to targeted interventions. Therefore, we attempted to identify risk factors occurring under age 5 that might predict the development of nocturnal enuresis after age 5 years. Our primary hypothesis was that hyperfiltration early in life would be associated with nocturnal enuresis; however, we did not identify a difference in eGFR values occurring at age 3-5 years between participants with and without subsequent nocturnal enuresis. Interestingly, in univariate analysis of the longitudinal evaluation of eGFR after age 5, we did find that patients with enuresis had higher GFR levels. However, when including the very strong predictor of sickle cell genotype in the model, this association was no longer statistically significant. Nevertheless, these results suggest the need for future research into the impact of hyperfiltration, and other possible later renal effects that an early extreme elevation of eGFR might case later in life. Also, questions regarding the age at which pathologic differences in GFR occur and the adequacy of current methodology in detecting early renal dysfunction need to be addressed. Understanding the timing of when we can detect differences in kidney function, especially in young patients, is important for the design of future therapeutic interventions.

It is well-established that children with SCD develop hyposthenuria[9]. While it seems plausible that poor concentration of the urine is associated with enuresis, our study, using urine specific gravity as a biomarker for hyposthenuria, did not find this association. This result is consistent with a prior study that found no difference in maximum urinary concentration in individuals with SCD with and without enuresis[5].

More severe anemia or tubular exposure to free heme is associated with poor kidney outcomes[18]. We found that a lower hemoglobin was associated with an increased probability of currently having enuresis, when adjusted for age and sex. However, because hemoglobin and SCD type are closely correlated, the association with anemia was not significant when SCD type was included in the model. Earlier studies have shown that acute anemic episodes are a risk factor for the development of acute kidney injury in individuals with SCD[19] and hemolysis results in an increase in cell free hemoglobin and heme, which are known nephrotoxins[20]. It is possible that the release of heme during episodes of red blood cell lysis perpetuates damage to the nephron early in childhood, which later clinically presents as nocturnal enuresis. As this study evaluated mean hemoglobin levels over a two-year period, we could not determine the impact of acute anemic or hemolytic events on the development of enuresis.

Children who reported ongoing symptoms of nocturnal enuresis were more likely to have initiated hydroxyurea treatment at a younger age then those who did not. Additionally, these children had a higher fetal hemoglobin (HbF). These participants were probably initiated on hydroxyurea at a younger age due to having more severe disease[21]. A previous study noted that children on regular transfusion therapy were less likely to report current enuresis when compared to those not receiving transfusion[22]. We also assessed whether transfusion therapy prior to age 3 years would protect against enuresis but could not confirm it. Until a clear link between sickle cell pathology in the kidney and outcomes is demonstrated, the role of renoprotective interventions in ameliorating enuresis will remain uncertain.

Our study had several limitations. First, we relied on participants and family members to recall past symptoms of enuresis. We did not ask at what age enuresis started and therefore did not have a comprehensive

and accurate trajectory of this symptom. Second, we did not assess the specific gravity of the first morning urine after a water deprivation test, but instead utilized a random urine sample at the time of a patient visit. Future studies should evaluate hyposthenuria using a water deprivation test; however, acceptance of this test may be limited outside the setting of a clinical trial. Finally, in children without sickle cell disease, nocturnal bladder overactivity, sleep disordered breathing, neurological dysfunction and adverse psychological events are associated with nocturnal enuresis[6]. One previous report in children with sickle cell disease found that a lower functional bladder capacity was associated with nocturnal enuresis[23]. In our study, we did not evaluate these associations; however, these measurements could be incorporated into future studies as patients with sickle cell disease are known to have a higher prevalence of pulmonary, central nervous system, and psychologic complications.

Our study aimed to correlate early kidney findings with the development of nocturnal enuresis. However, eGFR and urine specific gravity early in life did not identify patients at risk for developing nocturnal enuresis. Overall, sickle cell genotype and male gender remained the strongest predictors of enuresis. Therefore, future research should focus on additional mechanisms and risk factors that could contribute to the high prevalence of nocturnal enuresis in children with sickle cell anemia. Due to the overall high prevalence of nocturnal enuresis, we recommend that children with SCD should be assessed for nocturnal enuresis, particularly in males and those with severe anemia. Future studies are still needed to determine the pathology of nocturnal enuresis in sickle cell patients and whether treatment using sickle cell-modifying therapies and additional behavioral interventions will reduce the risk of this frequent problem.

Conflict of Interest Statements:

JDL receives research support from NIH and is a consultant for Novartis on work that is not relevant to this work. JSH receives research support from Global Blood Therapeutics and consultancy fees from Global Blood therapeutics, bluebird bio, Vindico medical education, and UpToDate and received funding from U01HL133996-05, 1OT3HL152448, and NU58DD000019 during conduct of this work. JSP receives research support from K01HL125495.

All other authors have no relevant conflicts to report.

Acknowledgements

We would like to thank Rebecca Rupff, Courtney Mays, MBA and Jamilla Griffith for PEESC study coordination and data collection.

Variables	**Overall (N=217)**	**Lifetime Enuresis Yes (N=101)**	**Lifetime Enuresis No (N=116)**	**Current Enuresis[†] Yes (N=45)**
Sex: Male (N/%)	108 (49.77)	60 (59.41)**	48(41.38)**	26(57.78)
Genotype				
SS/SB0	151(69.59)	75(74.26)	76(65.52)	37(82.22)
SC/SB+	66(30.41)	26(25.74)	40(34.48)	8(17.78)
Height (cm)[b]	103.02(4.83)	103.69(5.35)	102.42(4.26)	102.84(5.3)
Weight (kg)[b]	16.87(3.17)	16.81(2.22)	16.92(3.84)	16.59(2.26)
Body Mass Index (kg/m^2)[b]	15.87(2.82)	15.58(1.08)	16.13(3.73)	15.62(1.04)
Age at PEESC enrollment (year)	11.63(3.47)	11.57(3.57)	11.68(3.4)	10.4(3.38)**
Hydroxyurea initiation age (year)	6.95(3.54)	6.9(3.54)	7(3.58)	5.66(3.23)*
eGFR ($cc/min/1.73m^2$)[b]	120.88(19.55)	121.61(19.85)	120.24(19.4)	121.82(20.14)
Hyperfiltration (N/%)[b]	33(25.19)	15(24.59)	18(25.71)	8(25)
HbF[b] (%)	15.9(8.41)	16.84(9.52)	15.05(7.25)	20.05(8.87)**
Hgb[b](gm/dL)	9.29(1.3)	9.01(1.24)*	9.53(1.31)*	9.15(1.21)
ANC[b]($x10^6/L$)	5583.86(2092.48)	5718.55(2030.66)	5467.62(2151.57)	5517.9(2068.51)
LDH[b](units/L)	565.37(283.29)	590.63(300.16)	543.41(268.03)	561.05(201.63)
USgravity[b]	1.01(0.0032)	1.01(0.0031)	1.01(0.0033)	1.01(0.0027)

Variables	**Overall (N=217)**	**Lifetime Enuresis**	**Lifetime Enuresis**	**Current Enuresis**
Hyposthenuria[b] (N/%)	40(31.5)	17(28.33)	23(34.33)	5(16.13)*

References

1. American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington V.

2. von Gontard A, Schaumburg H, Hollmann E, Eiberg H, Rittig S. The genetics of enuresis: a review. *The Journal of urology* . Dec 2001;166(6):2438-43. doi:10.1097/00005392-200112000-00117

3. Lottmann HB, Alova I. Primary monosymptomatic nocturnal enuresis in children and adolescents. *Int J Clin Pract Suppl* . Sep 2007;(155):8-16. doi:10.1111/j.1742-1241.2007.01464.x

4. Barakat LP, Smith-Whitley K, Schulman S, Rosenberg D, Puri R, Ohene-Frempong K. Nocturnal enuresis in pediatric sickle cell disease.*J Dev Behav Pediatr* . Oct 2001;22(5):300-5. doi:10.1097/00004703-200110000-00004

5. Readett DR, Morris JS, Serjeant GR. Nocturnal enuresis in sickle cell haemoglobinopathies. *Archives of disease in childhood* . Mar 1990;65(3):290-3. doi:10.1136/adc.65.3.290

6. Wolf RB, Kassim AA, Goodpaster RL, DeBaun MR. Nocturnal enuresis in sickle cell disease. *Expert Rev Hematol* . Apr 2014;7(2):245-54. doi:10.1586/17474086.2014.892412

7. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *The New England journal of medicine* . Jun 09 1994;330(23):1639-44. doi:10.1056/NEJM199406093302303

8. Etteldorf JN, Tuttle AW, Clayton GW. Renal function studies in pediatrics. 1. Renal hemodynamics in children with sickle cell anemia.*AMA Am J Dis Child* . Feb 1952;83(2):185-91.

9. Itano HA, Keitel HG, Thompson D. Hyposthenuria in sickle cell anemia: a reversible renal defect. *The Journal of clinical investigation* . Sep 1956;35(9):998-1007. doi:10.1172/JCI103360

10. Alvarez O, Miller ST, Wang WC, et al. Effect of hydroxyurea treatment on renal function parameters: results from the multi-center placebo-controlled BABY HUG clinical trial for infants with sickle cell anemia. *Pediatric blood & cancer* . Oct 2012;59(4):668-74. doi:10.1002/pbc.24100

11. Lebensburger JD, Aban I, Pernell B, et al. Hyperfiltration during early childhood precedes albuminuria in pediatric sickle cell nephropathy. *American journal of hematology* . Apr 2019;94(4):417-423. doi:10.1002/ajh.25390

12. Hankins JS, Estepp JH, Hodges JR, et al. Sickle Cell Clinical Research and Intervention Program (SCCRIP): A lifespan cohort study for sickle cell disease progression from the pediatric stage into adulthood.*Pediatric blood & cancer* . May 24 2018:e27228. doi:10.1002/pbc.27228

13. Schwartz GJ, Munoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *Journal of the American Society of Nephrology : JASN* . Mar 2009;20(3):629-37. doi:10.1681/ASN.2008030287

14. Allon M. Renal abnormalities in sickle cell disease. *Archives of internal medicine* . Mar 1990;150(3):501-4.

15. Mabiala Babela JR, Loumingou R, Pemba-Loufoua A, Londjongo W, Nzingoula S, Senga P. [Enuresis in children with sickle cell disease]. *Arch Pediatr* . Oct 2004;11(10):1168-72. L'enuresie chez l'enfant drepanocytaire. doi:10.1016/j.arcped.2004.05.017

16. Akinyanju O, Agbato O, Ogunmekan AO, Okoye JU. Enuresis in sickle cell disease. I. Prevalence studies. *J Trop Pediatr* . Feb 1989;35(1):24-6. doi:10.1093/tropej/35.1.24

17. Esezobor CI, Akintan P, Nwaogazie U, et al. Enuresis in children and adolescents with sickle cell anaemia is more frequent and substantially different from the general population. *PloS one* . 2018;13(8):e0201860. doi:10.1371/journal.pone.0201860

18. Saraf SL, Zhang X, Kanias T, et al. Haemoglobinuria is associated with chronic kidney disease and its progression in patients with sickle cell anaemia. *British journal of haematology* . Mar 2014;164(5):729-39. doi:10.1111/bjh.12690

19. Oakley J, Zahr R, Aban I, et al. Acute Kidney Injury during Parvovirus B19-Induced Transient Aplastic Crisis in Sickle Cell Disease.*American journal of hematology* . May 14 2018;doi:10.1002/ajh.25140

20. Qian Q, Nath KA, Wu Y, Daoud TM, Sethi S. Hemolysis and acute kidney failure. *American journal of kidney diseases : the official journal of the National Kidney Foundation* . Oct 2010;56(4):780-4. doi:10.1053/j.ajkd.2010.03.025

21. Wang WC, Ware RE, Miller ST, et al. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). *Lancet* . May 14 2011;377(9778):1663-72. doi:10.1016/S0140-6736(11)60355-3

22. Subarna C, de la Fuente J, Mohammed A. Prevalence Of Nocurnal Enuresis and Proteinuria In Children With Sickle Cell Disease and Its Relation To Severity Of Painful Crises. 2013.

23. Readett DR, Morris J, Serjeant GR. Determinants of nocturnal enuresis in homozygous sickle cell disease. *Archives of disease in childhood* . Jun 1990;65(6):615-8. doi:10.1136/adc.65.6.615

Figure Legends:

Figure 1. Proportion of children with persistence of nocturnal enuresis. Forty-five out of 215 children endorsed presence in symptoms of nocturnal enuresis on entrance into PEESC. Children between the ages of 6 and 8 were more likely to report symptoms of nocturnal enuresis.

Figure 2. Proportion of children with hyperfiltration (defined by eGFR above 133 ml/min/1.73m^2), and 95% confidence interval in children currently with and without enuresis. Upon repeated data analysis using generalized estimating equation (GEE), children with hyperfiltration, were more likely to experience current enuresis (OR: 1.01, CI: 1.00-1.02, p=0.038) after adjusting for age and sex. After further including SCD type in the GEE model, the association become suggestive (OR: 1.01, 95%CI: 1.00-1.02, p=0.11).

Hosted file

`Table 1 Enuresis .docx` available at https://authorea.com/users/732534/articles/710833-enuresis-and-hyperfiltration-in-children-with-sickle-cell-disease