ORIGINAL ARTICLE

Nocturnal enuresis in school-aged children with sickle-cell anemia: Any relationship with hyposthenuria?

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Abstract

Background: Reports show that children with sickle-cell anemia (SCA) have a tendency for nocturnal enuresis when compared with their counterparts with normal hemoglobin. Although nocturnal enuresis in SCA has been attributed to several factors including tubular and even bladder dysfunction, its relationship with hyposthenuria has been questioned in some studies.

Aim: The study aims to determine the relationship of hyposthenuria with nocturnal enuresis seen in school-aged children with SCA.

Subjects and Methods: A cross-sectional study of seventy school-aged children with SCA, who met the study criteria and seventy age- and gender-matched controls was conducted at the Sickle-cell Clinic, University of Nigeria Teaching Hospital in Enugu, Southeast Nigeria. The diagnosis of enuresis among the subjects and controls was based on the Diagnostic and Statistical Manual of Mental Disorders-IV criteria while urine specific gravity (USG) was determined on dipstick urinalysis. The frequencies of categorical variables were compared using Chi-square test or Fisher exact test as appropriate and the means of continuous variables with Student's *t*-test. The level of statistical significance was taken as $P < 0.05$.

Results: The prevalence of hyposthenuria was 4.5% and 8.3% among enuretic and nonenuretic subjects respectively, 6.7% and 10.9% among enuretic and nonenuretic controls and 4.5% and 6.7% among enuretic subjects and controls, respectively. The differences were not statistically significant. The mean ± standard deviation USG was significantly higher in the subjects than in the controls (1.02 ± 0.01 vs. 1.01 ± 0.01, $P = 0.013$) and enuretic subjects than enuretic controls (1.02 ± 0.01 vs. 1.01 ± 0.01, $P = 0.007$). The prevalence of nocturnal enuresis was significantly higher in male subjects compared to female subjects (odds ratio [OR] [95% confidence interval (95% CI)] =8.14 (2.12, 31.24), $\chi^2 = 12.21$, $P < 0.001$) and male controls ($\chi^2 = 5.57$, $P = 0.018$). Enuretic subjects had a significantly higher prevalence of parental history of childhood enuresis (OR [95% CI] =10.39 [2.45, 44.05], $P < 0.002$) than the enuretic controls. The relationship between the enuretic subjects and controls with respect to age of attainment of urinary control, family size, socioeconomic class, and sibling history of enuresis were not statistically significant.

Conclusions: Nocturnal enuresis in children with SCA may not be related to hyposthenuria. However, male gender and parental history of childhood enuresis are significant risk factors.

Key words: Hyposthenuria, nocturnal enuresis, sickle-cell anemia

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Introduction

The renal complications in sickle-cell anemia (SCA) begin in childhood[1] and consist of abnormalities of tubular function[2-4] and renal hemodynamics.[5] Hyposthenuria defined as urine specific gravity (USG) <1.010 on dipstick urinalysis,[6] is the most common and one of the earliest renal tubular defects in sickle-cell disease.[7] It is almost universally evident by the time the affected child reaches the age of 3 years and results in an obligatory urine output of more than 2000 mL/day.[2]

Intravascular sickling occurs more readily in the kidney than any other organ,[7] and its medullary microvasculature is especially sensitive to hypoxia-induced by sickling and vaso-occlusion.[8] Ischemia and infarction of the renal medulla lead to the destruction of the vasa recta and juxtamedullary nephrons which are responsible for urine concentration,[9] resulting in failure to concentrate urine which is thought to manifest as polyuria and enuresis.[10]

Although several reports indicate that children and adolescents with SCA may be at a higher risk of nocturnal enuresis than those with normal hemoglobin (Hb) genotype,[11-14] Readett *et al.*[15] did not demonstrate any clear relationship between enuresis and disease severity in SCA; thus, they disagreed with the assumption that it is linked to hyposthenuria. In addition, Readett *et al.*,[16] in another study, noted that both urine osmolality and overnight urine volume after fluid restriction were similar in enuretic and nonenuretic children with SCA and implied that factors other than these variables determine the presence of enuresis. Among the identified factors were low maximum functional bladder capacity and a high overnight urine volume to functional bladder capacity ratio.[16]

Therefore, although enuresis is a recognized renal complication of SCA in children, the underlying mechanisms are not clearly understood. Moreover, the link between nocturnal enuresis and hyposthenuria remains unresolved. This study was conducted to determine the relationship of hyposthenuria with nocturnal enuresis seen in school-aged children with SCA.

Subjects and Methods

Study design and subjects

The study (conducted between October and December 2011) was descriptive and cross-sectional. The subjects were recruited consecutively from school-aged children with SCA attending the Paediatric Sickle-cell Clinic of University of Nigeria Teaching Hospital (UNTH). The minimum sample size was determined using the formula for proportions for population size <10,000.[17,18] (The subjects were a finite group of SCA patients in a hospital):

$$nf = \frac{n}{1+\frac{n}{N}}$$

n = the desired sample size from a similar but previous study with population >10,000 (in this instance 374),

$$nf = \frac{374.33}{1+\frac{374.33}{85}} = 69.27$$

n = an estimate of n which corresponds to the total number of SCA patients in UNTH who are of primary school-age, 5–11 years. This was estimated to be 85.

This minimum sample size was approximated to 70. Using 20% of attrition rate of the calculated sample size which is 14 brought the calculated sample size to 84. Of the 84 subjects and controls initially recruited, only 70 had complete data, so the final sample size used for the study was 70. After obtaining ethical approval from the Health Research and Ethics Committee of the hospital and written informed consent from the parents, the subjects were recruited based on the following criteria: Hb SS genotype confirmed by Hb electrophoresis, clinical status suggestive of steady state, age between 5 and 11 years, clinic attendance for at least 6 months prior to the study, and primary school attendance within Enugu metropolis. Subjects who had a history and urine sugar level suggestive of diabetes mellitus, a personal history of epilepsy, a history suggestive of urinary tract infection, and a history of diuretic medication were excluded from the study.

Study procedures/protocol

The controls were their respective age- and sex-matched classmates who had Hb AA genotype. The primary schools were ten registered public schools and 54 registered private schools. The choice of classmates of subjects as controls was informed by the need to remove bias related to socioeconomic factors and to control for age. Following approval from the school authorities and the parents through phone contacts and home visits, the class register was used to select, consecutively, as the controls appeared in the register, the pupil next to the subject who was of the same age and sex as him/her. The same exclusion criteria used for the subjects were applicable to them.

Thus, there were seventy subjects with SS Hb genotype and seventy controls with AA Hb genotype recruited for the study.

A 15-item pro forma was used to obtain the following information from the subjects and controls; bio-data, home and school addresses, family history of enuresis, family size, age of attainment of urinary control while awake, parental occupation, and highest educational attainment.

Historical evaluation for enuresis based on the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria[19] and exclusion of confounding factors such as the history of epilepsy, diabetes mellitus, urinary tract infection, and diuretic intake. The DSM-IV definition of nocturnal enuresis was summarized for adoption as the repeated voiding of urine into bed or clothes, which may be involuntary or unintentional, at a frequency of two nights a week for at least three consecutive months by a child who is 5 years or older, the behavior not being due exclusively to substance effect or a medical condition.[19]

All enrolled subjects and controls were clinically examined with emphasis on general examination, anthropometry (height and weight measurements using standardized methods), and body mass index calculation using the formula: Weight in kilogram/height in meters.[2] Blood samples were collected from the control for the determination of Hb genotype. The blood sampling was done in the presence of the head or class teacher at the headteacher's office or in a separate room in the participant's home in the presence of the parent/care-giver. Determination of the Hb genotype was done at hematology laboratory of the same health facility utilizing Centrifuge (Model 80-2, Microfield Instruments, England) and Electrophoresis tank (Shandon. Vita, UK).

Midstream, clean-catch, first voided morning urine samples from both cohorts (following an overnight fluid restriction) were subjected to dipstick urinalysis using Combi-11 multistix urinalysis strip (Cybow™, Gyung Nam, Korea). The urine collection procedures were explained to the parents/care-givers and older participants while full comprehension was ensured by their repeating of same instructions to the investigator. Phone calls were made as reminders at night before and the morning of the urine sample collection. The procedure and interpretation of the results were as recommended by Cheesebrough[6] and the reagent strip manufacturer (CybowTM Reagent Strips for Urinalysis. Gyung Nam. Batch No. 70417; 2011) USG <1.010 was regarded as low while a value >1.030 was taken as higher than normal.

Data analysis

Statistical Package for Social Sciences (SPSS) version 17.0 software (SPSS Inc., Chicago, IL., USA). The difference between the frequencies of categorical variables was tested using Chi-square test or Fisher's exact test as appropriate. Means were compared between continuous variables using Student's *t*-test. Results were also presented in tables. All the tests were two-tailed, and the results were taken as statistically significant at $P < 0.05$.

Results

Prevalence of enuresis/hyposthenuria

Twenty-two (31.4%) of the subjects and 15 (21.4%) of the controls had nocturnal enuresis. The difference in the prevalence of nocturnal enuresis between these two groups was not significant ($\chi^2 = 1.80$, $P = 0.180$). Among the enuretic subjects ($n = 22$), only 1 (4.5%) had hyposthenuria while 4 (8.3%) of the 48 nonenuretic subjects had hyposthenuria. Only 1 (6.7%) of the enuretic controls ($n = 15$) and 6 (10.9%) of their nonenuretic counterparts ($n = 55$) had hyposthenuria. The difference in the prevalence of hyposthenuria between the enuretic subjects and controls was not significant (Fisher's Exact test = 1.000).

Means of variables of subjects versus controls

The mean ± standard deviation (SD) age and USG of subjects and controls are shown in Table 1. The subjects and the controls had same mean ± SD ages. Remarkably, the subjects had a significantly higher mean ± SD USG ($t = 2.515$, $P = 0.013$) than the controls.

Means of variables of enuretic versus nonenuretic subjects

As displayed in Table 2, the mean ± SD age of the enuretic subjects was similar to those of the nonenuretic subjects. Both groups had the same mean ± SD USG of 1.02 ± 0.01.

Enuretic controls versus nonenuretic controls

A comparison of the enuretic and nonenuretic controls showed that the enuretic controls were significantly younger than the nonenuretic controls. Mean ± SD age (7.20 ± 1.78,

Table 1: Comparison of mean±standard deviation age and urine specific gravity of subjects and controls

Variable	Subjects (*n*=70)	Controls (*n*=70)	*t*	*P*
Age in years	8.37±2.02	8.37±2.02	0.00	1.000
USG	1.02±0.01	1.01±0.01	2.51	0.013

USG=Urine specific gravity

Table 2: Comparison of mean±standard deviation age and urine specific gravity of enuretic and nonenuretic subjects

Variable	Enuretic subjects (*n*=22)	Nonenuretic subjects (*n*=48)	*t*	*P*
Age in years	8.500±2.44	8.31±1.82	0.36	0.722
USG	1.02±0.01	1.02±0.01	1.63	0.108

USG=Urine specific gravity

Table 3: Comparison of mean±standard deviation age and urine specific gravity of enuretic and nonenuretic controls

Variable	Enuretic controls (*n*=22)	Nonenuretic controls (*n*=48)	*t*	*P*
Age in years	7.20±1.78	8.69±1.98	2.64	0.010
USG	1.01±0.01	1.02±0.01	0.07	0.948

USG=Urine specific gravity

8.69 ± 1.98), (t = 2.637, P = 0.010) [Table 3]. However, the difference in mean ± SD USG of the two groups was not statistically significant.

Enuretic cohorts versus nonenuretic cohorts

Further comparisons were made for the mean ± SD of the same variables between the enuretic subjects and controls [Table 4] and the nonenuretic subjects and controls [Table 5]. Enuretic controls had significantly lower mean ± SD USG (t = 2.84, P = 0.007). Although the mean ± SD age of the enuretic subjects was higher than those of the controls, the difference was not statistically significant.

The prevalence of nocturnal enuresis was significantly higher in male subjects compared to female subjects (odds ratio [OR] [95% confidence interval (95% CI)] = 8.14 (2.12, 31.24), χ^2 = 12.21, P < 0.001) and male controls (χ^2 = 5.57, P = 0.018). There was no significant difference in the prevalence of nocturnal enuresis between male and female controls (χ^2 = 0.14, P = 0.706) or between female subjects and controls (Fisher's Exact Test P = 0.473) [Table 6].

Relationship between the prevalence of enuresis and attainment of urinary control, family size, socioeconomic status, and family history of enuresis

The mean ± SD age of attainment of daytime urinary control was 2.2 ± 0.53 years in subjects with enuresis versus 1.7 ± 0.75 years in subjects without enuresis (t = 0.32, P = 0.58) and 1.7 ± 0.75 years in enuretic controls versus 1.9 ± 0.73 years in nonenuretic controls (t = 0.41, P = 0.53). The differences were not statistically significant. The mean family size was 6 ± 1.6 in subjects with enuresis versus 6 ± 1.4 in nonenuretic subjects (t = 0.61, P = 0.45) and 6 ± 1.4 in enuretic controls versus 6 ± 1.7 in nonenuretic controls (t = 0.93, P = 0.34). The differences were not statistically significant. There was also no statistically significant relationship between enuretic subjects and controls regarding their distribution among the different socioeconomic classes [Table 7].

Table 8 shows the association between the prevalence of nocturnal enuresis and a history of enuresis in the parents. There was no significant difference between enuretic subjects and enuretic controls in the prevalence of a positive history of enuresis in the parents (75.0% vs. 41.2%; P = 0.071). Among the subjects, the prevalence of enuresis was significantly higher in those whose parents had a positive history of enuresis in childhood (OR [95% CI] = 10.39 [2.45, 44.05]; P = 0.002). Among the controls, the difference in prevalence among parents with a positive history of enuresis versus those without was not statistically significant (41.2% vs. 15.1%; P = 0.060) [Table 8]. The siblings of 25 subjects (35.7%) and 19 controls (27.1%) had enuresis. The difference was not statistically significant (χ^2 = 1.19; P = 0.276). There was no significant difference in the prevalence of a positive sibling history in enuretic versus nonenuretic subjects (χ^2 = 2.85; P = 0.091) and enuretic versus nonenuretic controls (Fisher Exact Test P = 0.347). There was also no significant difference between the enuretic subjects and controls in the prevalence positive history of enuresis in the siblings (P = 0.402).

Table 4: Comparison of mean±standard deviation age and urine specific gravity of enuretic subjects and controls

Variables	Subjects (n=22)	Controls (n=15)	t	P
Age in years	8.50±2.45	7.20±1.78	1.762	0.087
USG	1.02±0.01	1.01±0.01	2.839	0.007

USG=Urine specific gravity

Table 5: Comparison of mean±standard deviation age and urine specific gravity of the nonenuretic subjects and controls

Variables	Subjects (n=48)	Controls (n=55)	t	P
Age in years	8.31±1.82	8.69±1.98	1.00	0.318
USG	1.02±0.01	1.02±0.01	0.52	0.604

USG=Urine specific gravity

Table 6: Prevalence of nocturnal enuresis in relation to gender

Gender	Subjects		Controls		χ^2	P
	N	n (%)	N	n (%)		
Male	39	19 (48.7)	39	9 (23.1)	5.97	0.018
Female	31	3 (9.7)	31	6 (19.4)	NA	0.473
χ^2/P		12.21/<0.001		0.14/0.706		

N=Number studied; n (%)=Number (percentage) with enuresis; NA=Not applicable

Table 7: Relationship between nocturnal enuresis and socioeconomic status

SEC	Subjects		Controls		χ^2/P*
	N	n (%)	N	n (%)	
Lower	21	7 (33.3)	15	3 (20.0)	NA/0.622#
Middle	27	8 (29.6)	27	6 (22.2)	0.39/0.535
Upper	22	7 (31.8)	28	6 (21.4)	0.69/0.406
χ^2/df/P**		0.08/2/0.962		0.03/2/0.986	

*Prevalence of nocturnal enuresis in subjects versus controls; **Prevalence of nocturnal enuresis in lower versus middle versus upper SECs, #Fisher exact test. SECs=Socioeconomic classes; N=number studied; n (%)=Number (percentage) with enuresis; NA=Not applicable

Table 8: Relationship between the prevalence of nocturnal enuresis and history of enuresis in the parents of subjects and controls

Enuresis in childhood in parents	Subjects		Controls		χ^2/P
	N	n (%)	N	n (%)	
Present	12	9 (75.0)	17	7 (41.2)	3.25/0.071
Absent	58	13 (22.4)	53	8 (15.1)	0.97/0.325
P (Fisher exact test)		0.002		0.060	

N=Number studied; n (%)=Number (percentage) with enuresis

Discussion

In this study, the prevalence of hyposthenuria in children with SCA and their controls as well as in enuretic and nonenuretic subjects was comparable. These findings suggest that other factors rather than hyposthenuria may be the cause of enuresis. Readett *et al*.[15] had challenged the association of hyposthenuria with enuresis as they failed to demonstrate a clear relationship between enuresis and disease severity in SCA. Readett *et al*.,[16] in another study, observed that low maximum functional bladder capacity and high overnight urine volume to maximum functional bladder capacity ratio were the determinants of enuresis in SCA rather than low urine osmolality and high overnight urine volume. Although Noll *et al*.[20] reported hyposthenuria as the main determinant of enuresis in SCA, causal factors such as low maximum functional bladder capacity, a high ratio of overnight urine volume to maximum functional bladder capacity, difficulty in arousal from sleep and genetic predisposition all observed in the general population have also been documented.[16] Furthermore, a more recent study in Port Harcourt, Southeast Nigeria noted a significantly higher prevalence of hyposthenuria in children with SCA.[21] The authors also used dipstick urinalysis in the investigation of the first early morning voided urine and set the cutoff level of low USG at <1.010. However, they studied a large number of subjects below the school age. Since preschool children have lower USG,[22] this may have accounted for the higher prevalence of hyposthenuria reported in the study. Moreover, the Port Harcourt study[21] did not demonstrate any link between hyposthenuria and enuresis.

In general, USG reflects the concentrating ability of the kidneys and also gives an important insight into the patient's hydration status.[23] Its interpretation should, therefore, be related to the patient's clinical state. USG ranges from 1.003 to 1.030.[24] A value less 1.010 indicates relative hydration while a value >1.020 points to relative dehydration.[23] In our study, the higher USG values noted in enuretic sicklers may thus be explained by their greater tendency to dehydration.

Nevertheless, the direct (gravimetry) and indirect methods (refractometry and reagent strip) of measuring the USG (which provides a fair estimate of urine osmolality) have their limitations based on their underlying physical properties.[25] Several studies[25-27] have reported positive and acceptable correlations between osmolality and hydrometry or refractometry but not with USG determined by reagent strips. Notably, higher values of USG were obtained for reagent strips.[27] Again, this may also have contributed to the higher values of USG observed in our study. Despite its drawback, the reagent strip is a readily available and cheap tool in screening for abnormal urine osmolality, especially in resource-poor settings: Provided the USG is interpreted with regard to the pH and protein content of the urine sample. Therefore, nonutilization of a more reliable method of USG estimations such as refractometry as well as the lack of exclusion of some confounding factors such as diabetes insipidus are major limitations of our study. The findings in this study have thus highlighted a future research need: Namely to establish if there is actually a link between nocturnal enuresis in SCA provided more reliable methods of USG determination are used.

The male preponderance of nocturnal enuresis in SCA noted in this study had been earlier reported[12,14,15] as also for normal children.[28-31] The reason for this male preponderance is not clear. However, it may be due to the preferential treatment of the male child over his female counterpart in this environment, especially on health issues.[32] An association between the prevalence of enuresis in the subjects and parental childhood history of enuresis as against sibling enuresis was observed in this study. This is in keeping with the observation of Jordan *et al*.[13] and underscores the fact that genetic factors in enuresis may be influenced by both somatic and psychosocial modulatory effects.[33] The absence of a significant impact of socioeconomic background on the prevalence of nocturnal enuresis as found in this study is similar to that reported by Readett *et al*.[15] and Hansakunachai[31] but contrasts with the findings of earlier studies[28-31,34] in normal children in which enuresis was more frequent in those from the lower[28-31] or higher socio-economic classes.[34] Readett *et al*.,[15] in Jamaica, attributed the observed absence of an association between socioeconomic background and the prevalence of nocturnal enuresis in SCA to the relative unreliability of social amenities in predicting social status. The lack of association between nocturnal enuresis and socioeconomic status of families in both SCA and normal children in this study may reflect improved awareness of health and health-related matters across the social classes. Thus, factors which contribute to enuresis in normal children, such as genetic factors, slower maturation in boys, reduced responsiveness to toilet training in male children,[30] and more frequent developmental delays,[33] are also important in children with SCA.

Conclusions

This study has shown that nocturnal enuresis in children with SCA may not be related to hyposthenuria. The enuresis may be related to other causal factors which also apply to the general population.

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Conflicts of interest

There are no conflicts of interest.

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