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CLINICAL & BASIC RESEARCH

The Role of Hyposthenuria in Enuresis Among Paediatric Patients With Sickle Cell Disease

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abstract: ***Objectives:*** Enuresis is common among children with sickle cell disease (SCD). Many risk factors have been postulated, but its relation to hyposthenuria is debatable. This study aimed to determine the prevalence of enuresis in children with SCD in Basrah, Iraq, and to examine its relation with hyposthenuria. ***Methods:*** A cross-sectional epidemiological study was performed on children with SCD who met the inclusion criteria at the Basrah Center for Hereditary Blood Diseases from December 2020 to May 2021. A questionnaire was used to collect relevant data. Blood samples were tested for haemoglobin genotype, certain blood indices and serum haemoglobin. Urine was tested for albumin and creatinine, and the specific gravity was measured using urine dipsticks. The relationships between enuresis and various sociodemographic and clinical variables were assessed. Binary logistic regression analysis was done to examine the independent risk factors of enuresis. ***Results:*** A total of 161 out of 200 eligible children were included in this study (response rate: 80.5%). The majority of participants (60.9%) were males. The mean age of the participants was 10.9 ± 2.9 years. Enuresis was reported in 50 (31.1%) patients. The independent risk factors for enuresis included family history of enuresis (adjusted odds ratio [OR] = 5.94, 95% confidence interval [CI]: 2.54–13.89; P <0.001), hyposthenuria (OR = 3.76, 95% CI: 1.25–11.30; P = 0.018) and sleep disorders (OR = 2.90, 95% CI: 1.19–7.06; P = 0.019. ***Conclusion:*** Enuresis is common among children with SCD in Basrah, Iraq. Hyposthenuria was significantly associated with enuresis. Family history of enuresis and sleep disorders were also found to be significantly related to enuresis.

Keywords: Enuresis; Sickle Cell Disease; Children; Prevalence; Iraq.

Advances in Knowledge

- *Enuresis is prevalent among children with sickle cell disease (SCD); however, the role of hyposthenuria as a determinant of enuresis is controversial. This study found that hyposthenuria was a significant predictor of enuresis in children with SCD.*
- *To the best of the authors' knowledge, this is the first study in Iraq to examine the association between hyposthenuria and enuresis in children with SCD.*

Application to Patient Care

- *The results of this study may contribute towards understanding the underlying mechanisms of enuresis in children with SCD.*

Sickle cell disease (SCD), an autosomal-recessive haemoglobin disorder, is one of the most common heritable diseases in the world.[1] Some Eastern Mediterranean countries, including Iraq, have reported on this disease. In Basrah, Iraq, 6.48% of the population has the sickle cell trait.[2] Enuresis is more common among children with SCD compared to those with normal haemoglobin; however, prevalence rates vary widely, ranging from 26.4–51%, depending on study methodology and enuresis definition criteria.[3]

SCD is a multisystem disease, with one of the most typically afflicted organs being the kidneys due to medullary ischaemia and infarction. The underlying aetiopathogenesis of enuresis in SCD is not fully known. It has been related to tubular dysfunction manifested as defects in urinary concentration (hyposthenuria) and acidification, low functional bladder capacity and high overnight urine volume and glomerular hyperfiltration caused by increased prostaglandin production.[3–6] Eneh *et al.*, on the other hand, revealed that enuresis in children with SCD is related to other causative variables that are common in the general population as opposed to hyposthenuria.[7] Similarly, other studies have found that potential mechanisms underlying nocturnal enuresis in patients with normal haemoglobin genotype (haemoglobin AA) are equally relevant in SCD patients.[5,8]

The role of hyposthenuria as a predictor of enuresis in SCD patients is debatable, and there is a lack of studies on the subject in Basrah, Iraq. Therefore, this study aimed to verify the role of hyposthenuria in enuresis among children with SCD.

Methods

This cross-sectional study was conducted at the Basrah Center for Hereditary Blood Diseases, Basrah, Iraq, from December 2020 to May 2021. Children with steady-state SCD were included. Subjects with diabetes mellitus, epilepsy, features of urinary tract

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infection, isolated daytime incontinence, known renal dysfunction/impairment and diabetes insipidus and those on desmopressin or diuretic medication were excluded.

Patients and/or their parents were interviewed using a structured questionnaire that was developed for this study and completed by one of the researchers. It consisted of two parts: the first part contained information about the child's and parents' sociodemographic features (age, sex and birth order of the child, exposure to stressful life events such as death or divorce of parents, number of siblings, parental level of education and monthly family income). Parents were asked if any of the following life events had occurred in the family within the last 12 months: death or divorce of parents, death of someone in close proximity, relocation of the child to another address or school, conflicts with neighbours or friends and financial problems.[9] The second part sought information on enuresis (type, time and frequency or severity of enuresis), family history of enuresis and medical history of the child, including disorders in initiating and maintaining sleep (such as snoring, difficult arousal, sleep breathing disorders and insomnia). Parents were ensured that all the information received would be kept private and anonymous. Two paediatric experts and two community medicine consultants in the field of research methodology validated the questionnaire.

The type of SCD for all the patients was recorded depending on the results of baseline haemoglobin electrophoresis and high performance liquid chromatography. Blood samples were collected for complete blood count using an automated haematology analyser (SYSMEX KX-21N Automated Hematology Analyzer, Illinois, United States). The method of urine collection was explained to the parents or caregivers and older participants. The urine samples sent for analysis were the first-voided morning, clean-catch, mid-stream samples. Specific gravity was measured using dipstick urinalysis (ACON Laboratories, Inc., California, USA). A urinalysis was done to check for urinary tract infection; those with positive results were sent for urine culture and sensitivity. Urine albumin was determined using immunoturbidimetric assay. Urinary creatinine was measured by the alkaline picrate method. The urinary albumin/creatinine ratio (ACR) was computed and classified as normal when it was less than 30 mg/g, microalbuminuria when ACR = 30–300 mg/g and macroalbuminuria when it was more than 300 mg/g.[10]

Enuresis was defined as follows: "repeated involuntary or unintentional urine voiding into the bed or clothes that occurs exclusively during sleeping periods and not related to medication by the age of five years or older, with a minimum frequency of once monthly for at least three consecutive months".[3,11,12] Secondary enuresis was reserved for children who had been 'dry' for more than six months. Otherwise, it was referred to as primary enuresis.[12] Hyposthenuria was defined as urine specific gravity <1.010 on dipstick analysis.[13]

Data were compiled and analysed using the Statistical Package for the Social Sciences (SPSS), Version 23.0 (IBM Corp, Armonk, New York, USA). T-test, Chi-squared test, or Fisher's exact test was used for comparison of covariates where applicable. Binary logistic regression analysis was done to determine possible independent risk factors associated with enuresis. The level of significance was chosen at a *P* value of <0.05.

The Ethical Committee of the College of Medicine, University of Basrah authorised this study (Project ID: 030407021-2019). Informed consent was obtained from the parents of the children before they were included in the research.

Results

A total of 161 children were included in this study (response rate: 80.5%). Of the 200 eligible children, 34 children were excluded because they either reported a history of recurrent urinary tract infection or were proven to have it upon urine analysis. Other exclusion criteria led to the exclusion of five more children. Among the participants, 98 (60.9%) were males and 63 (39.1%) females; their mean age was 10.9 ± 2.9 years (10.9 ± 2.8 for males and 11.0 ± 3.1 for females). A total of 50 (31.1%) children were found to have enuresis. Among the enuretic children, 45 (90.0%) had primary enuresis and five (10.0%) had secondary enuresis. Diurnal enuresis was reported in four (8.0%), nocturnal in 33 (66.0%) and both diurnal and nocturnal in 13 (26.0%). Daily enuresis was found in 22 (44.0%) children, several times a week in 15 (30.0%), once a week in five (10.0%) and once or more per month in 8 (16.0%) [Table 1].

No significant difference was noticed between children with and without enuresis regarding age, sex, birth order, family income, stressful life events and parents' level of education. However, family history of enuresis and higher number of siblings were found to be significantly associated with enuresis (*P* <0.001) [Table 2].

Of the studied children, 75 (46.6%) had sickle cell anaemia (SCA) and 86 (53.4%) had sickle/β thalassaemia. None of the children was found to have other types of SCD. In univariate analysis, children with enuresis were found to exhibit a significantly

Table 1: Types of enuresis reported among the studied sickle cell disease patients (N = 50)

Variable	n (%)
Onset of enuresis	
Primary	45 (90.0)
Secondary	5 (10.0)
Time of enuresis	
Diurnal	4 (8.0)
Nocturnal	33 (66.0)
Both	13 (26.0)
Frequency	
Daily	22 (44.0)
Several times/week	15 (30.0)
Once/week	5 (10.0)
Once or more/month	8 (16.0)

higher proportion of hyposthenuria than those without enuresis (24.0% versus 6.3%; *P* = 0.002). Although enuretic children had a higher percentage of sleep disorders and hospitalisation rate and frequency during the previous 12 months than non-enuretic children, the difference was not found to be significant. Furthermore, haemoglobin genotype, albuminuria, serum haemoglobin level and red blood indices (MCH, MCV and MCHC values) were not significantly different between the two groups [Table 3].

The results of the logistic regression analysis showed that the following three variables were found to be independent predictors of enuresis: family history of enuresis (adjusted odds ratio [OR] = 5.94, 95% confidence interval [CI]: 2.54–13.89; *P* <0.001), hyposthenuria (OR = 3.76, 95% CI: 1.25–11.30; *P* = 0.018) and sleep disorders (OR = 2.90, 95% CI: 1.19–7.06; *P* = 0.019) [Table 4]. None of the other investigated variables were found to be independent predictors of enuresis.

Discussion

The present study revealed that the prevalence rate of enuresis was 31.1% among paediatric patients with SCD. Other studies have reported varying rates of enuresis in this group of patients: 35.7% in London, United Kingdom, 38% in Sudan, 48.6% in Saudi Arabia and 49.4% in Nigeria.[11,14–16] Such variation in the prevalence rates might be due to disparities in the definition of enuresis, different sampling methods, socio-cultural differences and varied study designs, i.e. whether the study was population- or health institute-based.[17,18] Earlier studies in Iraq have indicated lower

Table 2: Association of enuresis with sociodemographic characteristics (N = 161)

Variable	n (%)		*P* value
	Enuresis (n = 50)	No enuresis (n = 111)	
Mean age in years ± SD	10.4 ± 2.8	11.2 ± 2.9	0.119
Age in years			0.369
6–7	9 (18.0)	21 (18.9)	
8–9	11 (22.0)	13 (11.7)	
10–11	10 (20.0)	20 (18.0)	
12–13	11 (22.0)	24 (21.6)	
14–15	9 (18.0)	33 (29.7)	
Male sex	34 (68.0)	64 (57.7)	0.228
Number of siblings			0.018
0	4 (8.0)	1 (0.9)	
1	2 (4.0)	11 (9.9)	
2	5 (10.0)	21 (18.9)	
3	9 (18.0)	33 (29.7)	
4	12 (24.0)	18 (16.2)	
≥5	18 (36.0)	27 (24.3)	
Birth order			0.316
First	12 (24.0)	37 (33.3)	
Second	11 (22.0)	33 (29.7)	
Third	12 (24.0)	22 (19.8)	
Fourth	5 (10.0)	7 (6.3)	
Fifth or higher	10 (20.0)	12 (10.8)	
Family history of enuresis			<0.001
Yes	24 (48.0)	16 (14.4)	
No	26 (52.0)	95 (85.6)	
Per capita family monthly income in IQD			0.402
<2500,000	33 (66.0)	84 (75.2)	
250,000–500,000	15 (30.0)	22 (19.8)	
>500,000	2 (4.0)	5 (4.5)	
Father's education in years			0.418
<12	41 (82.0)	83 (74.8)	
≥12	9 (18.0)	28 (25.2)	
Mother's education in years			0.412
<12	37 (74.0)	89 (80.2)	
≥12	13 (26.0)	22 (19.8)	
Stressful life event			0.101
Yes	15 (30.0)	20 (18.0)	
No	35 (70.0)	91 (82.0)	

SD = standard deviation; IQD = Iraqi Dinar.

Table 3: Association of enuresis with certain clinical characteristics (N = 161)

Variable	n (%)		*P* value
	Enuresis (n = 50)	No enuresis (n = 111)	
Haemoglobin genotype			
SCA	23 (46.0)	52 (46.8)	0.999
SC/thalassaemia	27 (54.0)	59 (53.2)	
Hyposthenuria	12 (24.0)	7 (6.3)	0.002
Sleep disorders	15 (30.0)	19 (17.1)	0.064
Hospitalisation during the last year	42 (84.0)	78 (72.2)	0.115
Frequency of hospitalisation			
No	8 (16.0)	33 (29.7)	0.068
1–3 times	13 (26.0)	33 (29.7)	
4–6 times	14 (28.0)	29 (26.1)	
>6 times	15 (30.0)	16 (14.5)	
Albuminuria in mg/g			
<30	43 (86.0)	89 (80.2)	0.296
30–300	2 (4.0)	13 (11.7)	
>300	5 (10.0)	9 (8.1)	
Hb in g/dL	9.4 ± 1.7	9.4 ± 0.9	0.954
MCH in pg/cell ± SD	25.5 ± 5.0	26.9 ± 3.6	0.579
MCV in fL ± SD	75.5 ± 11.4	80.8 ± 9.7	0.408
MCHC in g/dL ± SD	33.5 ± 1.7	33.2 ± 1.2	0.742

SCA= sickle cell anaemia; SC= sickle cell; Hb= haemoglobin; MCH= mean corpuscular haemoglobin; SD = standard deviation; MCV= mean corpuscular volume; MCHC= mean corpuscular haemoglobin concentration.

Table 4: Logistic regression analysis

Parameter	B-coefficient	OR (95% CI)	*P* value
Family history of enuresis	1.781	5.94 (2.54–13.89)	<0.001
Hyposthenuria	1.326	3.76 (1.25–11.30)	0.018
Sleep disorders	1.066	2.90 (1.19–7.06)	0.019

OR = odds ratio; CI = confidence interval.

prevalence of enuresis among children without SCD, ranging from 7.5–29.5%.[18–20] Many studies have consistently found a strong relationship between SCD and enuresis.[21,22] SCD significantly affects renal structure and function, as reflected in a variety of renal syndromes and diseases, including abnormal haemodynamics, glomerulopathies and hyposthenuria (impaired urine concentrating ability).[23]

The logistic regression analysis showed that hyposthenuria was independently and significantly associated with enuresis (OR = 3.76, 95% CI: 1.25–11.30; *P* = 0.018). Earlier, hyposthenuria-induced nocturnal polyuria was thought to be the cause of nocturnal enuresis in SCA patients.[24] This theory is supported by the fact that hyposthenuria is a common and early infarction-related renal complication.[25] Ugwu and Ekelater demonstrated the same results.[26] However, Eneh *et al.* and Readett *et al.* found no association between enuresis and hyposthenuria, and after water deprivation, SCD children with enuresis was found to have the same maximum voided urine volume as those without enuresis; they attributed enuresis to reduced functional bladder capacity and other factors such as social and environmental influences and decreased arousal during sleep.[7,27]

Factors other than hyposthenuria were found to be significantly and independently associated with enuresis. Family history of enuresis was found to be an independent predictor of enuresis, with an adjusted OR of 5.94 (95% CI: 2.54–13.89; *P* <0.001), which is consistent with previously reported results.[18,28] Such an association highlights the importance of genetic roots in the aetiology of enuresis.[28]

Although univariate analysis indicated that the rate of sleep disorders was higher among enuretic children (30.0%) than among non-enuretic children (17.1%), the difference was not significant (*P* = 0.064). However, after adjustment for other variables, sleep disorders were observed to be an independent predictor of enuresis (OR = 2.90, 95% CI: 1.19–7.06; *P* = 0.019). Other studies have found that children with SCD are more likely to have sleep difficulties, which prevent them from waking up in response to a full bladder, resulting in enuresis.[29,30] A variety of factors, including pain and environmental, psychological and treatment factors (which were not investigated in the current study), have been reported to influence sleep disorders.[31] These factors might thus confound this relationship. Hence, the precise relationship between sleep disorders and enuresis needs to be further investigated. Furthermore, the absence of polysomnography and reliance on the data reported by the parents made defining sleep problems difficult. Lehmann *et al.*, who reported an association between sleep disorders and enuresis, recommended that children with SCD and enuresis be referred to a pulmonologist for the evaluation of sleep-disordered breathing.[32]

Nocturnal enuresis in individuals with airway obstruction is thought to be caused by increased

synthesis of atrial natriuretic peptide, which raises the arousal threshold during sleep.[33]

The aggregation of two or all of the three independent risk factors mentioned above was significantly higher in enuretic children than in non-enuretic children. Among the enuretic children, 37 (74.0%) had 0–1 risk factor, 11 (22.0%) had two risk factors and two (4.0%) had all three factors. In comparison, 109 (98.2%) had 0–1 risk factor, two (1.8%) had two risk factors and none (0.0%) had all three factors (P <0.001) among the non-enuretic children.

Family income, parents' level of education and the child's birth order did not affect the association with enuresis, a result that is consistent with those of several previous studies.[20,34] However, other studies have reported socio-economic status to have a significant impact on the enuresis prevalence rates.[15,35] Thus, it seems that there is no agreement on the significance of socio-economic status as a risk factor for enuresis. This could be attributed to the relative inaccuracy of social basic facilities in determining social rank, or it might reflect increased knowledge and awareness regarding health and health-related issues among all socioeconomic groups.[27]

The findings of the present study revealed that the well-documented decrease in the prevalence of enuresis with age in children without SCD was less evident in children with SCD, implying that some SCD-related morbidities, such as intravascular sickling and vaso-occlusion, improved less spontaneously in children with SCD.[20,25,36,37] This result is consistent with the findings of previous studies.[11,37] Among children without SCD, although enuresis is frequently reported to be more prevalent among boys than among girls, gender was not associated with enuresis in the present study.[34] This finding is consistent with the findings of Esezobor *et al*.[11] According to one possible theory, several sickle cell-related characteristics may be related to enuresis. Readett *et al*. observed a higher rate of enuresis among children with haemoglobin SS as well as a lower fetal haemoglobin level.[27] In agreement with Esezobor *et al*., no association was identified between enuresis and history of hospitalisation during the 12 months preceding the study.[11]

Though the number of siblings had a significant association with enuresis in univariate analysis (P = 0.018), the logistic regression analysis revealed no effect after adjusting for other variables. This result is consistent with those reported by others.[38]

One of the limitations of this study is that it was a cross-sectional study; thus, no causal relationships between variables could be established. Furthermore, polysomnography was not done to assess the pattern of sleep disordered breathing. Recall bias cannot be entirely eliminated. The form and content of questions as well as connecting exposure to specific life events may all have an impact on recall accuracy. SCD impacts psychosocial well-being and quality of life in general; therefore, parents who have children with the disease are more likely to recall previous exposure of their children.

The study's strength is that it is the first in Iraq to measure the prevalence and determinants of enuresis in children with SCD with special emphasis on the most controversial determinant—hyposthenuria.

Conclusion

Enuresis is common among paediatric patients with SCD in Basrah, Iraq. Hyposthenuria, family history of enuresis and sleep disorders were significant independent predictors of enuresis. Children with SCD, especially those with a family history of enuresis, should be assessed frequently for enuresis and kidney function.

AUTHORS' CONTRIBUTION

JN, MK and AM designed and planned the study. AM and DS collected the data. JN and MK contributed to the data analysis and drafting of the manuscript. All authors reviewed and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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