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Nocturnal enuresis among Sudanese children with sickle cell disease.

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Abstract

Background: Nocturnal enuresis (NE) is prevalent in patients with sickle cell disease. This has been attributed to a decreased ability to concentrate urine caused by sickling-induced nephropathy (hyposthenuria).Whether this is true in Sudanese children with sickle cell anemia is unknown.
Objective: To determine the frequency of NE in Sudanese children with sickle cell anemia and to see if hyposthenuria is the cause of NE in these patients.
Method: A hospital based cross sectional descriptive study of 87 children with sickle cell anemia who met the study criteria and age sex matched 53 children with sickle cell trait and 50 children with normal hemoglobin genotype as control was conducted in the outpatient's clinic of a major pediatric hospital in Khartoum. A questionnaire was used to collect relevant data; urine specific gravity was measured using urine dipsticks.
Results: NE is present in38%, 13% and 12% of children with sickle cell anemia, sickle cell trait and the control respectively. Hyposthenuria was not detected in children with or without enuresis.NE is common in siblings of enuretic children but not their parents.
Conclusion: NE is frequent in Sudanese children with homozygous sickle cell disease. The frequency is not increased in children with sickle cell trait. Hyposthenuria is not detected in these children. Familial tendency for NE is observed.

Keywords: Enuresis, Sickle cell, Children, Sudan.

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Introduction

Nocturnal Enuresis (NE) is defined according to DSM-IV as incontinence of urine at night after age 5 more than two times per week for at least 3 months [1]. It is usually divided clinically into primary (never being dry) and secondary (prior dry period) forms and monosymptomatic (absence of daytime symptoms) versus non-monosymptomatic (presence of daytime symptoms) enuresis [2].

The prevalence of NE in normal children seems to be the same throughout the world [1]. It has a prevalence of 7% for males and 3% for females at age five [3]. In Sudan, the prevalence rate vary from 6.5% to 33.5% depending on the definition of enuresis used [4-6].

Enuresis is frequent in children with sickle cell disease and its intensity is linked to severity of the disease [7]. In their review, Wolf et al. [8] reported the prevalence of NE in children and adolescent with SCD to range from 9-51%. This was constructed based on 10 relevant studies reported in the literature. This variation in prevalence rate was attributed to inconsistent definitions of NE [8].

NE in SCD is commonly hypothesized to be due to an impairment of urine concentrating ability (hyposthenuria), leading to nocturia and polyuria [9]. However, no significant differences were seen in more recent studies comparing the maximum concentrating ability of children with homozygous SCD and enuresis with age and sex matched children without enuresis, although children with SCD and enuresis were more likely to have low maximum functional bladder capacity [3].

SCD is prevalent in Sudan but there are no reports of NE in these patients. The objective of this study was to identify the frequency of nocturnal enuresis among Sudanese children with SCD, to test the hypothesis of hyposthenuria as a cause of NE in sickle cell patient and to look at the

previously suggested association between nocturnal enuresis and homozygous sickle cell disease.

Materials and Methods

Setting

Sickle cell clinic and general pediatrics outpatient clinics at Gaffer Ibn Ouf pediatrics Hospital. This is a specialized and central referral Hospital in Khartoum, Sudan.

Study Design, Period and Population

This is a Prospective, descriptive, hospital based study done during May 2012 to November 2012**.** The study group was children 5-16 years diagnosed as sickle cell anemia or sickle cell trait and confirmed by hemoglobin electrophoresis. Children attending general pediatric clinic who has no personal or family history to suggest sickle cell anemia and who have normal hemoglobin and hemoglobin electrophoresis were taken as control group (matching in sex and age). Children with constipation, snoring, mouth breathing, nasal congestion, diabetes mellitus, diabetes insipidus, chronic renal failure, nephritic syndrome, receiving diuretics and those with abnormal urine analysis were excluded from the study.

A Questionnaire for All Patient was filled by the Author (E), It Includes

History and physical examination: The history includes (personal data, past medical history (previous admissions, number of painful crisis and blood transfusion) family history and social history. The examination includes anthropometric measurements (weight, height and body mass index (BMI)) taken using standardized techniques and plotted on WHO standard charts. Children were examined for abdominal masses, abnormal neurological signs and anal tone. The spines were carefully inspected for evidence of spina bifida occulta. Urine analysis and urine specific gravity were done using urine dipsticks. Hemoglobin electrophoresis was obtained for all patients.

Statistical package of social science (SPSS) version 15 software was used for data entering and coding. Microsoft word and Excel had been used to generate graphs and tables.

Results

There were 140 children in the study group, 87 as sickle cell anemia and 53 as sickle cell trait and 50 children in the control group. The control group matched the study group in age and sex (Table 1).

In children with sickle cell anemia in the study group 33 (37.9%) had NE. Out of these 33 children 28 (84.8%) had primary NE and 5 (15.2%) had secondary NE. NE was present in 7 children (13.2%) out of 53 children with sickle cell trait in the study group. Five of these 7 children had primary NE (71.4%) and 2 (28.6%) had secondary NE (Table 1, Figures 1 and 2).

In the Control group 6 children (12%) were enuretic 5 (83.3%) had primary NE and 1 child (16.7%) had secondary NE (Table 1).

Males predominated in enuretic children (64% in sickle cell anemia and 65% in sickle cell trait) P<0.001 in both groups.

Anthropometric measurement:

Sickle cell anemia group:

Weight: Table 2

Weight below 3rd percentile was present in 58.8% of children with enuresis compared to 38.6% with no enuresis (P<0.05).

Height: Table 3

Height below 3rd centile was present in 47.1% of children with enuresis compared to 29.5% in children without enuresis (P<0.05).

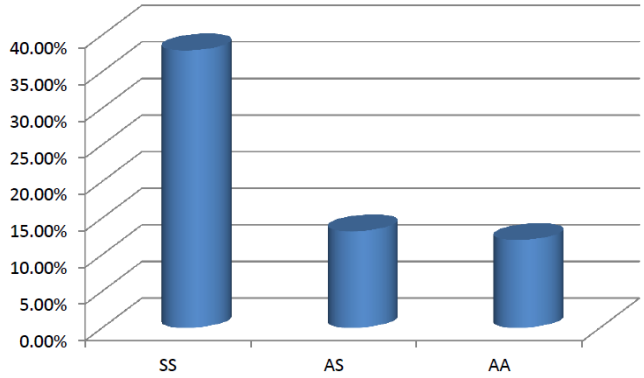
BMI: Table 4

BMI below 3rd centile was present in 50% with enuresis compared to 38% without enuresis (P<0.001).

Sickle cell trait:

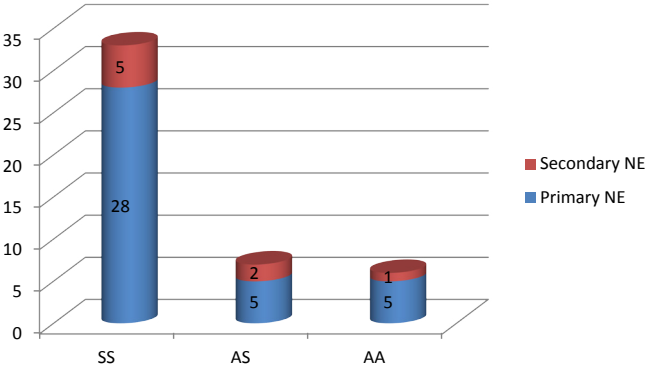
Table 1. *Demographic and clinical characteristics of patients in the study group and control group*

	Sickle cell anemia group N (87)	Control group N (50)	P	Sickle cell trait group N (53)	Control group N(50)	P
Age: range mean	5-16 (8.0 ± 1.3) years	5.5-16 (6.5 ± 1.6) years	0.07	5-16 (7.0 ± 2.1) years	5.5-16 (6.5 ± 1.6) years	>0.05
Male:female	1.85:1.0	1.94:1.0	0.3	2.1:1.0	1.94:1.0	0.4
NE: Yes **Age: years** **NE: No**	33 (37.9%) 7.5 ± 1.25 54 (62.1%)	6 (12%) 6.0 ± 1.3 44 (88%)	0.003 >0.05	7 (13.2%) 7.0 ± 1.4	6 (12.0%) 6.0 ± 1.3 46 (86.8%)	0.61 >0.05
No. of primary NE	28 (84.8%)	5 (83.3%)		5 (71.4%)	5 (83.3%)	
No. of secondary NE	5 (15.2%)	1 (16.7%)		2 (28.6%)	1 (16.7%)	
No. of siblings with NE	25 (67%)			5 (71%)	15 (30%)	
No. of parents with NE	0			0	5 (10%)	



SS: Sickle cell disease (P 0.003); AS: Sickle cell trait (P 0.61); AA: Control; Y axis shows % of NE

Figure 1. *Frequency of NE in the study and control group*



SS: Sickle cell disease; AS: Sickle cell trait; AA: Control; Y axis shows number of affected patients

Figure 2: *Types of NE in the study and control group*

Table 2. *Percentage (%) of patients with weight below third per centile in the study and control group*

Group	% of patients	P value
SS: NE: YES **NO**	58.8% 38.6	<0.05
AS: NE: YES **NO**	9.5 5.9	>0.05
AA: NE: YES **NO**	4.5 2.5	>0.05

Table 3. *Percentage (%) of patients with height below third per centile in the study and control*

Group	% of patients	P value
SS: NE: YES **NO**	47.1 29.4	<0.05
AS: NE: YES **NO**	23.4 11.8	0.322
AA: NE: YES **NO**	11.4 8.3	0.613

Table 4. *BMI in SS study group*

	Mean	Std.	Min	Max	<3rd centile
Enuretic	11.30	1.53	8.2	13.23	75.3
Non-enuretic	13.6	1.71	10.1	19.5	40.5

P value<0.001

BMI: Table 5

BMI below 3rd centile was present in 85% of children with enuresis compared to 28% in those without enuresis (P<0.001).

Control group:

BMI (Table 6): There was no significant difference between those with and without NE.

Family size and education level of parent had no significant effect on the frequency of NE.

Low socioeconomic status was present in 70% of children with NE in SCD group compared to 52% in children with no NE in the same group (P<0.05).

In the study group a positive family history of NE was significantly higher in enuretic children with SCD compared to non-enuretic (76.5% *vs.* 4.5% P<0.001) All of them were siblings**.** 54% of these enuretic siblings had sickle cell anemia and 46% were normal (Table 1).

Urine specific gravity was within normal range in all patients (1.030-1.007). The mean USG was 1.025 in enuretic children with SCA compared to 1.027 in non-enuretic children with SCA (P 0.15).

Discussion

This study used DSM-IV to define NE. We had used this definition when we reported on NE in normal Sudanese children (4) and it was also used by 4 other studies reporting NE in children with SCA (8). This consistent definition will allow comparison with these studies.

The present study confirmed the previously suggested association between homozygous sickle cell disease and nocturnal enuresis [10,11]. The frequency of NE in SS group was at least thrice that found in control subjects. A similar association could not be shown for children with sickle cell trait since they had an almost similar rate as the control group. It is interesting to note that the frequency of NE in the control group is almost double the rate we reported before in normal children (12% *vs.* 6.5 % [4]. If we used our previously reported rate of NE then children with sickle cell trait in this study would have been considered to have high frequency of NE. There are no reports in the literature about the prevalence of NE in such patients.

The rate of NE reported in this study was higher than the rates reported in other three studies that used a similar definition [7,12,13]. These studies had included adult patients and it is known that the rate of NE declined with age [8]. A comparable prevalence rate of NE was reported

Table 5. *BMI in AS group*

	Mean	Std.	Min	Max	<3rd centile
Non-enuretic	14.6	1.65	9.8	18.9	14%
Enuretic	9.2	1.14	8.1	12.52	85%

P<0.001

Table 6. *BMI in the control group*

	Mean	Std.	Min	Max	<3rd centile
Non-enuretic	15.9	2.58	12.2	23.6	2.3%
Enuretic	14.6	1.51	11.1	19.5	7.5

P>0.05

by Ali and Chakraborty who used a similar definition and a similar age range like ours [14].

In the current study NE was common in boys with homozygous sickle cell disease and sickle cell trait. This had been reported previously in normal children as well as children with sickle cell anemia [3,4,7,15-19]. It is probable that factors contributing to enuresis in normal children like reduced responsiveness to toilet training and slower maturation in boys as well as the frequent developmental delay are also important in children with homozygous and heterozygous sickle cell disease [20,21]. However, there are no studies that determined the relative contribution of general pediatric and SCD in these factors [8].

NE was observed to be associated with low socioeconomic status in this study. This is different from what had been reported from Jamaica and Nigeria but similar to previous studies that noted enuresis to be more in normal children from lower socio-economic status [3,19,22,23]. Rahim, et al. [16] in a large epidemiological study, reported a prevalence of 88% of NE in Sudanese children, 3-15 years, living in a suburban area in Khartoum. According to the same study, the prevalence of NE remained higher than the rate in European children after the age of 9 years [6]. This can be partly explained by the fact that Rahim et al. [16] study was conducted exclusively in an area of low socioeconomic status. Thus we can assume that low socioeconomic status is associated with an increased risk of NE in Sudanese children with or without sickle cell disease.

The association between NE and homozygous sickle cell (SS) disease has been attributed to poor urinary concentrating ability and obligatory high urinary volumes [1,4]. Urine specific gravity, found to be as good as measuring urine osmolarity in normal urine specimen, was measured in a random urine sample for all patients [12]. There was no significant difference in urine specific gravity between enuretic and non-enuretic patients. No significant differences were also demonstrated in studies from Jamaica comparing the maximum concentrating ability of children with homozygous sickle cell anemia and enuresis with age and sex matched children without enuresis [3]. In ten children with homozygous sickle cell anemia and NE treated by Figueroa et al. [3] with intranasal desmopressin acetate (DDAVP), four responded completely and another two had a partial response [3]. These findings support the concept that, although this population has an increased prevalence of nocturnal enuresis, the causes and treatment for this condition may be the same as children without a hemoglobinopathy.

Early and progressive inability to concentrate urine had been reported in sickle cell disorders including sickle cell trait. This persists and/or worsens with age [24]. Despite that not all children with SCD or sickle cell trait develop NE and those who develop it the rate of NE declines with age [8]. Therefore it is difficult to link NE in SCD to hypothenuria.

Sickle cell anemia and NE, as chronic illnesses, are known to be associated with poor growth [25-27]. Poor growth was also documented in Sudanese children with sickle cell anemia (personal unpublished data).Weight; height and BMI was significantly lower in enuretic children with sickle cell anemia compared to nonenuretic children. BMI was significantly lower in enuretic children with sickle cell trait as well. In two reports in the literature growth status was not affected in patients with sickle cell trait [28,29]. Therefore, we can say that apart from the effect of sickle cell anemia, NE is associated with poor growth in these children.

In normal children insufficient cerebral maturation, as an important factor in the pathogenesis of primary nocturnal enuresis, was suggested by previous studies. The indicators of brain immaturity in these studies were inferred from abnormal neurophysiological studies of the brain, significant lag in bone age and brain microstructure abnormalities in areas that are involved in micturition control network [30-34]. Children with sickle cell anemia had been described to have significant retarded bone age at 8 years of age [35]. Various brain injuries were also described in children with sickle cell anemia; cortical thinning was described with the largest regions of thinning in the precuneus and the posterior cingulate [36]. Another abnormality is reduced gray matter volume and that was mainly observed in the caudate, thalamus and cortex [37,38]. Ischemia and/or infarction especially of the thalamus and basal ganglia were also described [39,40]. We can see that some of the areas affected in patients with sickle cell anemia are part of the micturition control network making brain immaturity a possible explanation for NE in this population like normal children.

Low (but still within the normal reference value) serum vitamin B12 and folate level were reported in two studies in patients with primary NE when compared to the control group. This was suggested to have a role in the delay of CNS maturation as well [41,42]. More than half of sickle cell anemia patients had inadequate dietary folate intake. Despite adequate folate supplementation 15% of children with sickle cell anemia had low serum folate.B12 intake was adequate with only 3% had B12 deficiency [43]. Therefore low serum folate level might play a similar role in patients with sickle cell anemia and NE like that in enuretic normal children.

Neveus stated that NE is not only a nocturnal problem but also a disorder of sleep [44]. A systematic analysis of the literature from 1980 to 2010 identified nocturnal enuresis in 31% of children who had Sleep Disordered Breathing (SDB). After adenotonsillectomy the rate dropped to 16% [45]. Using polysomnography in children with sickle cell anemia the prevalence of Sleep Disordered Breathing (SDB), specifically habitual snoring and obstructive sleep apnea hypopnea syndrome, was 35% to 79% [46,47]. Using polysomnography Lehmann et al. demonstrated that habitual snoring and SDB with and without habitual snoring are associated with enuresis in children with SCA [48]. 23.5% of their cohort had SDB without habitual snoring. This means the absence

of habitual snoring in a child with SCD and enuresis does not exclude SDB. In our study we had excluded children who were snoring or had history of snoring .We did not perform sleep studies to identify those with other sleep disorders like apnea and hypopnea which might be associated with NE.

There is an anatomic evidence for an association between 25-hydroxy vitamin D (25(OH) D) and sleep patterns. Vitamin D receptors are present in the same areas that are thought to play important roles in the initiation and maintenance of sleep [49]. Moreover, clinical studies suggested that vitamin D supplementation for patients with sleep disorders may contribute to significant improvements in sleep quality [50-52]. Low 25(OH) D was reported to be associated with an increased risk of NE in normal children aged five to seven years [53]. Vitamin D deficiency in children and adolescents with sickle-cell disease is prevalent and was associated with painful crisis [54]. Low vitamin D level was detected in 63% of Sudanese children with SCA compared to 38% in the control (personal unpublished data). It is plausible to assume that low vitamin D might contribute to NE in patients with SCA through its effect on sleep or by increasing pain episodes that will add to sleep disturbance.

The existence of familial history of nocturnal enuresis in enuretic children with and without sickle cell anemia had been documented [4,55-60]. This had been shown also in this study as well further supporting the genetic predisposition to enuresis. Few gene loci associated with nocturnal enuresis in normal children had been identified [61], but no such work had been done in enuretic children with SCA.

Limitations of the Study

This study did not differentiate between monosymptomatic and nonmonosymptomatic enuresis. The exclusion of those with snoring had possibly led to a lower prevalence rate of NE than it should be.

Conclusion

Sudanese children with SCD are at higher risk to develop NE than normal children. We reported for the first time on the prevalence NE in children with sickle cell trait which is similar to that in normal children. We had also shown the significant adverse effect of NE on the BMI of enuretic children with sickle cell trait. We found no association between NE and hypothenuria. Further research is needed to look at vitamin D level as a possible modifiable cause of enuresis in children with sickle cell anemia.

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