Chapter

Nocturnal Enuresis in Children with Sickle Cell Anemia

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Abstract

Sickle cell anemia (SCA) is the commonest hemoglobin disorder among the black population worldwide. Children with SCA may eventually end up with end-organ complications: the kidneys being one of the most frequently affected organs. The renal complications arise from medullary ischemia and infarction leading to features of tubular dysfunction such as hyposthenuria and renal tubular acidosis. Early in life, children with SCA may present with hyposthenuria: one of the earliest renal defects in the disease which results in an obligatory urine output of more than 2 l in a day. The symptomatic manifestation as nocturnal polyuria is thought to be the reason for nocturnal enuresis observed in these children. In spite of the more prevalent occurrence of nocturnal enuresis in children with SCA than in their non-SCA colleagues, its precise underlying mechanisms still remain controversial, with divergent conclusions regarding its pathogenesis. However, the consensus is now tilting towards a multifactorial etiopathogenesis in affected children. This book chapter aims to discuss the epidemiologic perspectives of nocturnal enuresis in SCA, as well as the current hypotheses on the etiopathogenesis of this complication.

Keywords: sickle cell anemia, nocturnal enuresis, hyposthenuria, multifactorial etiopathogenesis

1. Introduction

Sickle cell anemia (SCA) is the commonest hemoglobin disorder among the black population worldwide [1, 2]. As a genetic defect with the Mendelian autosomal-recessive inheritance, children with the sickle cell hemoglobin genes in the homozygous form have reversibly sickled and irreversibly sickled red blood cells. These abnormal red cells, which become rigid having lost their deformability, consequently block the microvasculature resulting in vasoocclusion. They are also prone to damage which leads to chronic hemolysis. Most of the clinical features of SCA are essentially related to these two events.

Children with SCA may eventually end up with end-organ complications: the kidneys being one of the most frequently affected organs. The renal complications arise from medullary ischemia and infarction leading to features of tubular dysfunction such as hyposthenuria and renal tubular acidosis [3]. As early as 3 years of age, children with SCA may present with hyposthenuria: one of the earliest renal defects in the disease which results in an obligatory urine output of more than 2 l in a day [4]. The symptomatic manifestation as nocturnal polyuria is thought to

be the reason for the observed nocturnal enuresis in these children. In spite of the more prevalent occurrence of nocturnal enuresis in children with SCA than in their normal colleagues, the precise underlying mechanisms have not yet been resolved. Research on the subject has led to divergent conclusions about the pathogenesis; one report had earlier suggested that hyposthenuria was a major determinant of enuresis in the disease [5], while other authors not only controverted this observation but had reported disparate etiopathogenic factors [6–8]. In fact, a recent review of published evidence on the subject indicates similar determinants of nocturnal enuresis for both SCA and non-SCA patients [9]. Thus, the role of hyposthenuria as the exclusive determinant of nocturnal enuresis in children with SCA remains debatable although the consensus is now tilting towards a multifactorial etiopathogenesis in affected children.

This book chapter aims to discuss the epidemiologic perspectives of nocturnal enuresis in SCA, as well as the current hypotheses on the etiopathogenesis of this complication.

2. Nocturnal enuresis in SCA: epidemiologic perspectives

Nocturnal enuresis has been defined as the persistence of urination in the bed (bedwetting) at night, two or more times per week after the age of 5 years, for a period of at least 3 months [10]. It can present as a primary form (no previous dry period) or a secondary form (previous dry period), and as monosymptomatic (absence of daytime symptoms) or non-monosymptomatic (presence of daytime symptoms) [9]. Studies which show that children with SCA have a tendency for nocturnal enuresis more than children with normal hemoglobin however reported different prevalence rates and epidemiologic patterns, depending on study methods and definition criteria (**Table 1**).

2.1 Presumed risk factors for nocturnal enuresis

For instance, the possible effect of sex and socioeconomic status on enuresis in children has been well documented in several studies [7, 11–16]. Firstly, male predominance was noted among children with SCA in some of the studies [7, 11, 13–15], whereas a female predominance was reported in one study [12]. Although the disparity could be due to study selection bias, a similar trend of male predominance has also been reported among non-SCA children [15, 17]. This gender bias suggests that contributory factors to nocturnal enuresis in non-SCA children such as slower maturation and reduced responsiveness to toilet training in boys [18], and more frequent developmental delays [19], may also apply to children with SCA. Secondly, there appears to be no significant impact of socioeconomic status on the prevalence of nocturnal enuresis in both SCA children [7, 14], and their non-SCA counterparts [16]. However, a previous report indicates that enuresis in non-SCA children was more frequent in those from lower socioeconomic classes [17], whereas another study noted a higher prevalence among non-SCA children from higher socioeconomic classes [20].

2.2 Global prevalence rates of nocturnal enuresis

There is a wide variation in the global prevalence rates of nocturnal enuresis among children with SCA (**Table 1**). Prevalence rates vary from 25–51% depending on methodology and definition of nocturnal enuresis adopted in each study. In the West African sub-region, prevalence rates of 41.6, 31.4 and 47.1% were reported in south-west [11], south-east [14], and north-west [15] regions of Nigeria respectively.

Study authors (Country)	Study method (age bracket)	NE definition	Prevalence rates (N)	Sex predominance	Effect of socioeconomic status
Eneh et al. (Nigeria)[†]	Prospective parental interview (5–11 years)	DSM-IV criteria	31.4% (70)	Male	Not significant
Akinyanju et al. (Nigeria)[‡]	Prospective parental interview (4–20 years)	Involuntary passage of urine during sleep>1/month	41.6% (209)	Male	Not reported
Ogunrinde et al. (Nigeria)[††]	Prospective parental interview (5–16 years)	≥3 bedwetting episodes/month (5–6 year old) or 1 episode/month (>6 year old)	47.1% (360)	Male	Not significant
Mabiala Babela et al. (Congo Brazzaville)	Cross-sectional study (5–20 years)	Micturition during sleep in a child aged >5 years	51% (456)	Female	Not reported
Portocarrero et al. (Brazil)	Prospective questionnaire (5–17 years)	Not stated	32% (155)	Not reported	Not reported
Barakat et al. (USA)	Prospective phone interview (5–22 years)	Nocturnal urinary incontinence >5 years of age (>2/week for 3 months)	39.2% (217)	Male	Not reported
Jordan et al. (USA)	Prospective interview (5–17 years)	Urinary incontinence >5 years of age (>2/week for 3 months)	25% (126)	Not reported	Not reported
Figueroa et al. (USA)	Prospective screening questionnaire (6–21 years)	Bed wetting at least 2/week	30% (91)	Not reported	Not reported
Field et al. (USA)	Prospective questionnaire (6–20 years)	Recurrent bed wetting	33% (213)	Not reported	Not reported
Lehmann et al. (USA)	Prospective questionnaire (4–19 years)	Pre-sleep bed wetting/month	39% (221)	Not reported	Not reported
Readett et al. (Jamaica)	Prospective interview (8 years)	Bed wetting 2 nights/week	45% (175)	Male	Not significant
Ekinçi et al. (Turkey)	Prospective questionnaire (6–40 years)	Bed wetting at night >1/week for 3 months	26.4% (55)	Not reported	Not reported

N = study population, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, USA = United States of America.[†]South East Nigeria.

[‡]South West Nigeria.
[††]North West Nigeria.

Table 1.
Nocturnal enuresis (NE) in children with sickle cell anemia: epidemiologic perspectives.

The study in south-east of the country prospectively interviewed parents of SCA subjects aged 5–11 years and parents of age- and sex-matched non-SCA controls; using the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV) criteria to define nocturnal enuresis [14]. In South West Nigeria, the authors also used prospective parental interview for subjects and controls aged 4–20 years, but defined nocturnal enuresis as 'involuntary micturition during sleep which occurred more often than once in a month' [11]. Conversely, the study in North West Nigeria used a structured questionnaire to obtain information from parents of enrolled 5- to 16-year-old subjects and controls; defining nocturnal enuresis as '3 or more episodes of bedwetting per month in a child aged 5 to 6 years and at least, once monthly in an older child' [15]. In Central Africa, a prevalence rate of 51% was reported in a cross-sectional study of 5- to 20-year-old SCA patients (with age- and sex-matched controls) in Congo-Brazzaville which used the defining criteria for nocturnal enuresis as 'complete act of urination most often during sleep in a child over 5 years' [12]. Elsewhere in South America, a Brazilian study which was conducted on 5- to 17-year-old Negroid children and adolescents with SCA reported a prevalence rate of 32% [21]. The authors prospectively administered a questionnaire on the caregivers of these subjects and their age-matched controls. In North America, studies in the United States conducted among African-Americans documented prevalence rates of 39% [6], 39.2% [13], 25% [22], 30% [23], and 33% [24]. In these studies, there was disparity in the age bracket of the study population and the definition adopted for nocturnal enuresis. A prospective phone interview was used in one study, which defined nocturnal enuresis as 'incontinence of urine at night after 5 years of age, more than twice a week for at least 3 months,' while the study population were aged 5–22 years [13]. Another study employed a prospective interview of parents whose children were aged 5–17 years, and defined nocturnal enuresis as 'incontinence of urine at night after 5 years of age, more than twice a week for at least 3 months' [22]. Two of the studies utilized prospective questionnaires [6, 24], but interviewed primary caregivers of subjects who were aged 6–20 years [6], and 4–19 years [24]; defining nocturnal enuresis as 'recurrent problem with bedwetting' [6], and 'wet bed in 1 month before sleep study' [24]. In the last of the studies, nocturnal enuresis was defined 'as wetting bed at least twice per week' [23]; primary nocturnal enuresis was studied among subjects aged 6–21 years with a prospective screening questionnaire. In the Caribbean, a Jamaican study which used the prospective interview method reported a prevalence rate of 45% among 8-year-old SCA patients [7]. The authors' definition of nocturnal enuresis was 'being wet for at least 2 nights per week.' A study in Turkey which adopted the definition criterion of nocturnal enuresis as 'wet bed at night more than once a week for at least 3 months,' reported a prevalence rate of 26.4% [25]. The investigators conducted semi-structured interviews with caregivers of pediatric and adult patients. Perhaps, the combination of SCA and thalassemia patients in the study population (with preponderance of the latter) as well as the wide age-bracket of 6–40 years accounted for this comparatively lower prevalence rate. Furthermore, it has been established that the prevalence of nocturnal enuresis decreases with advancing age, although this finding was essentially noted among non-SCA subjects [26, 27].

3. Nocturnal enuresis in SCA: hypotheses on etiopathogenesis

There are now several hypotheses on the etiopathogenesis of enuresis in children [9, 28, 29]. In fact, it is believed that children with SCA may have a tendency to develop nocturnal enuresis because of the common general etiopathogenic factors in childhood, SCA-related etiopathogenic factors or a combination of both [9]. Specifically, the unresolved questions include the following: What is the exact

role of hyposthenuria in SCA-related nocturnal enuresis? What are the contributory bladder-specific factors? Is there any relationship between sleep disordered breathing (SDB) and nocturnal enuresis in SCA? and Is there a difference in arousability threshold in normal subjects with nocturnal enuresis and those with SCA? [9]. Interestingly, the current hypotheses on the etiopathogenesis of SCA-related nocturnal enuresis revolve around these posers.

Firstly, the nocturnal polyuria resulting from hyposthenuria has long been suggested as the cause of nocturnal enuresis in SCA patients [5]. This hypothesis is supported by the fact that hyposthenuria is one of the commonest and earliest infarction-related renal complications, as intravascular sickling occurs more readily in the kidneys than in any other organs [30]. The microvasculature of the renal medulla is particularly susceptible to hypoxia induced by sickling and vasoocclusion [31]. Medullary ischemia and infarction result in the impairment of the urine-concentrating ability of the vasa recta and juxtamedullary nephrons, as failure of this function is thought to manifest as polyuria and enuresis [32, 33]. Although the 'hyposthenuria hypothesis' has been disputed by some authors who failed to establish a causal link between SCA and enuresis [7, 34], it has later been observed that both urine osmolality and overnight urine volume after fluid restriction were similar in enuretic and non-enuretic children with SCA; making the authors to conclude that low maximum functional bladder capacity and high overnight urine volume to maximum functional bladder capacity ratio were the determinants of nocturnal enuresis in affected children rather than low urine osmolality and high overnight urine volume [8].

Secondly, another hypothesis on nocturnal enuresis in the general population is that it results from an interaction of detrusor instability, delayed arousal from sleep and nocturnal polyuria [28]. Other authors also observed that in enuretic children, the nocturnal bladder capacity during sleep was significantly smaller than the diurnal functional capacity; thus highlighting the role of the inability to hold urine during sleep as an important etiopathogenic mechanism for nocturnal enuresis [29]. Nocturnal polyuria, nocturnal detrusor over-activity and high arousal thresholds are now regarded as crucial factors in the pathogenesis of enuresis, with an underlying mechanism on the brainstem level probably common to these pathogenic mechanisms [35]. In a review which appraised the possible etiopathogenic factors of primary nocturnal enuresis, the partly proven mechanisms were listed as maturational delay of the central nervous system, genetic factors, sleep disorders and SDB, and low levels of nocturnal anti-diuretic hormone (ADH) secretion [36]. Among these hypotheses, delayed functional maturation of the central nervous system is thought to be the most plausible mechanism for nocturnal enuresis as it reduces the child's ability to inhibit nocturnal bladder emptying [36]. This theory is supported by the observation of spontaneous improvement in enuresis which occurs with advancing age [26]. Despite bladder filling, the non-perception of the sensory output emanating from its stretching removes the cortical control on the contraction of the urethral sphincter. Failure of the sleep arousal mechanism due to high arousal thresholds may also contribute to this inability to inhibit nocturnal bladder emptying. Presumably, these hypotheses on etiopathogenesis also apply to nocturnal enuresis in children with SCA. For instance, in these children a strong link between nocturnal enuresis and urinary bladder dysfunction has been reported by several authors [8, 37, 38]. Another recent postulation is that SCA-related enuresis may be due to atonic detrusor muscle which results in an underactive bladder with defective emptying mechanism. This abnormality is thought to be a consequence of chronic bladder ischemia caused by recurrent cycles of ischemia-perfusion injury triggered by vasoocclusion [39]. Evidence for this hypothesis was reported by some authors who studied the urinary bladder function in a transgenic sickle cell disease murine model and found these pathophysiologic changes: reduced urine output, inability

to produce the typical bladder contraction and emptying, lower detrusor muscle, small bladder contraction and reduced urethral contraction [40].

Thirdly, the role of sleep disorders and SDB in the etiopathogenesis of nocturnal enuresis has also been advanced as a sleep-related study show that patients with nocturnal enuresis have difficulties in waking, and are thus considered as 'deep sleepers' [41]. In addition, nocturnal enuresis is associated with SDB as a result of upper airway obstruction in children; surgical relief by tonsillectomy, adenoidectomy or both was reported to have reduced nocturnal enuresis in up to 76% of patients [42]. In a recent study, enuresis has not only been linked to SDB in children with SCA but the severity of SDB has been observed to have a strong correlation with frequency of nocturnal enuresis [6]. Notably, SDB is a common sleep disorder comprising a spectrum from snoring to obstructive sleep apnea syndrome (OSAS) which may worsen nocturnal enuresis through disrupted sleep and neurologic dysregulation [9]. While the finding of a study suggests that SDB is more prevalent in children with SCA than in the general population [43], overwhelming evidence also shows that a significant relationship exists between SDB and nocturnal enuresis among non-SCA children [44–46].

Furthermore, the role of low levels of some vitamins in the etiopathogenesis of nocturnal enuresis has been highlighted in recent studies. For instance, enuretic children were observed to have lower serum vitamin B_{12} and folate levels than their non-enuretic counterparts [47, 48]. The reduced vitamin levels are believed to be associated with slow cortical maturation which has been linked to enuresis. Interestingly, significantly lower or deficient vitamin B_{12} levels have equally been reported in children with SCA compared to non-SCA controls [49, 50]. In addition, increased risk of nocturnal enuresis has been observed in vitamin D-deficient children as this vitamin deficiency directly correlated with severity of enuresis [51]. In a recent systematic review, the prevalence of vitamin D deficiency was reported to vary from 56.4% to 96.4% in children with SCA [52]. This link between vitamin D deficiency and nocturnal enuresis can be explained partly by its influence on SDB and nocturnal polyuria. Reports indicate that low level of serum 25 (OH) D was associated with increased risk of developing OSAS [53], as well as primary snoring [54]. The association of low vitamin levels with OSAS is reportedly mediated through promotion of adenotonsillar hypertrophy, chronic rhinitis and/or myopathy of airway muscle [55]. Better still, low vitamin D levels may result in nocturnal enuresis through obstructive sleep apnea, sleep fragmentation and nocturnal polyuria, which all occur in children with SCA [39].

Another etiologic consideration for nocturnal enuresis seen in SCA is its association with some involuntary movements such as periodic limb movement syndrome and restless leg syndrome. The prevalence of periodic limb movement syndrome in SCA has been documented as 20.5–29% [56–58], which was significantly higher than the rates of 1.2–8% reported for non-SCA children [59, 60]. Similarly, a prevalence rate of 11.1% has been observed for children with restless leg syndrome [56]. Notably, both involuntary movements are associated with sleep disruption [60]. Given that enuretic children have higher incidence of periodic limb movement and sleep fragmentation [59] and the higher rate of periodic limb movement syndrome associated nocturnal enuresis and sleep disruption in SCA patients, it is therefore not surprising to observe a high prevalence rate of nocturnal enuresis in them. To underscore the nexus between these aforementioned etiologic factors (low serum vitamin D level and restless leg syndrome), it has been observed that Vitamin D supplementation also improved the severity of this involuntary movement [61].

In summary, the etiopathogenic mechanisms involved in nocturnal enuresis among SCA and non-SCA children are multifactorial and not mutually exclusive, and they include hyposthenuria-related nocturnal polyuria, decreased bladder capacity or nocturnal bladder over-activity, high sleep arousal thresholds and SDB [9] (**Figure 1**).

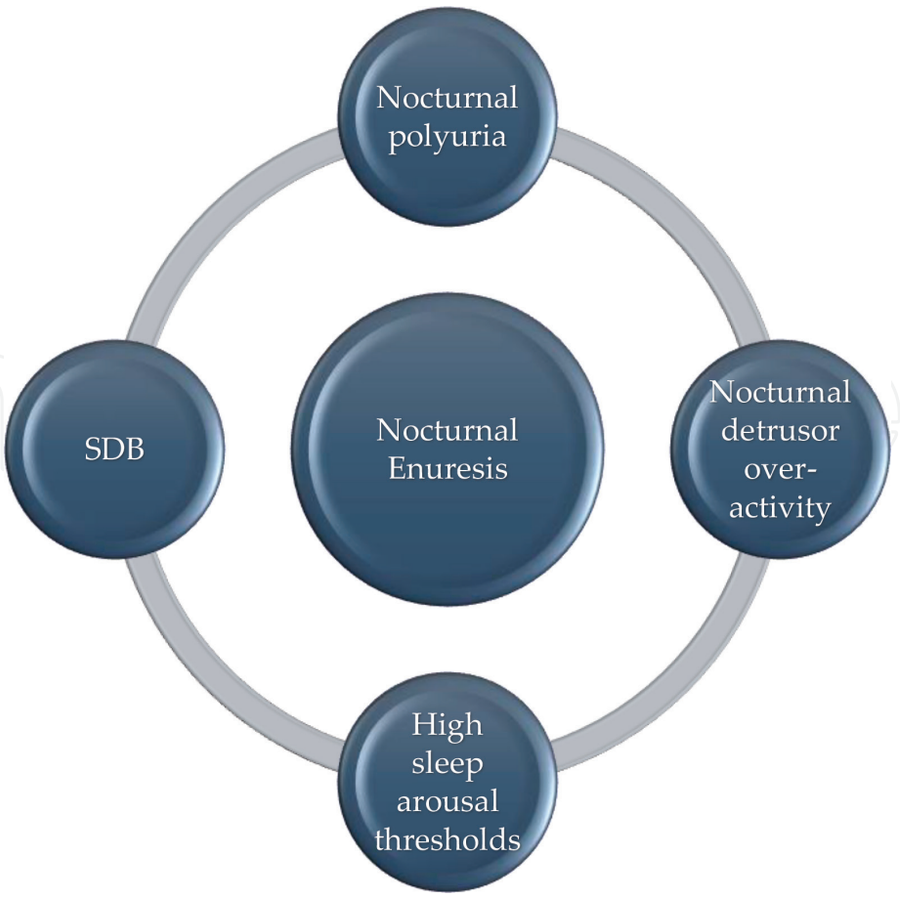

Figure 1.
The proposed etiopathogenic mechanisms for nocturnal enuresis. SDB, sleep-disordered breathing; nocturnal polyuria, induced by hyposthenuria. Concept and design: by SNU (one of the authors).

4. Conclusion

Although nocturnal enuresis appears more prevalent in children with SCA than in their non-SCA counterparts, the exact etiopathogenesis of enuresis is not completely understood. In fact, the suggested mechanisms for nocturnal enuresis in SCA children are also applicable to their non-SCA counterparts. Moreover, the multiregional variations in prevalence rates may be due to differences in definition criteria and study methods. Male predominance in enuretic children has been somewhat established, but there is no unanimity yet on the influence of socioeconomic status on prevalence rates. Perhaps, adopting standardized definitions and study methods may in future minimize the disparities in the reported prevalence rates. More importantly, further research is still required to establish the precise etiopathogenesis of nocturnal enuresis in children with SCA.

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Disclosure

The authors declare that there are no conflicts of interest.

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