Nocturnal enuresis in children with sickle-cell anemia: global prevalence rates, gender bias and hypotheses on pathogenesis

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1. Abstract

Nocturnal enuresis is a prevalent disorder in children and young adults with sickle-cell anemia (SCA): the most common hemoglobinopathy affecting the Negroid population worldwide. Hyposthenuria is one of the earliest renal defects in the disease, but its role as the exclusive causal factor of nocturnal enuresis in SCA still remains debatable as it appears the etiology of nocturnal enuresis is multifactorial in affected children. Interestingly, studies that have elucidated the epidemiologic perspectives of enuresis in SCA have equally shown inconsistent findings regarding for instance, gender predominance and the impact of socio-economic status. This narrative review therefore aims to appraise the multi-regional studies which have reported the prevalence rates, gender bias and determinants of nocturnal enuresis in these children.

Although children with SCA show a tendency to develop nocturnal enuresis more than their non-SCA counterparts with a male predominance, the exact etio-pathogenesis is not completely understood. Possible mechanisms that underlie nocturnal enuresis in subjects with normal hemoglobin genotype appear to be applicable in individuals with SCA. The multi-regional variations in prevalence rates of nocturnal enuresis in SCA patients are due to differences in study definition criteria and methodology. Perhaps, adopting standardized definitions and study methods may in future minimize the disparities in the reported figures. Further research is still required to elucidate the exact pathogenesis of nocturnal enuresis in SCA.

Key words: Nocturnal enuresis; sickle-cell anemia; pathogenesis; prevalence; gender bias

2. Introduction

According to the criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV), nocturnal enuresis is 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 [1]. Clinically, nocturnal enuresis 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) [2]. It is a prevalent disorder in children and young adults with sickle-cell anemia (SCA) according to reports from several studies [3-12]; prevalence rates vary widely from 26.4% to 51% depending on study methods and definitions of nocturnal enuresis [2].

SCA is the most common hemoglobinopathy affecting the Negroid population worldwide [13, 14]; Nigeria accounts for the largest number of cases globally with a prevalence of about 20 per 1000 births [15]. Vaso-occlusion, hemolysis and propensity to bacterial infection are its clinical hallmarks. Serious end-organ complications ultimately result in chronic morbidities and even death. The kidneys are one of the most frequently affected organs as the resultant medullary ischemia and infarction lead to manifestations of tubulopathies such as hyposthenuria and renal tubular acidosis [16, 17], as well as abnormalities of renal hemodynamics [18]. Hyposthenuria is one of the earliest renal defects in the disease [19]: almost universally evident by the age of 3 years, and results in an obligatory urine output of more than 2000 ml per day [20]. It manifests symptomatically as nocturnal polyuria which results in nocturnal enuresis.

Nevertheless, the exact pathogenesis of nocturnal enuresis in SCA has remained controversial despite the higher prevalent rates in affected children when compared to their normal counterparts. While some authors had earlier reported hyposthenuria as the major determinant of enuresis in SCA [21], other investigators have later challenged this association having failed to demonstrate a definite relationship between enuresis and disease severity [11], and having documented different etio-pathogenic factors [10, 22].

Interestingly, studies that have elucidated the epidemiologic perspectives of enuresis in SCA have equally shown inconsistent findings regarding for instance, gender predominance [3, 4, 11, 23, 24], and the impact of socio-economic status among SCA and non-SCA children [11, 23-27].

Despite several studies on enuresis among children with this hemoglobinopathy worldwide, overwhelming evidence implicate the same determinants in both SCA and non-SCA subjects [2]. Thus, the role of hyposthenuria as the exclusive causal factor in SCA still remains debatable as it appears the etiology of nocturnal enuresis is multifactorial in affected children.

This narrative review therefore aims to appraise the multi-regional studies which have reported the prevalence rates, gender bias and determinants of nocturnal enuresis in these children. Using appropriate search terms, information was gathered from studies retrieved from the PubMed database, as well as from relevant textbooks on the topic.

a. Enuresis in SCA: prevalence rates and gender bias

Studies which show that children with SCA have a tendency for nocturnal enuresis more than children with normal hemoglobin have reported different prevalence rates and epidemiologic patterns. Some of the studies also evaluated the effect of gender and socio-economic background of the subjects on enuresis [3, 4, 5, 11, 23-27]. The disparities in the prevalence figures are obviously due to the diverse definition criteria and methodological approaches used in these studies [Table 1].

For instance, in Nigeria (West African sub-region) prevalence rates of 31.4% [23], 41.6% [3] and 47.1% [24] were reported in south-east, south-west and north-west regions of the country respectively. The study in south-east Nigeria was based on a prospective interview of parents, and the investigators used the DSM-IV criteria for the definition of nocturnal enuresis [23]. In the south-west of the country, the authors similarly used prospective parental interview as the study design but defined nocturnal enuresis as involuntary passage of urine during sleep more often than once in a month [3], while other researchers elsewhere in north-west Nigeria used a structured questionnaire to obtain information from parents of enrolled subjects; 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 [24]. In addition, while the south-west Nigerian study was conducted on subjects between 4 to 20 years, the authors in south-east and north-west Nigeria used subjects in the age ranges of 5 to 11 years and 5 to 16 years respectively.

In Congo Brazzaville (Central Africa), a prevalence rate of approximately 51% was documented [4]. The researchers conducted a cross-sectional study of two groups of participants (SCA patients and patients with normal hemoglobin) aged 5 to 20 years, and defined nocturnal enuresis as complete act of urination most often during sleep in a child over 5 years. For the three Nigerian studies, male predominance was also noted among the SCA children with nocturnal enuresis [3, 23, 24], whereas the study in Congo Brazzaville reported a female predominance [4]. To recap, the differences in prevalence rates and gender predominance can be explained by subject selection bias, differences in definition of enuresis, and non-exclusion of confounding variables like diabetes mellitus, epilepsy and urinary tract infection by some of the studies [3, 4]. These variables can potentially cause enuresis. Nevertheless, since a similar trend of male predominance has been observed among non-SCA children [24, 27], the gender bias suggests that contributory factors to nocturnal enuresis in non-SCA children such as slower maturation and reduced responsiveness to toilet training in males [28], and more frequent developmental delays [29], are also applicable to children with SCA.

In Brazil (South America), one study among the Negroid population reported a prevalence rate of 32% [12]. The authors administered a prospective questionnaire on care-givers of SCA children and adolescents, as well as controls; their ages ranging from 5 to 17 years. In the United States (North

America), several studies among African-Americans have documented prevalence rates of 39.2% [5], 25% [6], 30% [9], 33% [8], and 39% [10]. The authors used different definitions for enuresis and studied subjects with different age groups. In one of the studies, a prospective phone interview was used and nocturnal enuresis was defined as incontinence of urine at night after 5 years of age, more than twice a week for at least 3 months, while the age range of the children studied was from 5 to 22 years [5]. This study also noted a significant male predominance among the SCA patients. In a related study, the investigators conducted a prospective interview of parents whose subjects were aged 5 to 17 years; defining nocturnal enuresis as incontinence of urine at night after age 5 more than twice a week for at least 3 months [6].Two of the studies used prospective questionnaires [8, 10], but interviewed primary care-givers of subjects who were aged 6 to 20 years [8], and 4 to 19 years [10]; defining nocturnal enuresis as recurrent problem with bedwetting [8], and wet bed in 1 month before sleep study [10]. In the last of the studies, nocturnal enuresis was defined by the investigators as wetting bed at least twice per week [9]. Primary nocturnal enuresis was studied among children aged 6 to 21 years using a prospective screening questionnaire. Again, a comparative analysis of these studies still indicates that the slight differences in the prevalence rates could be explained by the varying age ranges of the study population as well as the different definition criteria used by the researchers for enuresis.

Elsewhere in Jamaica (the Caribbean), another study that adopted the prospective interview method recorded a prevalence rate of 45 % among 8 year-old SCA patients; also noting a male predominance [11]. The authors' definition of nocturnal enuresis was being wet at least 2 nights per week. However, in Turkey (Europe), other workers using the definition criterion of wet bed at night more than once a week for at least 3 months, reported a prevalence rate of 26.4 % [7]. They conducted semi-structured interviews with care-givers of pediatric and adult patients. It was likely that the combination of SCA and thalassemia patients in the sample size (with more of the latter) and the very wide age range of 6 to 40 years partly accounted for this relatively lower figure. Secondly, it has been established that the prevalence of enuresis decreases with age albeit among non-SCA subjects [30-32]; an observation that was attributed to spontaneous improvement of nocturnal enuresis by some of the investigators [30].

b. Enuresis in SCA: the hypotheses on pathogenesis

Despite several studies on nocturnal enuresis in children with SCA, there is no unanimity on its exact pathogenesis. Interestingly, several hypotheses have been advanced about the pathogenesis of enuresis in childhood generally [2, 33-34]. In a recent in-depth review on the subject, it is believed that children with this hemoglobinopathy may have nocturnal enuresis because of the common general etio-pathogenic factors in childhood, SCA-related etio-

pathogenic factors or a combination of both [2]. Indeed, the questions that still remain unanswered include the following: the exact role of hyposthenuria in SCA-related nocturnal enuresis; the contributory bladder-specific factors; the relationship of sleep disordered breathing (SDB) and nocturnal enuresis in SCA; as well as the difference in arousability threshold in subjects with nocturnal enuresis and SCA [2]. The major hypotheses on pathogenesis revolve around these questions.

First, hyposthenuria-related nocturnal polyuria has been linked to nocturnal enuresis in SCA patients in one of the previously mentioned studies [21]. This hypothesis appears plausible given the fact that hyposthenuria is one of the most common and earliest infarction-related renal complications, as intra-vascular sickling occurs more readily in the kidneys than any other organs [19]. The renal medullary micro-vasculature is particularly prone to hypoxia induced by sickling and vaso-occlusion [35]. Ischemia and infarction of the medulla results in the destruction of the vasa recta and juxta-medullary nephrons responsible for urine concentration; failure of this function is thought to manifest as polyuria and enuresis [16, 36]. However, workers in Jamaica not only failed to establish any definite association between enuresis and disease severity in SCA [11], but also noted in another study that both urine osmolality and overnight urine volume after fluid restriction were similar in enuretic and non-enuretic children with SCA; they suggested 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 [22]. The conclusions of these investigators have been corroborated by the finding of another study in Nigeria [37], which reported a higher prevalence of hyposthenuria in children with SCA but documented no link between hyposthenuria and nocturnal enuresis.

Furthermore, another hypothesis of enuresis in the general population is that it results from an interaction of detrusor instability, delayed arousal from sleep and nocturnal polyuria [33]. Other authors also observed that in enuretic children, the nocturnal bladder capacity during sleep was significantly smaller than the diurnal functional capacity; underscoring the role of inability to hold urine during sleep as an important cause of nocturnal enuresis [34]. It has indeed been emphasized that nocturnal polyuria, nocturnal detrusor over-activity and high arousal thresholds are central in the pathogenesis of enuresis, with an underlying mechanism on the brainstem level probably common to these pathogenic mechanisms [38]. In one review that appraised the possible etio-pathogenic factors of primary nocturnal enuresis [39], the partly proven mechanisms were listed as maturational delay, genetic factors, sleep disorders and SDB, and low levels of nocturnal anti-diuretic hormone (ADH) secretion.

Among these concepts, the most commonly accepted mechanism for nocturnal enuresis is delayed functional maturation of the central nervous system, which reduces the child's ability to inhibit nocturnal bladder emptying

[39]. Evidence that tends to support this theory is the spontaneous improvement in enuresis (as previously mentioned) which is reported to occur with age [30]. Despite bladder filling, the sensory output emanating from the stretching of the bladder is not perceived, and thus obviates the central cortical control over the urinary sphincter contraction. Failure of the arousal mechanism due to high arousal thresholds may also contribute to this inability to inhibit micturition. This brings to the fore another pathogenic concept; the role of sleep disorders and SDB. A sleep-related study has shown that patients with nocturnal enuresis have difficulties in waking, and are considered as 'deep sleepers' [40]. Nocturnal enuresis has also been associated with SDB following upper airway obstruction in children, and surgical relief of the obstruction by tonsillectomy, adenoidectomy or both was reported to have reduced nocturnal enuresis in up to 76 percent of patients [41]. The findings of a more recent study in the USA have equally shown that enuresis is linked to SDB in children with SCA [10]. SDB is a common condition of sleep comprising a spectrum from snoring to obstructive sleep apnea syndrome (OSAS) which may increase nocturnal enuresis through disrupted sleep and neurologic dysregulation [2]. Overwhelming evidence suggests a strong relationship between SDB and nocturnal enuresis among children without SCA [42-45]. A report also shows that SDB is more prevalent in children with SCA than in the general population [46]. The study in the USA also demonstrated a significant relationship between increases in the severity of SDB and the frequency of nocturnal enuresis [10].

Another interesting hypothesis is the role of genetic factors in the etio-pathogenesis of enuresis. A family history of nocturnal enuresis is found in most children with the condition [39]. Heredity as an etiologic factor of primary nocturnal enuresis has been confirmed by the identification of a gene marker located on chromosome 13, according to a study by Danish investigators [47]. However, no specific gene locus has been identified. One of the studies reviewed in this paper suggests that parental history of nocturnal enuresis may play more role as a socio-demographic risk factor in children with SCA than in non-SCA children [23].

Finally, some studies indicate that children with enuresis did not show a normal rise in the nocturnal secretion of ADH [48, 49]. In other words, these children have low levels of nocturnal ADH secretion. Thus, abnormal nocturnal secretion of ADH may be a significant factor in the etio-pathogenesis of nocturnal enuresis in some children, although studies of gene markers do not correlate with abnormalities of ADH function [47]. In summary, the recent review on nocturnal enuresis in SCA concludes that the non-mutually exclusive causes of nocturnal enuresis in affected children should include hyposthenuria-related nocturnal; polyuria, decreased bladder capacity or nocturnal bladder over-activity, increased arousal thresholds and SDB [2].

c. Conclusions

Although children with SCA show a tendency to develop nocturnal enuresis more than their non-SCA counterparts as reported in several of the reviewed studies, the exact etio-pathogenesis is not completely understood. Possible mechanisms that underlie nocturnal enuresis in subjects with normal hemoglobin genotype are also applicable in individuals with SCA. The multi-regional variations in prevalence rates are due to differences in study definition criteria and methodology. Perhaps, adopting standardized definitions and study methods may in future minimize the disparities in the reported figures. In addition, further research is still required to elucidate the exact pathogenesis of enuresis in SCA.

d. Conflict of interests

None declared by the authors

g. References

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Table 1. Nocturnal enuresis in SCA: the regional differences in prevalence rates

Authors(countries)	Definition criteria	Study method (Age range of subjects)	Prevalence rate (N=sample size)	Gender pre-dominance
West Africa				
-Akinyanju et al [3]. (Nigeria)	- Involuntary passage of urine during sleep more often than once in a month	-Prospective parental interview (4 to 20 yrs.)	-41.6% (209)	-male
-Eneh et al [23]. (Nigeria)	-DSM -IV criteria	-Prospective parental interview (5 to 11 yrs.)	-31.4% (70)	-male
-Ogunrinde et al [24]. (Nigeria)	- Nocturnal enuresis as 3 or more episodes of bedwetting per month in a child aged 5 to 6 yrs. and at least, once monthly in an older child	-Prospective parental interview with structured questionnaire (5 to 16 yrs.)	-47.1% (360)	-male
Central Africa				
-Mabiala Babela et al [4]. (Congo Brazzaville)	- Complete act of urination most often during sleep in a child over 5 years	- (5 to 20 yrs.)	-51% (456)	-female
South America				
-Portocarrero et al [12]. (Brazil)	-	-Prospective questionnaire (5 to 17 yrs.)	-32% (155)	-
North America				
-Barakat et al [5]. (United States)	- Incontinence of urine at night after 5 years of age, more than twice a week for at least 3 months	-Prospective phone interview (5 to 22 yrs.)	-39.2% (217)	-male
-Jordan et al [6]. (United States)	- Incontinence of urine after age 5 more than two-times per week for at least 3 months	-Prospective interview (5 to 17 yrs.)	-25% (126)	-
- Figueroa et al [9]. (United States)	- Wetting bed at least twice a week	-Prospective screening questionnaire (6 to 21 yrs.)	-30% (91)	-
-Field et al [8]. (United States)	- Recurrent problem with bedwetting	-Prospective questionnaire (6 to 20 yrs.)	-33% (213)	-
-Lehmann et al [10]. (United States)	- Wet bed in one month before sleep study	-Prospective questionnaire (4 to 19 yrs.)	-39% (221)	-
The Caribbean				
- Readett et al [11]. (Jamaica)	-Wet at least two nights a week	-Prospective interview (8 yrs.)	-45% (175)	-male
Europe				
- Ekinci et al [7] (Turkey)	- Wet bed at night more than once a week for at least 3 months	-Prospective questionnaire (6 to 40 yrs.)	-26.4% (55)	-