



Cohort Study

New insights in treatment of monosymptomatic enuresis

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ABSTRACT

Objective: Nocturnal enuresis (NE) is defined as uncontrollable bed-wetting for at least three consecutive months in children over 5 years. Sleep could be dramatically altered in children with primary nocturnal enuresis (PNE); consequently, this helps to confirm the assumption that PNE appears to modify sleep structure, or it might be the result of an irregular sleep structure itself.

Method: This study conducted on 180 patients with monosymptomatic nocturnal enuresis. Their age was ranged from 6 to 18 years, and they were still having nocturnal enuresis episodes. We record two main points: first, if the child is a regular sleeper or not. The second point if the child is a regular bed wetter or not. This work fully compliant with the STROCCS criteria (Agha et al., 2019).

Result: A total of 180 children were included (Male 122, 67.8%, Female 58, 32.2%). The mean age was 8.9 (± 2.4). This study showed that children aged 7–10 years are significantly more inclined to be reported as specific time bed-wetter's, whereas those aged between 11 and 13 are significantly less likely to wet their bed at a specific time ($p = 0.001$). Children who tend to sleep more often near a specific time each night are 6.74 times more prone to bed-wet around a particular time during their sleep ($p < 0.001$).

Conclusion: This study can be considered as hypothesis-generating that shed light on the possible correlation between the adherence to sleep at a specific time and its effect on the time of enuresis and the number of bedwetting.

1. Introduction

Nocturnal enuresis (NE) is a common complaint among the pediatric age group. It is defined as uncontrollable bedwetting for at least three consecutive months in children over 5 years [1]. The prevalence of enuresis declines with age. For instance, 15% of children at the age of 5 experience nocturnal urinary incontinence compared to 5–10% at the age of 7 years and only 1–2% for ≥ 15 years old [2–4]. Furthermore, it might be influenced by racial, cultural, socio-economic, and environmental factors [5]. Boys are more likely than girls to wet their beds. Overall, 60% of bed-wetter are males. Additionally, 90% of bedwetting

occurs at night [6,7].

Nocturnal enuresis is classified into Monosymptomatic Nocturnal Enuresis (MNE) with no daylight urinary manifestations and Non-Monosymptomatic Nocturnal Enuresis (NMNE) when followed by daytime urinary symptoms such as urgency, dysuria, frequency, or dribbling [8,9]. Moreover, MNE is subcategorized into primary and secondary types. Primary Nocturnal Enuresis (PNE) is referred to patients who may have never reached a satisfactory duration of night-time dryness, and it is found that 80% of the children with NE complaining of this type. In contrast the secondary form is defined as children who experience enuresis after at least 6 months of dry phase [10]. Historically, NE has

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been seen as a part of the lower urinary tract symptoms [11]. However, recent advancements in circadian biology and sleep science indicate that it may be necessary to consider NE as a type of circadian dysfunction [12]. Nevertheless, studies have shown that disrupted sleep itself is potentially harmful and drastically worsening the quality of life and having a strong association with malignancies, hypertension, diabetes, and mental disorders [13,14]. This study aims to determine if regular sleep patterns have a relationship to the regularity of wet episodes in enuretic patients, by monitoring children with over 3 episodes/week. The circadian rhythm oscillation due to irregularity in going to bed might explain the differences between responders and non-responders to medical treatment and might aid in enhancing urotherapy.

2. Method

2.1. Study population and data collection

This prospective study was conducted at the urology department in Prince Hamza Hospital during 9/2019 to 12/2019. Ethical approval was taken from the hospital ethical committee. Patients were considered eligible for inclusion in the study if they were 6–18 years old, diagnosed with MNE, were previously treated or not, and were still having NE episodes and their parents willing to give informed consent. Patients were excluded from the study if they were diagnosed with NMNE, patients with diurnal symptoms, and those whose parents are unwilling to give informed consent.

The study was performed over for two weeks. The primary caregiver instructed to let the child behave as usual and records two main points: first if the child is going to bed regularly at a specific time every night, which is called a regular sleeper or is not called an irregular sleeper. The second point was to instruct the primary caregiver to monitor the child's bed every hour till the child awake to notice when the child wets the bed, we called the child who wets the bed at specific time as a regular bed wetter and whom not as an irregular bed wetter. Initially, we enrolled a total of 230 patients with monosymptomatic nocturnal enuresis. However, 50 patients were omitted from the study due to the inability of primary caregivers to follow their children throughout the observation.

All patients attending the urology clinic at Prince Hamza Hospital during the data collection period were screened carefully by taking a detailed medical history, performing a physical examination, and doing a routine investigation to exclude any underlying organic causes and detect diurnal symptoms. Additionally, informed consent was obtained from all patient's parents recruited to participate in this study.

This study registered in research registry with the number [researchregistry6772].

<https://www.researchregistry.com/register-now#user-researchregistry/registerresearchdetails/6087358f098243001c691c5d/>

2.2. Variables

The variables used in this study included: Height, weight, number of family members, socioeconomic class, sex, age, age categories where the patient's age was divided into four categories (6 years, 7–10 years, 11–13 years, and 14–18 years) if the child sleeps regularly at the same time per night and does bed-wetting around the same time each night.

2.3. Statistical analysis

All data were analyzed using the SPSS statistical software package (version 25.0). Continuous variables were presented as means \pm standard deviations (SDs) and Student t-tests were used to compare the mean of the two groups. Categorical variables were presented as numbers and percentages and chi-squared (χ^2) tests were used to compare the two groups. To establish the combined association between children's sex, age, and their tendency to sleep around a specific time each night with

their odds of bedwetting near a specific time at night, a multivariable logistic regression analysis was performed with p-value < 0.01 .

3. Result

A total of 180 participants were included in this study (Male 122, 67.8%, Female 58, 32.2%). The age of the study sample ranged from 6 to 18 years (mean 8.9 ± 2.4 years). More than half of the participants were 7–10 years old with a percentage of 61.1%.

Regarding the children sleeping time, most of the child tended to sleep around the same time each night ($n = 132$ (73.3%)), whereas only 26.7% of the children did not sleep around such specific time habitually. Additionally, the study showed that most of the children tended to wet their beds around a specific time each night 70% compared to 30% of the children who tended to wet their beds during various times each night. Children's demographic and sleep and enuresis characteristics in this study are presented in Table 1. Additionally, Patient's Body Mass Index (BMI), number of family members and socioeconomic class are shown in Table 1.

This study revealed that there was no association between the child's sex and their likelihood of bedwetting around specific times at night ($p = 0.626$). However, according to an independent samples t-test, children whose parents believed their enuresis times were peculiarly around a specific time at night were significantly younger (Mean age = 8.6, SD = 2.2) than those whose parents reported the child's enuresis took place on a sporadic time (mean age = 9.6, SD = 2.9), $t(82.2) = 2.61$, $p = 0.020$, denoting those children who had nocturnal enuresis around specific times each night were significantly younger than those who had not. In addition, it was found that those aged 7–10 years are significantly more inclined to be reported as specific time bedwetter's, and those aged between 11 and 13 are significantly less likely to wet their bed at a specific time ($\chi^2(3) = 15.45$, $p = 0.001$). The results are displayed in

Table 1
Children's demographic and sleep and enuresis characteristics (N = 180).

	Frequency	Percentage
Sex		
Male	122	67.8
Female	58	32.2
Age (years), Mean \pm SD	8.9 \pm 2.4	
Body Mass Index (BMI)		
6 Years	15.1 \pm 0.7	
7–10 Years	16.6 \pm 0.5	
11–13 Years	18.1 \pm 1	
14–18 Years	25.8 \pm 1.2	
Age categories		
6 Years	25	13.9
7–10 Years	110	61.1
11–13 Years	36	20
14–18 Years	9	5
Number of family members		
1–2	10	5.6
3–5	146	81.1
More than 5	24	13.3
Income^a		
Low	27	15
Medium	141	78.3
High	12	6.7
Regular sleeping at the same time per night		
Yes	132	73.3
No	48	26.7
Bed-wetting around the same time each night		
Yes	26	70
No	54	30

^a Low less than 700 US dollar, Medium 701–2000 USD, High more than 2001USD.

Table 2

The associations between the children’s demographic and regularity of sleep time with their tendency to bedwetting at around specific times at Night (N = 180).

Variables, N (%)	Bed-wetting around the specific time each Night		test statistic	p-value
	Yes = 126	No = 54		
Sex			$\chi^2(1) = 0.237$	0.626
Male	84 (66.7%)	38 (70.4%)		
Female	42 (33.3%)	16 (29.6%)		
Age, Mean ± SD	8.6 ± 2.2	9.6 ± 2.9	t (82.2) = 2.61	0.020
Age Categories:			$\chi^2(3) = 15.45$	0.001
6 Years	16 (12.7%)	9 (16.7%)		
7–10 Years	88 (69.8%)	22 (40.7%)		
11–13 Years	17 (13.5%)	19 (35.2%)		
14–18 Years	5 (4%)	4 (7.4%)		
Regular sleeping at the same time per night			$\chi^2(1) = 32.9$	<0.001
Yes	108 (85.7%)	24 (44.4%)		
No	18 (14.3%)	30 (55.6%)		

Table 2.

As shown in Table 3 the multivariate analysis suggested that more than one of the tested predictor variables had a significant association with the children’s enuresis around a specific time each night $\chi^2(5) = 40.42$, $p < 0.001$. For instance, children who tend to sleep more often near a specific time each night are 6.74 times more prone to bed-wet around a particular time during their sleep ($p < 0.001$). Moreover, male and female children were found to be equally inclined to bed-wet around a specific time at night, $p = 0.739$. Also, children aged above 13 years, and those aged 6 years did not differ in the likelihood of bed-wetting considering the other variables are equal, $p = 0.462$, $p = 0.220$, respectively. It was also found that children aged between 11 and 13 years were 0.25 times less likely to develop nocturnal enuresis compared to children aged between 7 and 10 years.

Table 3

A Multivariate Logistic Regression analysis explaining the combined association between children’s sex, age, and their incitement to sleep around a specific time with their odds of bedwetting near a specific time at night (N = 180).

	B	S.E.	OR	95% CI for OR		Sig.
				Lower	Upper	
Sex = Male	-0.14	0.41	0.87	0.390	1.952	0.739
Sleeps around specific time at Night = Yes	1.91	0.39	6.74	3.136	14.488	0.000
Age categories						0.029
6 Years	-0.65	0.53	0.52	0.186	1.472	0.220
11–13 Years	-1.37	0.46	0.25	0.103	0.629	0.003
14–18 Years	-0.58	0.79	0.56	0.118	2.643	0.462
Constant	0.05	0.39	1.05			0.893

Reference age comparison group = Children aged 7–10 years. Dependent Variable = Tendency to Bed-wet around specific time at Night. OR = adjusted Odds Ratio.

4. Discussion

Enuresis refers to the involuntary wetting of clothes or bedding by urine through the day or nighttime in children older than 5 years of age [8]. The incidence of enuresis varies with age [1]. It is classified into MNE and NMNE forms. The previous subdivision depends on the presence or absence of concomitant lower urinary tract symptoms or a history of bladder dysfunction. It differs clinically, therapeutically, and pathogenesis [8]. There are three main factors that may play an important role in the pathophysiology of enuresis: high nocturnal urine production, bladder capacity or increased detrusor activity, and the threshold of arousability [1]. In addition, a positive family history is reported in many children [15]. However, the precise etiology of enuresis is still mysterious. It forms a high priority for the physician since enuresis may negatively influence the child’s psychosocial development as well as present with various comorbidities such as learning disabilities, neurological diseases, attention difficulties, and sleep disturbances. The last one might be considered to be the most important comorbidity in enuretic children [16,17].

Sleep could be dramatically altered in children with PNE, consequently, this helps to confirm the assumption that PNE appears to modify sleep structure, or it might be the result of an irregular sleep structure itself [7,18]. However, according to a recent study in sleep science and circadian biology show that it is also important to consider NE as a sort of circadian dysfunction [12]. Additionally, the normal circadian rhythm of glomerular filtration rate (GFR), sodium excretion, and diuresis were reported to be absent in MNE patients [19]. It is widely believed that inadequate nocturnal increase of antidiuretic hormone (ADH) in children with nocturnal polyuria (NP) leads to a high rate of diuresis overnight with low osmolarity. Nevertheless, there is a strong evidence that the primary pathogenetic factor in these patients is a drop in ADH overnight [20,21]. Normally during sleep, ADH secretion gradually increases in order to allow the nocturnal urinary output to become a highly concentrated and low volume. The circadian rhythm is absent in many children with NP. desmopressin is more likely to help children with NP because the nocturnal vasopressin levels have been shown to be low in a large number of patients. Thus, using desmopressin, (a synthetic analog of AVP) is considered as the first-line management for children with MNE and NP [21,22].

This study revealed that the majority of children who sleep at a particular time suffer from NE at a specific time and are younger than the rest of the children, while children who sleep at an unspecified time suffer from multiple bedwetting at an undetermined time. One study shares the same finding regarding the age, where it mentioned that children with NE particularly older boys had sleep problems more than those without NE [23]. This may be explained by the fact that younger children adhere to the instructions of their parents and sleep at the same specified time every day, compared to older children who do not abide by the instructions of their parents to sleep at the same specified time. Although we are not able to explain how sleeping time affects the bed-wetting time, this finding may play an important role in the management of NE by predicting the time of enuresis.

In research concerning Nocturnal enuresis; which is limited by time and as it supposed that each trial necessitate standardization the trial condition and one of it is to control sleep time indeed; we don’t have a clear idea about patient habit of sleep in real life; also patient motivation and compliance usually overwhelming normal behave and habits [29], Comparing the response of desmopressin to placebo in his review Glazener et al, found that 70% of patient respond over placebo to desmopressin [26]. Johan et al. stated as an expert opinion for him which we also agreed with him that it needs 2–6 weeks for desmopressin to take its effect in an acceptable way which needs to be taken 1 h before sleep to get the maximum response [27],utilizing this observations, putting in mind that we found that 70% of our sample we their beds at regular time at night, which is only observation without interference or standardize the patient condition we can use this to conclude that in fact this

percentage of patients who responds to desmopressin or being compliant with medication regime are already persons whom their attitude fits with the requirement of research and clinical trials.

In his study Van Herzeele et al., for studying poor compliance for the treatment of NE he found that, attention to explain response to medication which gives the highest success rate and mainly desmopressin; factors such as functional bladder capacity, nocturnal polyuria, medication pharmacokinetics and differences in the primary nocturnal enuresis definition, but little studied the compliance and adherence for medication protocol in his clinical trial, he found that as the starting of the study 91% committed to protocol and with time for 3 months compliance reached 71% [29], another study found that mean commitment to the medical regime was 70% to both parents and child [28].

In [26,28,29] they trigger a new factor that might help understanding why there is responders and non-responders, which in their opinion was poor compliance to medical regime includes timing of medication, taking the medication and family observation for their child. Literature lack studying this variable which is the natural time of child to go to bedroom without being observed in home or in laboratory, we used their findings indirectly by studying the natural life of child with MNE which in our observational study found that 73% of observed child go to sleep at regular time and over all wets their beds regularly were about 70%, which indirectly we can say that the first factor that is not studied adequately the child behave out the standardization of research which is in fact their mode of sleeping at specific time, by this observation in fact we can explain this poor compliance which is about 30%, and non-fully responders also on desmopressin by claiming that rhythmicity in sleep with respecting light/dark cycle and it is effect on circadian dysfunction.

Many studies conducted about the relation between the NE and sleep disorders in terms of depth of sleep, bedtime resistance, daytime sleepiness, sleep patterns [23–25]. However, up to our knowledge this the first study that shed light on the possible correlation between the adherence to sleep at a specific time and its effect on the time of enuresis which may give a new insight on MNE, enlighten a new understudied hidden etiology, helping in raising the response rate of urotherapy and desmopressin.

4.1. Limitation

One of the limitations of our study is it was conducted at a single institution and the data were based on self-reporting which is subject to recall bias and income was not included in the analysis.

5. Conclusion

The present study showed that the chronobiology of micturition plays a vital role in the regulation of bedwetting in MNE children. Therefore, it should be considered in future research for the pathophysiology of NE. Irregularity in going to bed for sleep which initially goes on as a habit led to a disturbance in the physiological clock. This might be a hidden cause for MNE and might explain the failure of urotherapy and medical therapy [30].

Ethical approval

Ethical approval was taken from the hospital ethical committee at Prince Hamza Hospital.

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Author contribution

Morad Bani-Hani, Abdullah Alhourri and Alaa Sharabi were responsible for the conception and design of the study, analysis and interpretation of data, drafting and final approval of the manuscript. Saiel Saleh, Sager Nawafleh, Mohammad Al-zubi, Hassan Alkhatatbeh, Y altal, Radi M.A. Siouf and Hasan Nabil Al Hourri were actively involved in collecting, interpretation and analyzing data and approved the final manuscript.

Please state any conflicts of interest

There is no conflict of interest.

Registration of research studies

1. Name of the registry: New Insights in Treatment of Mono-symptomatic Enuresis.
2. Unique Identifying number or registration ID: researchregistry6772.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): <https://www.researchregistry.com/browse-the-registry#home/>

Guarantor

Morad Bani-Hani, MD, Abdullah Alhourri, MD, Alaa Sharabi, MD, Saiel Saleh, MD, Sager Nawafleh, MD, Mohammad Al-zubi, MD, Hassan Alkhatatbeh, MD, Y altal, MD, Radi M.A. Siouf, MD, and Hasan Nabil Al Hourri, MD.

Consent

Informed consent was obtained from all patient's parents who were recruited to participate in this study.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amsu.2021.102470>.

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