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ORIGINAL ARTICLE

Sleep features of nocturnal enuresis: relationship between rapid eye movement sleep latency prolongation and nocturnal enuresis

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Abstract

Nocturnal enuresis, or bed wetting, is the involuntary urination during sleep. One of its causes is difficulty awakening during sleep, suggesting a relationship between Nocturnal enuresis (NE) and sleep. However, no studies have yet clarified the relationship between NE and sleep, and the effects of sleep structure in NE children are not yet known. Assuming that changes in sleep structure are related to NE, there would be a difference in sleep structure between days with and without NE. We measured the sleep electroencephalograms of 27 at home patients aged 6–16 years, evaluated the differences between days with and without NE, and examined the NE-associated sleep characteristics associated. The evaluation items were total sleep time, sleep efficiency, the ratio of rapid eye movement (REM) to non-REM sleep, REM sleep latency, and non-REM sleep latency. Factors influencing NE were examined by logistic regression analysis, with NE presence/absence as the dependent variable and each evaluation item as the independent variable. Given that 2–6 measurements were made for each patient, Generalized Estimating Equations was used in the analysis. NE positively correlated with prolonged REM sleep latency, but no significant differences were found in other sleep structures. A positive correlation exists between NE and prolonged REM sleep latency. Changes in sleep structure in the early stages of sleep may lead to increased nocturnal urine volume and increased NE frequency.

Keywords Nocturnal enuresis · Sleep architecture · REM sleep latency · Anxiety

Introduction

Nocturnal enuresis (NE), or commonly known as bed wetting, refers to the involuntary urination during sleep. According to the International Children's Continence Society (ICCS), it is a "symptom of incontinence, at least once a month, lasting at least 3 months, at age 5 years or older" [1]. The male-to-female ratio is 1.5:1; thus, it occurs more frequently in boys than in girls, with an overall prevalence of 10–15% in children [2]. In particular, the prevalence is 5–10% and 3% in children aged 7 and 10 years, respectively, and 0.5–1.0% in adults [3]. Approximately 15% of patients with NE recover spontaneously each year [2, 3]. NE has two types: monosymptomatic NE (MNE) without lower urinary tract symptoms (LUTS) and non-monosymptomatic NE (NMNE) with LUTS. MNE is caused by excessive nocturnal urine production, decreased bladder capacity, and inability to awaken from sleep [4]. The ICCS has established criteria for nocturnal polyuria and decreased bladder capacity [1]. Various studies have reported the correlation between nocturnal bladder capacity and NE, including its frequency, severity [5], and response to treatment [6]. However, the relationship of NE with sleep remains insufficiently understood.

The relationship between NE and sleep has been studied using various methods. For example, questionnaires [7], actigraphy [8, 9] to detect body movements, PSG [10–12] to evaluate sleep based on electroencephalogram (EEG), respiration, and muscle movements.

Currently, no study has clarified the relationship between sleep and nocturia. Although the timing of nocturia during sleep has been extensively studied, no clear rule of thumb has been established [13].

For example, regarding nocturia and arousal from sleep, children with NE have been hypothesized to less likely be aroused by loud noises during sleep than normal children

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[7]; however, a study evaluating the EEG of children with NE by PSG revealed that cortical arousal was more common in them than in normal children [10]. Some studies reported that the frequency of cortical arousal increases when the urge to urinate is transmitted from the bladder to the brain during the night [11], while others considered the possibility that cortical arousal frequency may be a trigger for NE [9].

Other studies have examined various factors, such as hemodynamics, hormone secretion, and sleep apnea, but the role of sleep in NE etiology remains unclear [13].

The frequency of NE varies among individuals, and each patient may have NE on some days and NE on other days. Sleep also changes from day to day, influenced by daytime activities and the sleep environment, and changes in sleep may highly likely influence the presence or absence of NE.

Therefore, this study aimed to analyze the sleep structure of NE using EEG to evaluate the influence of daily sleep structure (sleep structure and sleep onset latency) on the presence or absence of NE.

Materials and methods

Participants

We enrolled patients with NE aged 5 years or older who attended Showa University Fujigaoka Hospital (Kanagawa, Japan) between November 2017 and February 2021. We proposed to evaluate the quality of sleep using EEG and explained the study objectives to the patients and their guardians by written and verbal communication. Those who gave consent to participate in the study using EEG were included.

Patient background was obtained from the medical records, but the details of NE treatment at the time of measurement were not asked.

Design

This single-center, case–control study retrospectively reviewed the medical records of patients who gave consent, and the measurement data retained by the hospital.

Materials

The following data were collected for all patients.

Sleep diary

Patients were instructed to write in a sleep diary the time of going to bed, the time of waking up, the presence or absence of NE, and time of NE, if possible (which is equal to the time of alarm activation for patients on alarm therapy). For those who could not keep a sleep diary because of age, we instructed their parents to write the diary on their behalf. For those whose parents recognized NE by alarm activation, the time of NE occurrence was noted in the diary.

Sleep scope analysis

Polysomnography (PSG) is the gold standard in the conventional sleep research. However, it has generated some problems, including the need to wear numerous sensors, such as EEG and EMG; the need to perform the procedure in a special laboratory, and the possibility that the timing of the test may not capture sleep-related events [14].

Sleep EEG in children with NE was measured using a single-channel portable electroencephalograph (Sleep Scope; SleepWell Co., Osaka, Japan). Sleep Scope has two small electrodes: one placed on the center of the forehead and the other behind one ear. This device is very easy to apply and can be worn at home by the patient or a family member. Therefore, it has the advantages of allowing multiple measurements without any burden on the patient and not requiring a special laboratory.

In addition, the small number of items worn is expected to minimize the effect on sleep. Sleep has a characteristic called the first night effect (FNE), which is often called into question in studies using PSG [14]. FNE is considered as an alteration in sleep structure observed before the patient adapts to sleep in the laboratory, which is different from the usual sleep environment; thus, it is a problem in assessing the physiological sleep of patients. Sleep Scope home-EEG measurements may be freer from FNE than the conventional PSG.

The accuracy of Sleep Scope's sleep EEG measurement has been reported to be consistent with that of PSG [14], and comparison with the existing studies is also possible. These characteristics suggest that Sleep Scope is suitable for comparing sleep structure in NE children, because it is easier to perform and has less influence on the patients.

EEG data were classified into five sleep stages: wake, non-REM stage 1 (N1), non-rapid eye movement (REM) stage 2 (N2), non-REM stage 3 (N3), and REM. Using these data, we examined the following: total sleep time (TST); wake time after sleep onset (WASO); sleep efficiency; the percentage of N1, N2, N3, and REM sleep; sleep latency; REM sleep latency; non-REM sleep latency; sleep cycle (average and 1st), and Delta power. These factors increase in the non-REM period and are associated with sleep quality [15]. Furthermore, we examined the following PSG variables: TST, WASO, sleep efficiency, REM sleep latency, and the percentage of N1, N2, N3, and REM sleep. We calculated sleep efficiency by dividing the amount of TST by the total amount of time in bed. The time from the lights-off to the first epoch of any sleep stage defined the sleep latency.

The REM sleep latency and non-REM sleep latency were the time duration a person reaches the first REM sleep and the N3 stage from sleep onset, respectively. Sleep efficiency, which is a measure of sleep quality, is the percentage of time that non-WASO occupies in the TST.

Sleepscopes were loaned out for at least 1 week. Electroencephalographs were analyzed for 1–6 times/person. Data were analyzed on days when no problems (e.g., electrode dislodging) occurred. Additionally, to reduce the influence of electrode placement, days with longer duration from the start of placement were selected. Whenever possible, both NE and non-NE days were selected for analysis for a single patient.

Statistical analysis

In this study, the Sleep Scope was analyzed 1–6 times for each patient. Therefore, the sample included several measurements obtained from the same patient, and not all samples were independent. Therefore, we used Generalized Estimating Equations (GEE), which is suitable for analyzing repeated measurements or other correlated observations, such as clustered data. Dependent variables included the NE days and non-NE days, whereas independent variables included the TST, WASO (%), REM (%), N1 (%), N2 (%), N3 (%), sleep latency, REM sleep latency, REM sleep latency, and non-REM sleep latency.

Statistical data were analyzed using IBM SPSS Statistics version 28.0 (IBM, Armonk, NY). In addition, a p value of less than 0.05 was considered statistically significant.

Results

Patients

A total of 30 NE patients consented to participate in the experiment. Among those who took measurements, one dropped out due to the inability to adequately wear the device, whereas two dropped out due to the inability to keep a sleep diary. Finally, measurement data from 27 patients was collected. The median age of the 27 patients was 9 years (range: 6–16 years). Among them, 16 were boys (59.3%). Seven patients had NMNE, and two among them had improved LUTS during the measurement. Three children were also taking ramelteon prescribed by a doctor from other hospital. The current study randomly divided the patients into groups and made comparisons without considering whether the patients had NMNE or MNE or what treatment was provided for NE and other diseases. A total of 74 measurements were taken, 37 (50.0%) of which were taken on the day the NE occurred.

Sleep parameters and NE

Table 1 shows the results of the analysis for each item. Table 2 presents the results of the analysis using GEE based on the obtained results.

As mentioned, logistic regression analysis was used in evaluating the parameters used in this study. TST, with 60 min as one unit, obtained an odds ratio of 1.464 (95% confidence interval [CI] 0.963–2.226), indicating no statistical significance. Likewise, the parameters REM (%), N1 (%), N2 (%), N3 (%), and WASO (%), each with 1% as one unit, did not obtain statistically significant results. Sleep efficiency, with 1% as one unit, had also not achieved a statistically significant result. For sleep latency and non-REM sleep latency, 10 min was considered as one unit; however, both did not obtain statistically significant results. Only REM sleep latency, for which 10 min was considered as one unit, had a statistically significant result, with an odds ratio of ratio of 1.15 (95% CI 1.006–1.250), indicating a positive correlation with NE frequency.

Table 1 Sleep parameters

	Total ($N = 74$)	NE ($N = 37$)	Non-NE ($N = 37$)
Total sleep time	491.25 (449.4–528.5)	513.5 (454.8–532.8)	479 (442.3–512.3)
REM (%)	21.7 (18.3–24.6)	21.3 (17.8–23.4)	21.9 (18.5–25.1)
N1 (%)	12.0 (9.3–15.3)	12.0 (8.8–15.8)	12.2 (9.2–15.0)
N2 (%)	36.1 (31.2–40.7)	36.1 (30.9–40.9)	36.1 (31.2–40.7)
N3 (%)	24.2 (21.1–27.3)	24.3 (22.4–27.3)	23.3 (20.4–27.6)
Wake after sleep onset (%)	4.9 (3.6–7.4)	5.1 (3.9–8.8)	4.5 (3.5–6.4)
Sleep efficiency (%)	91.3 (87.7–93.5)	90.8 (87.0–93.4)	91.4 (87.6–94.1)
Sleep latency (min)	13.5 (7.5–27.0)	13.0 (9.3–25.3)	15.0 (3.0–30.3)
REM sleep latency (min)	129.0 (80.5–158.0)	139 (93.3–168.8)	100 (76.5–149.3)
Non-REM sleep latency(min)	8.8 (6.4–11.5)	8.0 (6.3–11.3)	9.0 (6.0–12.3)

Data are presented as median (interquartile range)

Table 2 Relationship between each sleep parameter and nocturnal enuresis

	Odds ratio	95% Confidence interval	*p* value
Total sleep time (60 min)	1.464	0.963–2.226	0.074
REM (%)	0.928	0.840–1.026	0.143
N1 (%)	1.002	0.912–1.102	0.965
N2 (%)	1.021	0.973–1.071	0.403
N3 (%)	1.005	0.907–1.114	0.919
Wake after sleep onset (%)	1.151	0.976–1.357	0.095
Sleep efficiency (%)	0.997	0.937–1.062	0.937
Sleep latency (10 min)	1.008	0.780–1.304	0.949
REM sleep latency (10 min)	1.121	1.006–1.250	0.039*
Non-REM sleep latency (10 min)	0.790	0.271–2.302	0.665

*$p < 0.05$

Time of NE

Among the measurements taken on days when nocturia was present, the time of occurrence was known on 18 occasions. NE occurred between sleep onset and first REM sleep on 3 occasions, whereas NE occurred after first REM sleep on 15 occasions (between the first and second on 3 occasions, between the second and third on 5 occasions, between the third and fourth on 3 occasions, between the fourth and fifth on 2 occasions, and after the fifth on 2 occasions).

Discussion

First of all, we discuss the impact of NE on REM sleep latency. No previous studies have investigated the effects of discomfort on REM sleep latency. NE is generally followed by discomfort given that clothing gets wet. Hence, discomfort cannot have an effect on sleep depth or make it shallower. According to the previous reports [16], EEG similar to the transition from sleep to wakefulness has been detected before NE. In other words, nocturia may have the effect of making sleep more difficult.

The present study showed a positive correlation between REM sleep latency and the frequency of NE. REM sleep latency may have been affected by nocturia in at least 3 of 37 measurements on days when NE were present However, if the REM sleep latency of NE children is affected by bed wetting, we can infer that it becomes shorter. Therefore, the positive correlation between REM sleep latency and NE obtained in this study does not indicate that sleep quality was altered by NE but rather that it is a characteristic of sleep in children with NE.

However, the factors causing changes in REM sleep latency and the way on how changes in REM sleep latency affect the human body remain unclear. Therefore, we compared this phenomenon with other phenomena that showed similar changes and analyzed them from a common point of view.

Several studies have reported changes in REM sleep latency. These reports include the REM phase of sleep onset in narcolepsy [17] and shortening of REM sleep latency as a marker of early illness in patients with depression. Examples of prolongation of REM sleep latency include the FNE [18], restorative sleep after sleep deprivation [19], and daily caffeine intake [20].

In particular, FNE is caused by multiple factors, including discomfort caused by electrodes and discomfort with being observed [21]. Anxiety and stress may also be regarded as factors [18, 21], considering that anxious feelings may cause sleep changes such as prolonged REM sleep latency, as seen in FNE.

Similarly, negative psychological factors, such as anxiety and stress, may affect REM sleep latency.

A search of previous reports on the relationship between anxiety and nocturia revealed a US report that children with LUTS, including urinary urgency, daytime urinary incontinence, and NE, have higher rates of adverse childhood experiences, such as abuse and frequent mobility [22]. In Iran, the prevalence of generalized anxiety disorder is higher in patients with monosymptomatic nocturia than in normal children [23]. A meta-analysis reported that stress and anxiety, including parental separation, are associated with NE recurrence [24], suggesting an association between psychological instability and nocturia. In Italy, children hospitalized for surgery manifested nocturia [25], and in Turkey, some refugees from conflict areas reported developing NE [26]. Therefore, negative emotions such as anxiety are one of the triggers. Anxiety is also a common cause of phenomena that prolong REM sleep latency, such as NE and FNE. Hence, we hypothesized that anxiety may cause prolonged REM sleep duration, leading to NE (Fig. 1).

However, the mechanism by which anxiety causes nocturnal enuresis is not clear. Several previous studies investigated the correlation between nocturia volume and REM and

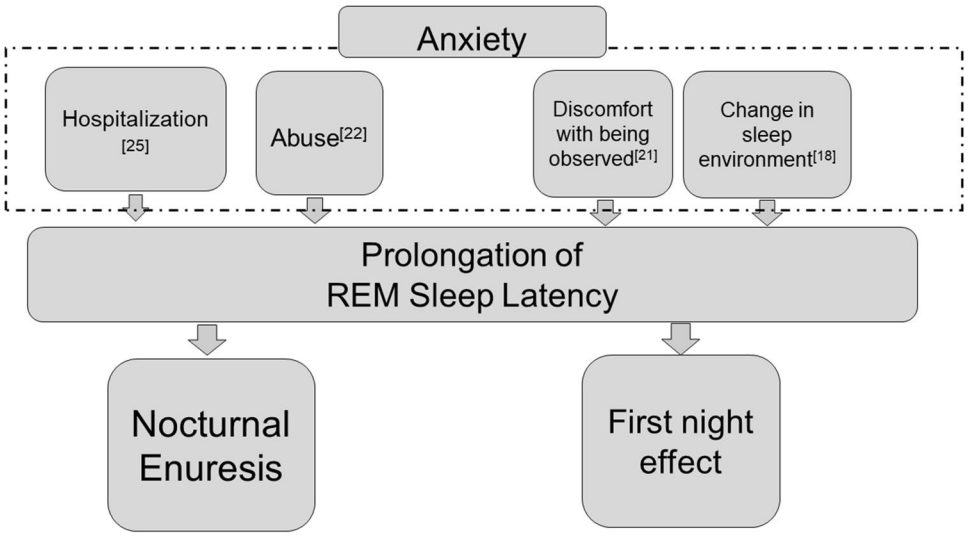

Fig. 1 Discomfort with being observed [21], changes in sleep environment [18], hospitalization [25], and abuse [22] are factors that make people anxious and cause prolongation of REM sleep latency, leading to first night effect and nocturnal enuresis

non-REM sleep. One report revealed that plasma renin activity (PRA) increases during non-REM sleep and decreases during the REM sleep phase [27]. This feature has also been associated with sleep disorders caused by diseases, such as narcolepsy, and changes in sleep quality. In addition, the amount of plasma renin secretion may change in response to changes in sleep. Among the data collected in this study, only the non-NE day data showed a significant negative correlation between prolonged REM sleep latency and REM sleep (%). Although the NE day changes the sleep structure after enuresis, the detailed causal relationship remains vague in this study. However, prolonged REM sleep latency possibly decreased REM (%) and increased PRA, resulting in increased nocturnal urinary output and NE.

This study has limitations that need to be addressed. First, while the existing studies have used PSG and actigraph for measurements, our study used Sleep Scope. Given that the accuracy of PSG, actigraph, and Sleep Scope had already been reported [14], considering this influence when comparing the parameters is unnecessary. Second, Sleep Scope was measured at each patient's home; thus, conditions, such as the time of falling asleep, room brightness, and room temperature, were not standardized. Uniformity of conditions is an important consideration when comparing sleep quality. However, this study rather intended to avoid the limitations of the previous day's bedtime and confounding factors (e.g., naps, light exposure, and daytime stress) and to measure regularly at night, when unfamiliar factors are generally few. Third, this study considered anxiety and REM sleep latency and the presence of NE; however, it did not assess "real" patients' anxiety on the day of measurement. Therefore, we cannot confirm whether anxiety actually affects sleep. Fourth, the insight into whether REM sleep latency changes before and after treatment for NE was not fully investigated. We had also not examined the correlation between changes in REM sleep latency and nocturnal urine volume or the secretion of hormones such as renin.

Conclusion

The frequency of NE has a positive correlation with prolonged REM sleep latency. Prolongation of REM sleep latency is caused not only by NE but also by FNE, which share the same background of anxiety. Future studies should clarify the relationship of anxiety and REM sleep latency with NE frequency.

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Declarations

Conflict of interest Takahiro Ono, Tsuneki Watanabe Chisato Oyake, Yuta Onuki, Yoshitaka Watanabe, Masaki Fuyama, Hirokazu Ikeda declare that they have no conflict of interest.

Ethical approval Showa University Fujigaoka Hospital Ethics Committee. No. [F2017O001].

Research involving human participants and/or animals Yes. Our research involving human participants. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from the patient and their guardians for publication of this article.

References

1. Austin PF, Bauer SB, Bower W, et al. The standardization of terminology of lower urinary tract function in children and adolescents: update report from the standardization committee of the international children's continence society. J Urol. 2014;191:1863-1865.e13. https://doi.org/10.1016/j.juro.2014.01.110.
2. Butler RJ, Heron J. The prevalence of infrequent bedwetting and nocturnal enuresis in childhood. A large British cohort. Scand J Urol Nephrol. 2008;42:257–64. https://doi.org/10.1080/00365590701748054.
3. Nevéus T, Fonseca E, Franco I, et al. Management and treatment of nocturnal enuresis-an updated standardization document from the international children's continence society. J Pediatr Urol. 2020;16:10–9. https://doi.org/10.1016/j.jpurol.2019.12.020.
4. Walker RA. Nocturnal enuresis. Prim Care. 2019;46:243–8. https://doi.org/10.1016/j.pop.2019.02.005.
5. Kim JM. Diagnostic value of functional bladder capacity, urine osmolality, and daytime storage symptoms for severity of nocturnal enuresis. Korean J Urol. 2012;53:114–9. https://doi.org/10.4111/kju.2012.53.2.114.
6. Ryu DS, Lee HW, Kwak KW, et al. Role of urodynamic study in nocturnal enuresis: urodynamic findings and treatment outcome correlation in children with pharmacotherapy-resistant monosymptomatic nocturnal enuresis or severe non-monosymptomatic nocturnal enuresis. Low Urin Tract Symptoms. 2014;6:88–93. https://doi.org/10.1111/luts.12024.
7. Nevéus T, Hetta J, Cnattingius S, et al. Depth of sleep and sleep habits among enuretic and incontinent children. Acta Paediatr. 1999;88:748–52.
8. Wolfish NM, Pivik RT, Busby KA. Elevated sleep arousal thresholds in enuretic boys: clinical implications. Acta Paediatr. 1997;86:381–4. https://doi.org/10.1111/j.1651-2227.1997.tb09027.x.
9. Cohen-Zrubavel V, Kushnir B, Kushnir J, Sadeh A. Sleep and sleepiness in children with nocturnal enuresis. Sleep. 2011;34:191–4. https://doi.org/10.1093/sleep/34.2.191.
10. Inoue M, Shimojima H, Chiba H, et al. Rhythmic slow wave observed on nocturnal sleep encephalogram in children with idiopathic nocturnal enuresis. Sleep. 1987;10:570–9.
11. Dhondt K, Baert E, Van Herzeele C, et al. Sleep fragmentation and increased periodic limb movements are more common in children with nocturnal enuresis. Acta Paediatr. 2014;103:e268–72. https://doi.org/10.1111/apa.12610.
12. Yeung CK, Diao M, Sreedhar B. Cortical arousal in children with severe enuresis. N Engl J Med. 2008;358:2414–5. https://doi.org/10.1056/NEJMc0706528.
13. Pedersen MJ, Rittig S, Jennum PJ, Kamperis K. The role of sleep in the pathophysiology of nocturnal enuresis. Sleep Med Rev. 2020;49:101228. https://doi.org/10.1016/j.smrv.2019.101228.
14. Matsuo M, Masuda F, Sumi Y, et al. Comparisons of portable sleep monitors of different modalities: potential as naturalistic sleep recorders. Front Neurol. 2016;7:110. https://doi.org/10.3389/fneur.2016.00110.
15. Long S, Ding R, Wang J, et al. Sleep quality and electroencephalogram delta power. Front Neurosci. 2021;15:803507. https://doi.org/10.3389/fnins.2021.803507.
16. Zhu B, Zou K, He J, et al. Sleep monitoring of children with nocturnal enuresis: a narrative review. Front Pediatr. 2021;9:701251. https://doi.org/10.3389/fped.2021.701251.
17. Zhang Y, Ren R, Yang L, et al. Polysomnographic nighttime features of narcolepsy: a systematic review and meta-analysis. Sleep Med Rev. 2021;58:101488. https://doi.org/10.1016/j.smrv.2021.101488.
18. Tamaki M, Nittono H, Hayashi M, Hori T. Examination of the first-night effect during the sleep-onset period. Sleep. 2005;28:195–202. https://doi.org/10.1093/sleep/28.2.195.
19. Jay SM, Lamond N, Ferguson SA, et al. The characteristics of recovery sleep when recovery opportunity is restricted. Sleep. 2007;30:353–60. https://doi.org/10.1093/sleep/30.3.353.
20. Weibel J, Lin YS, Landolt HP, et al. Regular caffeine intake delays REM sleep promotion and attenuates sleep quality in healthy men. J Biol Rhythms. 2021;36:384–94. https://doi.org/10.1177/07487304211013995.
21. Le Bon O, Staner L, Hoffmann G, et al. The first-night effect may last more than one night. J Psychiatr Res. 2001;35:165–72. https://doi.org/10.1016/s0022-3956(01)00019-x.
22. Logan BA, Correia K, McCarthy J, Slattery MJ. Voiding dysfunction related to adverse childhood experiences and neuropsychiatric disorders. J Pediatr Urol. 2014;10:634–8. https://doi.org/10.1016/j.jpurol.2014.06.012.
23. Salehi B, Yousefichaijan P, Rafeei M, Mostajeran M. The relationship between child anxiety related disorders and primary nocturnal enuresis. Iran J Psychiatry Behav Sci. 2016;10:e4462. https://doi.org/10.17795/ijpbs-4462.
24. von Gontard A. Does psychological stress affect LUT function in children? ICI-RS 2011. Neurourol Urodyn ICI-RS. 2011;2012(31):344–8. https://doi.org/10.1002/nau.22216.
25. Messina M, Molinaro F, Meucci D, et al. Preoperative distraction in children: hand-held videogames vs. clown therapy. Pediatr Med Chir. 2014;36:98. https://doi.org/10.4081/pmc.2014.98.
26. Nasıroğlu S, Çeri V. Posttraumatic stress and depression in Yazidi refugees. Neuropsychiatr Dis Treat. 2016;12:2941–8. https://doi.org/10.2147/NDT.S119506.
27. Brandenberger G, Charloux A, Gronfier C, Otzenberger H. Ultradian rhythms in hydromineral hormones. Horm Res. 1998;49:131–5. https://doi.org/10.1159/000023159.

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