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The Relationship Between Primary Monosymptomatic Enuresis Nocturna and Chronotype: A Controlled Study

Primer Monosemptomatik Enürezis Nokturna ve Kronotip İlişkisi: Kontrollü bir Çalışma

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Abstract

Objective: In the present study, we aimed to investigate the relationship between primary monosymptomatic enuresis nocturna (MEN) and chronotypes in children.
Materials and Methods: Fifty children diagnosed with primary MEN and 50 healthy children were included in the study. All participants underwent the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)-based psychiatric, and a semi-structured interview, the Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version, K-SADS-PL. The information obtained from the socio-demographic data form and Children's Chronotype Questionnaire (CCTQ) for the patient and the control groups were recorded and statistical analyses were carried out.
Results: Evening chronotype was significantly more often observed in the patient group (X^2=6,225, SD=2, p=0.044). No difference was found between the groups with regard to morning and intermediate chronotypes. In the patient group, the time of going to bed, turning off the lights, the time to start sleeping and mid-sleep time were significantly delayed in free days (p=0.001, p=0.005, p=0.004, and p=0.004, respectively). The sleep duration and the time spent in bed were also significantly shorter in the patient group (p=0.029, p=0.004, respectively).
Conclusion: Primary MEN is associated with circadian rhythm disorders and evening chronotype. As the mechanisms that lead to this condition is not clear yet, further studies with randomized controlled design and larger sample size are required to determine etiopathogenesis and treatment options, and also to reveal the association between MEN and chronotypes.

Keywords: monosymptomatic enuresis nocturna, circadian rhythm, chronotype

Öz

Amaç: Bu çalışmamızda çocuklarda primer monosemptomatik enürezis nokturna (MEN) ve kronotip ilişkisini değerlendirmeyi amaçladık.
Gereçler ve Yöntemler: Çalışmaya, primer MEN tanısı konulan 50 hasta ve 50 sağlıklı çocuk dahil edildi. Tüm katılımcılara Ruhsal Bozuklukların Tanısal ve İstatistiksel El Kitabı, Beşinci Baskıya dayalı psikiyatrik görüşme ve Okul Çağı Çocukları için Duygulanım Bozuklukları ve Şizofreni Görüşme Çizelgesi- Şimdi ve Yaşam Boyu şekli yarı yapılandırılmış görüşmesi uygulandı. Hasta ve kontrol gruplarına ait sosyodemografik veri formu ve Çocukluk Dönemi Kronotip Anket Formundan elde edilen veriler kaydedilip istatistiksel olarak analiz edilerek karşılaştırıldı.
Bulgular: Kronotip türleri açısından bakıldığında hasta grubunda akşamcı kronotip, kontrol grubuna göre anlamlı oranda yüksek bulundu (X2=6,225, SD=2, p=0,044). Sabahçı tip ve ara tip açısından ise gruplar arasında fark yoktu. Hasta grubunda serbest günlerde yatağa girme zamanı, ışıkları kapatma zamanı, uyku başlangıç zamanı ve uyku orta noktası kontrol grubuna göre anlamlı şekilde daha geçti (sırasıyla p=0,001, p=0,005, p=0,004, p=0,004). Ayrıca hasta grubunda uyku süresi ve yatakta geçirilen süre anlamlı derecede kısaydı (sırasıyla p=0,029, p=0,004).
Sonuç: Primer MEN sirkadiyen ritim bozuklukları ve akşamcı kronotip tercihi ile ilişkilidir. Bu duruma neden olan mekanizmalar henüz net olarak kanıtlanmamış olduğundan MEN kronotip ilişkisi üzerinde etyopatogenez ve tedavi seçeneklerini belirlemeye yardımcı olacak randomize kontrollü, geniş örneklemli ileri araştırmalara ihtiyaç vardır.

Anahtar kelimeler: monosemptomatik enürezis nokturna, sirkadien ritim, kronotip

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Introduction

Enuresis nocturna (EN) is defined as the recurrent lack of urinary control during night sleep for at least 2 times a week during 3 months [1]. EN is classified in two separate categories as simple (monosymptomatic) and complicated (polysymptomatic), and also as primary and secondary. While as lower urinary tract symptoms only enuresis nocturna is seen in monosymptomatic enuresis nocturna (MEN), lower urinary tract symptoms such as urgency, frequency, decreased urinary flow are also seen in polysymptomatic EN. While the child is never dry since birth in primary EN, there is at least 6 months of dry period in secondary EN [2]. Despite methodological variations, the prevalence of MEN has been reported as 15-20% around 5, 10% around 7, 5% around 10 and less than 1% around 15 years of age [3]. The etiology of MEN is multifactorial including genetic factors, waking disorder, nocturnal polyuria, increased detrusor activity, low urinary bladder capacity at night and obstructive sleep apnea [4-8].

Human body is regulated by an endogenous clock that controls daily rhythms, sleep/wake cycles, behavior, and physiological functions (melatonin excretion, cortisol levels, cell replication, etc.). This biological clock is repeated at every 24 hours and is therefore defined as the "circadian" rhythm that encompasses approximately one day [9]. The suprachiasmatic nucleus in the hypothalamus serves as the master pacemaker that sets the timing of circadian rhythm by regulating neuronal activity, body temperature and hormonal signals [10]. Light is the strongest stimulus in the regulation of circadian rhythm [11]. The vast majority of etiological factors of MEN such as the level of being stimulated during sleep, urine production and urinary bladder storage are closely related to the circadian rhythm [12].

Chronotype, an external marker of circadian rhythm, is defined as the time when the best mental and bodily performances are exhibited [13]. Morning, evening and intermediate chronotypes have been defined. Morning chronotypes (larks) wake up early and feel more active during the first part of the day and exhibit a higher physical and cognitive performance during these hours. Evening chronotypes (owls) go to bed late and have difficulty in waking up in the morning and exhibit a better performance in the afternoon and evening. The most common intermediate chronotypes show the features of both types [14-16].

Evening chronotypes are more prone to medical problems like diabetes mellitus, hypertension, obesity, and asthma [17]. Evening chronotypes experience psychiatric problems such as anxiety, depression and substance abuse more often, and severely compared to morning chronotypes [18,19].

MEN, which is among the most common problems in childhood, is usually self-limited and spontaneously resolves without sequelae. However, some individuals may have significant emotional and social problems like poor sense of self, poor self-esteem, social restriction, and family conflict. Therefore, it is of great importance to determine the etiologic factors of MEN and to apply behavioral, psychotherapeutic, and pharmacologic treatments based on individual assessment. As the etiology of MEN is enlightened, more effective treatments may become available.

In the present study, we aimed to evaluate the relationship between MEN and chronotypes in children.

Materials and Methods

Study Design

The ethics committee approval was obtained from the University of Health Sciences, Erzurum Regional Training and Research Hospital (date: June 17, 2019; decision number: 2019/09-79) prior to the study. Fifty patients who had been priorly evaluated at the Child and Adolescent Psychiatry Outpatient Clinic of Erzurum Regional Research and Training Hospital between July 2019 and July 2021 and diagnosed with primary MEN at the urology clinic of the same hospital were included in the patient group. The control group consisted of 50 children matched with primary MEN patients as for socio-demographic characteristics and had been admitted to the general pediatrics outpatient clinic. All participants underwent the DSM-V-based psychiatric examination and Schedule for Affective Disorders and attended Schizophrenia for School Age Children-Present and Lifetime Version (K-SADS-PL) interviews conducted by the child psychiatrist at the outpatient clinic. The parents of volunteering participants signed a written informed consent. The parents filled out the socio-demographic data, and the Children's Chronotype Questionnaire (CCTQ) forms. The data were recorded, and statistical comparisons were made.

Exclusion Criteria

Children who had a chronic neurological, metabolic, genetic (epilepsy, cerebral palsy, diabetes, obesity, obstructive sleep apnea syndrome, etc.), psychiatric disorders (schizophrenia, bipolar affective disorder, depressive disorder, anxiety disorder, autism spectrum disorder) that could affect the chronotype and sleep parameters or who were using any medications that affected their sleep patterns were excluded from the study.

Scales

Children's Chronotype Questionnaire (CCTQ)

Children's Chronotype Questionnaire (CCTQ) scale was developed by Werner et al., in 2009 [20] and the Turkish validity and reliability study of the scale was done by Dursun et al. [21]. The scale is composed of 3 parts. The first part of the scale includes 16 questions about sleep/wake parameters (time of going to bed, turning off the lights, sleep latency, wake time, time of getting off the bed, snaps during the day, etc.) for scheduled and free days separately. The second part includes 10 5-Likert type questions that determine the morning/evening chronotype scores morning (≤23), intermediate (24-32), and evening (≥33) chronotypes are categorized according to the indicated scores they obtain. In the last part, parents are informed about the short definition of chronotype and asked a single question to determine the chronotype of the child. The sleep/wake parameters that are calculated based on responses to the CCTQ items by parents are demonstrated in **Figure 1** [20].

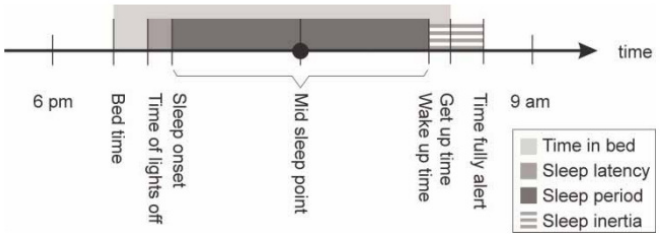

Figure 1. Parent-reported sleep/wake parameters computed from items on the Children's Chronotype Questionnaire (CCTQ)

Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version (K-SADS-PL)

Using this scale, the previous and current psychiatric disorders of the children and adolescents between the ages of 6 and 18 are questioned through the information obtained from the parents and children, and clinical diagnosis is made by integrating the obtained information with the observations of the clinician. The presence and the severity of the symptoms are decided by combining the opinions of the child or the adolescent, parents, and the clinician. If the positive symptoms are recorded through the screening interview, an additional symptom list is used in order to evaluate the psychopathology in detail. The Turkish validity and reliability study of the scale was done by Gökler et al. [22,23].

Statistical Analysis

Power analysis was performed according to the "bedtime on free days" variable. According to the post-hoc power analysis (Group 1; 23.20 ± 1.09, Group 2; 22.32 ± 1.14), the effect size was 0.78 with 99% power and 0.05 α error, and sample of 48 patients were found to be sufficient for performing statistical analysis in each group. The study data were analyzed using the Statistical Program for Social Sciences (SPSS for Windows, 22.0). For comparison of the continuous variables, the independent groups t-test was used for the normally distributed variables and the Mann- Whitney U test for the non-normally distributed data. The chi-square test was used for the comparison of the categorical variables. The level of statistical significance was set at $p<0.05$ for all analyses.

Results

Fifty children (12 girls and 38 boys) were allocated to the patient group and 50 children (19 girls and 31 boys) to the control group. Any statistically significant intergroup difference was not determined with regard to gender distribution (p=0.13). The mean age was 9.13±2.05 (age range 8-14 years) years in the patient, and 9.61±2.20 (age range 8-14 years) years in the control group. Any statistically significant difference was not determined between the patient and the control groups with regard to age (p=0.263).

The number of evening chronotypes was significantly higher in the patient group (X^2=6,225, SD=2, p=0.044). No difference was found between the groups with regard to morning and intermediate chronotypes. The distribution of chronotypes according to the groups is presented in **Table 1**.

In the patient group, the time of going to bed, turning off the lights, time to start sleeping and the mid-sleep time were significantly delayed in free days. The sleep duration and the time spent in bed were also significantly shorter in the patient group. No significant difference was detected between the groups with regard to other data. The sub-scores of CCTQ are displayed in **Table 2**.

Discussion

Circadian rhythm related urination rhythm disorders have been reported in individuals with enuresis nocturna. It has been reported that these disorders can occur in three main fields including arousal during sleep, urine production and urinary bladder storage [12]. As has been reported in the literature children with MEN have difficulty in arousal during sleep and had higher wake threshold. While some studies have reported more difficult waking in all stages of sleep in enuretic children, some others have indicated that these children sleep deeply only during enuresis; because they have a doze in the remaining part of the sleep [24-26]. Furthermore, it has been reported that unlike healthy children in the MEN group, antidiuretic hormone (ADH) that reduces the urine production does not increase during sleep with resultant increased urine output at night [5]. In many studies, ADH secretion was shown to be affected by the circadian cycle, and patients with enuresis were reported to have abnormal circadian ADH levels [27,28]. Studies on the role of bladder storage in the etiopathogenesis of enuresis have proposed that there is a defect in the regulatory mechanisms of diurnal change in functional bladder capacity rather than structural bladder size [12]. In our study, given the evidence on MEN and circadian rhythm in the literature, we evaluated the relationship between MEN and circadian rhythm using the CCTQ Form. We compared parameters such as chronotype preference and sleep/wake parameters between the patient and the control groups.

Erdogan et al. investigated the relationship between MEN

Table 1. Chronotype preferences

		Patient (n=50)	Control (n=50)
Chronotype	Morning	6 (12%)	7 (14%)
	Intermediate	25 (50%)	35 (58,3%)
	Evening	19 (38%)	8 (16%)

X^2=6,225; SD=2; p=0,044

Table 2. CCTQ scores in the patient and control groups

	Patient (Mean±SD)	Control (Mean±SD)	p value
Bedtime on scheduled days (h:min)	22:09±01:01	22:05±01:08	0,755
Bedtime on free days (h:min)	23:20±01:09	22:32±1:14	**0,001**
Time of lights off on scheduled days (h:min)	22:27±01:03	22:24±01:08	0,820
Time of lights off on free days (h:min)	23:33±1:11	22:50±1:16	**0,005**
Time in bed on scheduled days (h:min)	9:34±1:04	9:28±0:59	0,620
Time in bed on free days (h:min)	10:04±0:57	10:38±0:56	**0,004**
Sleep onset on scheduled days (h:min)	22:38±1:07	22:40±1:14	0,901
Sleep onset on free days (h:min)	23:49±1:14	23:05±1:16	**0,004**
Sleep period on scheduled days (h:min)	8:59±1:08	8:46±0:58	0,314
Sleep period on free days (h:min)	9:32±0:59	9:58±0:58	**0,029**
Wake up time on scheduled days (h:min)	7:38±0:52	7:28±0:44	0,280
Wake up time on free days (h:min)	9:18±1:17	9:02±1:08	0,270
Get up time on scheduled days (h:min)	7:45±0:53	7:35±0:45	0,190
Get up time on free days (h:min)	9:27±1:20	9:10±1:10	0,260
Midsleep point on scheduled days (h:min)	03:08±0:49	03:04±0:53	0,690
Midsleep point on free days (h:min)	04:33±1:10	04:03±1:11	**0,043**

independent sample t test; h:min=hours:minute

and chronotypes and reported lack of any preferential difference between the patient and the control groups. They proposed that this condition resulted from the fact that early waking problems due to a full bladder in children in MEN group could mask the preference for the evening chronotype, and also reported that the problems concerning the onset and maintenance of sleep and waking at night were observed more frequently in children with MEN which could be a marker of circadian rhythm-related disorders in MEN [29]. In another study Wei et al., demonstrated that enuresis that continues into adulthood was related to evening chronotype and interpreted that enuresis in adulthood could be a predictor of psychiatric morbidity in evening chronotypes [30]. In our study, significantly higher number of children with MEN were preferentially evening chronotypes. These results were consistent with the limited literature data investigating enuresis nocturna and chronotype preference. Besides, the finding that the intermediate chronotype was the most common type in the control group was consistent with the literature data indicating that the intermediate chronotype is the most common in the normal population [16]. Higher rates of the evening chronotype in the MEN group may be the reflection of circadian rhythm disorders concerning arousal, urine production and storage that play a role in the etiology of MEN. In our study, the higher rates of evening chronotype in the MEN group supports the presence of circadian rhythm disorders-related pathologies in the etiopathogenesis of MEN.

We determined that the children in the MEN group, fell asleep at later hours, stayed longer in bed, and the sleep period was shorter in free days. The studies investigating duration and characteristics of sleep have reported that the sleep duration was shorter in the MEN group and these patients more often demonstrate resistance to sleeping time and sleep late [31]. In studies investigating sleep properties in children with MEN, in parallel with the results of our study, the sleep duration was shorter and the delay to start sleeping was more common in MEN. These studies have mostly emphasized that enuresis forces the child to wake up and leads to sleep deprivation [31,32]. The sleep duration in children with MEN was reported to be shorter both on weekdays and at the weekends [31]. In our study, in the MEN group, the sleep duration was found to be shorter than that in the control group only at weekends. We consider that this condition may be due to the fact that children sleep late at night on holidays when they can show their chronotype preferences more objectively, and they have problems waking up early in the morning due to a full bladder. In our study, the finding that there was no difference between the MEN and the control group in terms of morning waking hours and mid-sleep point scores despite children in the MEN group fall asleep in the late hours, supports our opinion. In addition, the fact that individuals can display their chronotype preferences more objectively on free days (weekends) rather than scheduled days (school days for the children in our study), may cause differences between scheduled and free days in terms of chronotype preferences.

Our study has some limitations. Firstly, the chronotype data of children were evaluated with a subjective assessment tool, instead of an objective tool like actigraphy. Secondly, measurements related with circadian rhythm may have an etiologic association with MEN. Accordingly, measurements of nocturnal ADH and the nocturnal functional urinary bladder capacity were not made or evaluated. Thirdly, the data of our

study could not be generalized to all children with MEN due to the small sample size. Despite all these limitations, our study is one of the limited clinical studies in the literature that support the presence of the circadian rhythm-related pathologies in the etiopathogenesis of MEN and reveal the association between MEN and evening chronotype.

Conclusion

Primary MEN is related with circadian rhythm disorders and evening chronotype. As the mechanisms of this condition have not been fully revealed yet, further randomized controlled studies with larger sample size are required to determine the etiopathogenesis and treatment options on the relationship between MEN and chronotype preference.

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences, Erzurum Regional Research and Training Hospital (Approval date and number: June 17, 2019; 2019/09-79).
Informed Consent: An informed consent was obtained from all the patients.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – E.Y.D.; Design – E.Y.D., S.O.D.; Supervision – E.Y.D., Y.A.; Resources – E.Y.D., S.O.D., I.K.; Materials – E.Y.D., G.T.Y.; Data Collection and/or Processing – E.Y.D., G.T.Y.; Analysis and/or Interpretation – E.Y.D., S.O.D., G.T.Y.; Literature Search – E.Y.D., S.O.D., I.K.; Writing Manuscript – E.Y.D., S.O.D.; Critical Review – I.K., Y.A.
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