



# Evaluation of Etiological Risk Factors of Primary Monosymptomatic Enuresis

Primer Monosemptomatik Enürezisin Etiyolojik Risk Faktörlerinin Değerlendirilmesi

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**Cite this article as:** Yanaral F, Eroğlu A, Çilesiz NC, Gezmiş CT, Tandoğdu Z, Balcı MBC, et al. Evaluation of Etiological Risk Factors of Primary Monosymptomatic Enuresis. JAREM 2018; DOI: 10.5152/jarem.2018.1997

## ABSTRACT

**Objective:** A child who has not been dry previously for more than 6 months without any lower urinary tract symptoms is considered to have primary monosymptomatic nocturnal enuresis (MNE). The aim of this study was to investigate the etiological risk factors in primary MNE.

**Methods:** We retrospectively evaluated the medical records of children with enuresis. Children with known anatomic malformations, non-monosymptomatic enuresis, and seconder enuresis were excluded. Only children with primer MNE were included in the study. Control group was defined as healthy children with no history of bed-wetting. The etiological risk factors were compared between groups.

**Results:** Eighty-nine children with primary MNE (mean age: 9.7) and 70 healthy children (mean age: 9) were included in the study. Both groups were similar for age, gender, birth type, birth weight, gestational duration, and duration of sleep. The mean body mass index (BMI), mean duration of only breastfeeding and mean duration of breastfeeding with infant formula were 19.1 and 16.8 kg/m<sup>2</sup>, 5.4 and 7.3 months and 13.2 and 17.9 months, in enuresis group and control group, respectively (p=0.012, p=0.005, p=0.034). The family history for enuresis was positive in 58 (65.2%) and 12 (17.1%) patients, in enuresis group and control group, respectively (p= 0.001). Multivariate regression analysis identified family history and breastfeeding as independent risk factors for enuresis (p=0.001, p=0.012).

**Conclusion:** We have documented that high BMI, positive family history, and low duration of breastfeeding are risk factors for enuresis. The present study has shown that longer breastfeeding is protective for bedwetting.

**Keywords:** Breast feeding, etiology, enuresis, risk factors, urinary incontinence

## Öz

**Amaç:** Primer monosemptomatik enürezis nokturna (PMEN) gündüz alt üriner sistem semptomları olmayan ve 6 aydan daha uzun süre kuru kalmamış enürezisi olan hastaları tanımlamaktadır. Bu çalışmada PMEN tanılı hastalarda etiyolojik risk faktörlerini araştırmayı amaçladık.

**Yöntemler:** Enürezisi olan hastaların dosyaları geriye dönük incelendi. Anatamik malformasyonu, nonmonosemptomatik ve sekonder enürezisi olanlar çalışma dışı bırakıldı, sadece PMEN tanılı çocuklar çalışmaya dahil edildi. Kontrol grubu olarak yatak ıslatma öyküsü olmayan sağlıklı çocuklar belirlendi. Her iki grup etiyolojik risk faktörleri açısından karşılaştırıldı.

**Bulgular:** Ortalama yaşları sırasıyla 9,7 ve 9 olan, PMEN tanılı 89 çocuk ve kontrol grubunda 70 sağlıklı çocuk çalışmaya dahil edildi. Her iki grup yaş, cinsiyet, doğum tipi, doğum kilosu, gebelik süresi ve uyku süresi açısından benzerdi. Ortalama vücut kitle indeksi (VKİ), ortalama sadece anne sütü süresi, ortalama anne sütü ve ek gıda süreleri enürezis ve kontrol grupları için sırasıyla 19,1 ve 16,8 kg/m<sup>2</sup>, 5,4 ve 7,3 ay, 13,2 ve 17,9 aydı (p=0,012, p=0,005, p=0,034). Ailede enürezis öyküsü, enuresis ve kontrol gruplarında sırasıyla, 58 (%65,2) ve 12 (%17,1) çocukta pozitifliği (p=0,001). Multivariate regresyon analizinde aile öyküsü ve anne sütü süresi enuresis için bağımsız risk faktörleridir (p=0,001, p=0,012).

**Sonuç:** Vücut kitle indeksi, pozitif aile öyküsü ve kısa anne sütü alım süresi enürezis için risk faktörleridir. Bu çalışma, bebekken uzun süre anne sütü ile beslenmenin çocukluk çağında enürezis gelişimine karşı koruyucu olduğunu göstermiştir.

**Anahtar kelimeler:** Emzirme, etiyoloji, gece idrar kaçırma, risk faktörleri, üriner inkontinans

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This study was presented as an oral presentation at the 23<sup>rd</sup> National Urology Congress and published in the abstract book, 16 October 2014, Antalya, Turkey.  
Bu çalışma 23. Ulusal Üroloji Kongresi'nde sözlü bildiri olarak sunulmuş ve özet kitabında yayınlanmıştır, 16 Ekim 2014, Antalya Türkiye.



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Received Date / Geliş Tarihi: 23.02.2018 Accepted Date / Kabul Tarihi: 13.06.2018  
Available Online Date / Çevrim İçi Yayın Tarihi: 05.07.2018

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DOI: 10.5152/jarem.2018.1997

## INTRODUCTION

The International Children's Continence Society defines enuresis as incontinence of urine in discrete episodes while sleeping in a child aged  $\geq 5$  years (1). Enuresis term is used irrespective of whether existing other lower urinary tract symptoms. When only enuresis exists in children in the absence of a history of lower urinary tract dysfunction, the disorder is termed monosymptomatic enuresis. Enuresis in a child with bladder dysfunctions is termed as non-monosymptomatic enuresis (2).

Monosymptomatic enuresis can also be classified as primary and secondary forms. Child who has never achieved at least six months period of nighttime dryness diagnosed as primary enuresis, whereas secondary enuresis is defined as enuresis that start after a dry period of more than six months (3). Thus, a child who has not been dry for more than six months previously without any bladder dysfunction is regarded as primary monosymptomatic nocturnal enuresis (MNE).

Enuresis is an important psychosocial problem for both parents and children. Although it is one of the most prevalent conditions in childhood, there is still debate in the etiology. It is generally accepted that multiple pathologic factors are probably involved. The aim of present study was to investigate the etiological risk factors in primary MNE.

## METHODS

We retrospectively evaluated the medical records of children with enuresis. Data were recorded prospectively by direct interview with the families and the children by history, physical examination, urinalysis and voiding diary by a single observer. Verbal informed consent was obtained from the parents of the children participating in this study. The research was conducted according to the principles of the World Medical Association Declara-

tion of Helsinki "Ethical Principles for Medical Research Involving Human Subjects". Only children (older than 5 years of age) with primer MNE (at least 2 times per week) were included in the study. Controls were selected from a general pediatric practice during well-child visits. Healthy children who had normal developmental history and who did not have enuresis after 4 years of age were included in the control group.

A history of the frequency of bedwetting, primary or seconder enuresis, associated daytime symptoms, any period of dryness, constipation and encopresis were noted. Additionally, birth type, birth weight, gestational week, duration of breastfeeding, duration of infant formula, number of sibling, body mass index (BMI), family history and duration of sleep were recorded. The external genitalia and lumbosacral spine was examined. A voiding diary in the form of a frequency volume chart was recorded including voided volume along with the time of each micturition for at least 24 hours for identifying any underlying bladder dysfunction. Urinalysis was performed to exclude urinary tract infections. Children with known anatomic malformations, non-monosymptomatic enuresis, seconder enuresis, and recurrent urinary tract infection were excluded.

### Statistical Analysis

The Statistical Package of the Social Sciences version 20 (SPSS IBM Corp.; Armonk, NY, USA) was used for statistical analysis. For the analysis of quantitative data, the normal distribution suitability was examined by the kolmogorov simirnov test; parametric methods were used for analysis of normal distribution variables, and nonparametric methods were used for analysis of variables that did not show normal distribution. Independent t test was used to compare independent groups, pearson correlation test to examine the relationship between variables, and pearson chi-square, chi-square and fisher exact tests were used to compare categorical data. Multivariate analysis was performed by logistic

**Table 1. Demographic datas**

	Groups		p
	Enuresis (n=89)	Control (n=70)	
Gender (girls/boys)	28/61	32/38	0.138
Age (year)*	9.69 $\pm$ 2.91	9.06 $\pm$ 2.53	0.265
Body mass index (kg/m <sup>2</sup> )*	19.15 $\pm$ 4.89	16.86 $\pm$ 3.18	0.012
Family history	58 (65.2%)	12 (17.1%)	0.001
Gestational duration (week)*	38.91 $\pm$ 2.00	39.54 $\pm$ 0.92	0.078
Gestational duration (pre-term/term/postterm)	7/82/0	2/66/2	0.836
Birth weight (gram)*	3247.67 $\pm$ 534.54	3270.14 $\pm$ 643.83	0.849
Birth weight (low/normal/large for gestational age)	5/79/5	10/52/8	0.079
Birth type (vaginal delivery/cesarean section)	66/23	44/26	0.212
Duration of only breastfeeding (month)*	5.42 $\pm$ 2.85	7.31 $\pm$ 4.29	0.005
Duration of breastfeeding with infant formula (month)*	13.24 $\pm$ 10.84	17.97 $\pm$ 11.34	0.034
Duration of sleep (hour)*	9.20 $\pm$ 1.52	9.53 $\pm$ 1.34	0.265
*: Mean $\pm$ standard deviation			

**Table 2. Multivariate analyses**

	Odds ratio*	p
Gender	0.42 (0.13-1.35)	0.144
Family history	12.29 (3.65-41.35)	0.001
Birth weight	0.22 (0.03-1.61)	0.070
Body mass index	0.85 (0.14-5.33)	0.759
Breastfeeding	8.87 (1.63-48.34)	0.012
Birth type	1.33 (0.47-3.79)	0.588
Logistic regression analysis, 95% confidence interval		

regression analysis from the parameters that were significant in univariate analysis. Quantitative data were expressed as mean  $\pm$  standard deviation values on tables. Categorical data are expressed as n (frequency) and percentages (%). Data were analyzed at 95% confidence level and statistical significance was considered when p value  $<0.05$ .

## RESULTS

Eighty-nine children with primary MNE aged between 5-16 (mean: 9.7) and 70 healthy children aged between 6-15 (mean: 9) were included in the study. The enuresis group and control group were similar for age, gender, birth type, and birth weight, gestational duration, and duration of sleep. However, there were significant differences between groups for BMI, family history, duration of only breastfeeding and duration of breastfeeding with infant formula (Table 1).

The mean BMI, mean duration of only breastfeeding and mean duration of breastfeeding with infant formula were 19.1 and 16.8 kg/m<sup>2</sup>, 5.4 and 7.3 months and 13.2 and 17.9 months, in enuresis group and control group, respectively ( $p=0.012$ ,  $p=0.005$ ,  $p=0.034$ ). The family history for enuresis was positive in 58 (65.2%) and 12 (17.1%) patients, in enuresis group and control group, respectively ( $p=0.001$ ) (Table 1).

Sixty-five (73%) children wet every night and 72 (80%) children had severe enuresis. In enuresis group 56 (63%) children exclusively breastfeed for the first six months as World health Organization (WHO) suggestion. In control group this rate was 64/70 (91%). Multivariate regression analysis identified family history and breastfeeding as independent risk factors for enuresis ( $p=0.001$  and  $p=0.012$ , respectively) (Table 2).

## DISCUSSION

The overall prevalence of MNE was found to be 3.8-18.9% in different countries (4, 5). In Turkey, Gumus et al. (6) reported the prevalence of enuresis as 15%, and Serel et al. (7) reported as 11%. The prevalence decreases with age; about 10% of seven years old children, 5% of all ten years old children and 0.5-1% of adults are effected. Spontaneous cure rate is around 15% annually, and 1% of cases are resistant to all treatment methods (1, 8). In the present study, groups were similar for age and sex ( $p=0.265$  and  $p=0.138$ , respectively). This equivalence is very important because bed-wetting is more common in younger chil-

dren and boys. Similar to the literature, in our study enuresis was more common in boys (68%) (9).

This is a common health problem; however, the causes of this problem have not yet been fully defined. Enuresis pathophysiology is complicated, including the central nervous system (CNS), circadian rhythm, and bladder function disorders (10). Enuresis, most likely, is a disorder caused by a combination of these etiologies in a multi-factor manner. In general, enuresis occurs when nighttime urine volume surpasses functional bladder capacity and the child cannot inhibit bladder emptying due to lack of awakening. These etiologies are associated to delayed maturation of a normal developmental process as they are seen as normal in younger age (10).

It is well known that enuresis is strongly associated with family history. Bakwin showed that the incidence of enuresis was 15% in children from non-enuretic parents, while 44% and 77% of children were enuretic when enuresis is present in one or two parents, respectively (11). In the present study, a family history of enuresis was more likely among the enuretic children (65.2%) compared with controls (17.1%) ( $p=0.001$ ). Moreover, we found family history as an independent risk factor for enuresis in multivariate analysis ( $p=0.001$ ). Several candidate enuresis genes have been found, but at the same time it became clear that there was no one gene to explain all cases of enuresis, and that genotype and phenotype showed poor correlation (12, 13).

Children with nocturnal enuresis are reported to have lower bladder capacity (functional), even though they have no daytime complaints (11). Whether sleep disorders are a consequence of enuresis or whether it conduce to the pathophysiology of enuresis remains controversial. A study showed that children with enuresis were slightly sleeping in reality, but they not wake before voiding. Authors suggested that the arousal center might be suppressed by signals from the bladder (14). It is unclear whether enuresis is caused by sleep disturbances or problems with the bladder-brain communication. Yeung et al. have demonstrated that children with enuresis have detrusor instability while asleep, but not while awake (15). Although the relationship between sleep parameters and MNE is interesting; we did not find a relationship between sleep duration and MNE ( $p=0.265$ ).

The extended family structure, low socioeconomic status, low birth weight, prematurity vote, the neuromotor retardation, male gender and low school achievement has been reported as a risk factor for MNE (16). In our study there was no significant difference in the mean of birth type, gestational duration, and birth weight between groups ( $p=0.212$ ,  $p=0.836$  and  $p=0.849$ , respectively). We found the mean BMI was significantly high in enuresis group than controls ( $p=0.012$ ). This result was similar to the study reported by Weintraub et al in 2013. They showed that enuresis is more common in obese children than in normal weight control subjects (17). Probable explanations for this are common comorbidities in these patients, such as obstructive sleep apnea and type 2 diabetes mellitus (18). Obese children may have a slightly underestimated enuresis; warrants close attention to prevent unnecessary psychological distress in these children.

In enuretic children, psychiatric disorders are higher than in the healthy children. This relationship may be due to etiological as-

sociation or due to enuresis symptoms or it may be coincidental (19). It has been suggested that both enuresis and attention deficit hyperactivity disorder may be due to delays in the CNS maturation. The hypothesis that there is a difference in the CNS maturation in children with primary enuresis compared with controls is supported by neurophysiologic data (20, 21). Progressive maturation of bladder stability occurs in conjunction with electroencephalogram findings. That suggests that CNS may suppress the onset of detrusor contraction. In some studies among children with enuresis, it was found that the incidence of delayed language and slowed motor performances were increased (22). Most of the MNE cases resolve spontaneously, which is considered to be the result of a delayed maturation of the normal developmental period (10).

In the progress of time, bladder stability and striated urinary sphincter control are reached through neurologic development and neurologic maturation. Breastfeeding may provide visual, cognitive and neurologic developmental advantages to children, compared with infant formula (23). In addition, studies have showed that preterm infants fed with formula have lower scores in visual and developmental tests than breastfed preterm infants (24, 25). Gumus et al. analyzed clinical factors related with enuresis and showed no difference between enuretics and non-enuretics by breastfeeding (6). However, Barone et al. (26) evaluated the relationship between breastfeeding and enuresis in 55 children and they showed a significant difference in the incidence of enuresis when breastfed for longer than three months. Singh et al. (27) examined the relationship between enuresis and several clinical factors in 100 children. The authors concluded that the rate of enuresis was higher in babies fed with infant formula compared to babies fed with mother's milk. Similar to the previous studies we found the duration of only breastfeeding and breastfeeding with infant formula were statistically low in enuresis group ( $p=0.005$  and  $p=0.034$ , respectively). Based on multivariate analysis, breastfeeding was an independent risk factor for enuresis ( $p=0.012$ ). This finding showed the importance of breastfeeding in the prevention of the enuresis in children probably by providing neurodevelopment advantages. This may be due to the fact that high n-3 and n-6 long chain polyunsaturated fatty acids in the breast milk have significant effect on neural development (23). We also known that breastfeeding establishes a link between mother and baby and has a positive psychological effect.

Sancak et al. (28) investigated the effect of breastfeeding on spontaneous resolution of monosymptomatic enuresis on 181 children. The authors found that at least 5 months of breastfeeding may contribute to the age of spontaneous recovery of enuresis in children. World health Organization recommends mothers to exclusively breastfeed infants for the child's first six months to achieve optimal growth, development and health. Thereafter, they should be given nutritious complementary foods and continue breastfeeding up to the age of two years or beyond (29). In our study, the mean duration of only breastfeeding was 5.4 and 7.3 months, in enuresis and control groups, respectively. ( $p=0.005$ ). The duration of breastfeeding in enuresis group was below the WHO recommendation. However, it is appropriate in control group. The mean duration of breastfeeding with infant

formula was significantly lower in enuresis group. Yet, this period was below the WHO recommendation in both groups.

The study has some limitations including its retrospective nature and absence of population-based data. However single observer nature of the procedure and the prospectively collection of data were the strengths of the study.

## CONCLUSION

Enuresis is a disorder with self-healing in most of the cases which support the delayed maturation in children with enuresis. We have documented that high BMI, positive family history, and low duration of breastfeeding are risk factors for enuresis. The present study has shown that longer breastfeeding is protective for bedwetting. This effect is both in exclusively breastfeeding and breast milk supplemented with formula and it may be another good reason to encourage breastfeeding. Prospective, population based trials should be performed to support this finding.

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**Ethics Committee Approval:** Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

**Informed Consent:** Verbal informed consent was obtained from patients' parents who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - F.Y.; Design - Z.T.; Supervision - B.N., M.B.C.B.; Re-sources - A.E., C.T.G.; Materials - N.C.Ç.; Data Collection and/or Processing - A.E.; Analy-sis and/or Interpretation - N.C.Ç., Z.T.; Literature Search - C.T.G.; Writing Manuscript - F.Y.; Critical Review - B.N., M.B.C.B.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

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**Etik Komite Onayı:** Yazarlar çalışmanın World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013) prensiplerine uygun olarak yapıldığını beyan etmişlerdir.

**Hasta Onamı:** Sözlü hasta onamı bu çalışmaya katılan hastaların ailelerinden alınmıştır.

**Hakem Değerlendirmesi:** Dış bağımsız.

**Yazar Katkıları:** Fikir - F.Y.; Tasarım - Z.T.; Denetleme - B.N., M.B.C.B.; Kaynaklar - A.E., C.T.G.; Malzemeler - N.C.Ç.; Veri Toplanması ve/veya İşlemesi - A.E.; Analiz ve/veya Yorum - N.C.Ç., Z.T.; Literatür Taraması - C.T.G.; Yazıyı Yazan - F.Y.; Eleştirel İnceleme - B.N., M.B.C.B.

**Çıkar Çatışması:** Yazarlar çıkar çatışması bildirmemişlerdir.

**Finansal Destek:** Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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