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Original Article *Özgün Araştırma*

THE CLINICAL AND LABORATORY DIFFERENCES BETWEEN MONOSYMPTOMATIC AND NONMONOSYMPTOMATIC ENURESIS

Monosemptomatik ve Monosemptomatik Olmayan Enürezis Arasındaki Klinik ve Laboratuvar Farklılıklar

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ABSTRACT

Objective: The present study aimed to determine the differences between monosymptomatic and non-monosymptomatic enuresis in light of clinical and laboratory variables.

Material and Methods: We retrospectively reviewed the medical records of pediatric patients with enuresis who were followed up between 2010 and 2021 at XX University Hospital.

Results: One hundred and sixty-one patients with monosymptomatic nocturnal enuresis (MNE) and 86 patients with non-monosymptomatic enuresis (NMNE) were enrolled in this study. The patients with MNE were significantly older than the patients with NMNE (9.0±2.5 vs 7.6±2.4 years; p=<0.001). The proportion of females was significantly higher both in the MNE and NMNE groups (32.2% vs 17.4%; p=0.046; 54.7% vs 40.4%; p=0.032 respectively). The hemoglobin level was significantly lower in the NMNE group (12.8±0.8 vs 13.4±1.0 g/dl; p=0.05). The rate of constipation and fecal incontinence were significantly higher in NMNE group (27.9% vs 14.2%; p=0.009, and 11.6% vs 1.2%; p=0.002, respectively.) The univariable analyses using the above-identified parameters showed that a relatively low mean hemoglobin level was a risk factor for NMNE (OR=-0.603, 95% CI 0.346-0.867; p=0.01).

Conclusion: Making the differential diagnosis of MNE and NMNE and determining the risk factors earlier in the disease course are essential tasks to be accomplished in the initial evaluation of patients with enuresis. Relatively low Hb levels may be a novel risk factor for NMNE.

Keywords: *Monosymptomatic enuresis, non-monosymptomatic enuresis, hemoglobin, risk factor*

ÖZ

Amaç: Bu çalışmada monosemptomatik ve monosemptomatik olmayan enürezis arasındaki farkların klinik ve laboratuvar değişkenleri ışığında belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu çalışmada monosemptomatik ve monosemptomatik olmayan enürezis arasındaki farkların klinik ve laboratuvar değişkenleri ışığında belirlenmesi amaçlanmıştır.

Bulgular: Bu çalışmaya monosemptomatik enürezisli (MNE) 161 hasta ve monosemptomatik olmayan enürezisli (NMNE) 86 hasta dahil edildi. MNE'li hastalar NMNE'li hastalardan anlamlı olarak daha yaşlıydı (9,0±2,5 ve 7,6±2,4 yıl; p=<0,001). Kızların sayısı hem MNE hem de NMNE grubunda anlamlı olarak daha yüksekti (sırasıyla %32.2'ye karşı %17.4; p=0.046; %54,7'ye karşı %40.4; p=0,032). Hemoglobin düzeyi NMNE grubunda anlamlı olarak daha düşüktü (12.8±0.8 vs 13.4±1.0 g/dl; p=0.05). NMNE grubunda kabızlık ve fekal inkontinans oranı anlamlı olarak daha fazlaydı(sırasıyla %27.9'a karşı %14.2; p=0.009 ve %11.6'ya karşı %1,2; p=0.002). Yukarıda tanımlanan parametreleri kullanan tek değişkenli analizler, nispeten düşük bir ortalama hemoglobin seviyesinin NMNE için bir risk faktörü olduğunu göstermiştir (OR=-0.603, %95 CI 0.346-0.867; p= 0.01).

Sonuç: MNE ve NMNE ayırıcı tanısını yapmak ve hastalık seyrinde risk faktörlerini daha erken belirlemek, enürezisli hastaların ilk değerlendirmesinde yapılması gereken temel görevlerdir. Nispeten düşük Hb seviyeleri, NMNE için yeni bir risk faktörü olabilir.

Anahtar Kelimeler: *Monosemptomatik enürezis, monosemptomatik olmayan enürezis, hemoglobin, risk faktörü*

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INTRODUCTION

Nocturnal enuresis (NE) is defined as urinary incontinence during the sleep period at night. The International Children's Continence Society (ICCS) classifies nocturnal enuresis as monosymptomatic or non-monosymptomatic (1). Patients with isolated nocturnal urinary incontinence and without bladder dysfunction are classified as having monosymptomatic nocturnal enuresis (MNE) (1-3]. On the other side, nonmonosymptomatic nocturnal enuresis (NMNE) is accompanied by lower urinary tract symptoms or bladder dysfunction (4). Non-monosymptomatic enuresis is associated with daytime wetting and symptoms of urgency, leakage, frequency, and hesitancy. We emphasize that laboratory and clinical markers are needed to differentiate these symptoms to classify nocturnal enuresis. The present study aimed to determine the differences between these two entities in the light of clinical and laboratory variables.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of pediatric patients with enuresis who were followed up between 2010 and 2021 at Kırıkkale University Hospital. At the first visit, information on the patients' medical histories and voiding diaries were collected, and a physical examination was performed to determine the etiology of enuresis. At the time of data entry; demographic findings and laboratory tests were recorded, which included routine biochemical parameters, complete blood count, urine test, and renal ultrasonographic findings. This retrospective study enrolled children with MNE and NMNE aged between 5 and 15 years. They were classified into two groups, namely MNE and NMN, according to the criteria of The International Children's Continence Society (1). Patients with chronic kidney disease, renal parenchymal disease, diabetes mellitus tubulopathies, urinary tract infection and severe co-existent comorbidities were excluded.

The study data were analyzed using SPSS (Statistical Package for Social Science) 16.0 software package. The results were shown as mean±SD unless stated otherwise. Mann-Whitney U test and Chi-square test were used to assess differences between the two groups. The level of statistical significance was set at $p<0.05$. The ethics committee approval of the study was obtained from the Kırıkkale University Clinical Research Ethics Committee (Date:12.1.2022 / Decision no: 2022.01.06.)

RESULTS

One hundred and sixty-one patients with MNE and 86 patients with NMNE were enrolled in this study. The patients with MNE were significantly older than the patients with NMNE (9.0±2.5 vs 7.6±2.4 years; p=<0.001). The proportion of females was significantly higher in the NMNE group (54.7% vs 40.4%; p=0.032). The hemoglobin level was significantly lower in the NMNE group (12.8±0.8 vs 13.4±1.0 g/dl; p=0.05). There was no significant difference in the mean rates of secondary enuresis, hydronephrosis, and serum glucose, creatinine, urea, and sodium levels between the groups. The most frequent coexisting diseases were asthma and epilepsy (8 asthma patients, 4 epilepsy patients). There was no significant difference in the mean rates of asthma and epilepsy between the two groups. The rate of constipation and fecal incontinence were significantly higher in NMNE group (27.9% vs 14.2%; p=0.009, and 11.6% vs 1.2%; p=0.002, respectively.) The proportion of female patients was significantly higher in the MNE group (32.2% vs 17.4%; p=0.046) (Table 1).

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Table 1 : Comparison of clinical and laboratory data between groups

Variables*	MNE n=161	NMNE n=86	P-value
Gender (female) n (%)	**65(40.4)**	**47(54.7)**	**0.032**
Mean age	**9.0±2.5**	**7.6±2.4**	**<0.001**
Secondary enuresis	22(13.7)	13(15.1)	0.755
Hydronephrosis n (%)	8(4.9)	5(5.8)	0.933
Urinary density	**1020.1±8.6**	**1017.2±8.2**	**0.014**
Serum glucose (mg/dl)	102.8±68.9	91.7±10.5	0.234
Serum creatinine (mg/dl)	0.51 ±0.12	0.47 ± 0.11	0.09
Serum urea (mg/dl)	22.8±5.7	24.9±5.9	0.075
Serum Sodium (mEq/L)	139.4±2.6	139.9±2.6	0.381
Hemoglobin (g/dl)	**13.4±1.0**	**12.8±0.8**	**0.05**
Co-existence disease Asthma Epilepsy	 5(3.1) 2(1.2)	 3(3.4) 2(2.3)	 0.874 0.520
Constipation	**23(14.2)**	**24(27.9)**	**0.009**
Fecal incontinence	**2(1.2)**	**10(11.6)**	**0.002**
Family history	**52 (32.2)**	**15 (17.4)**	**0.046**

MNE: Monosymptomatic nocturnal enuresis, NMNE:Non-monosymptomatic nocturnal enuresis

The univariable analyses using the above-identified parameters showed that a relatively low mean hemoglobin level was a risk factor for NMNE (OR=-0.603, 95% CI 0.346-0.867; p=0.01). ROC curve analysis indicated that a cut off value of 13.2 g/dl can be used for Hb level for risk of NMNE (AUC(95%), p<0.05) with a sensitivity 61.8%, and specifity 57.1%. (Figure 1)

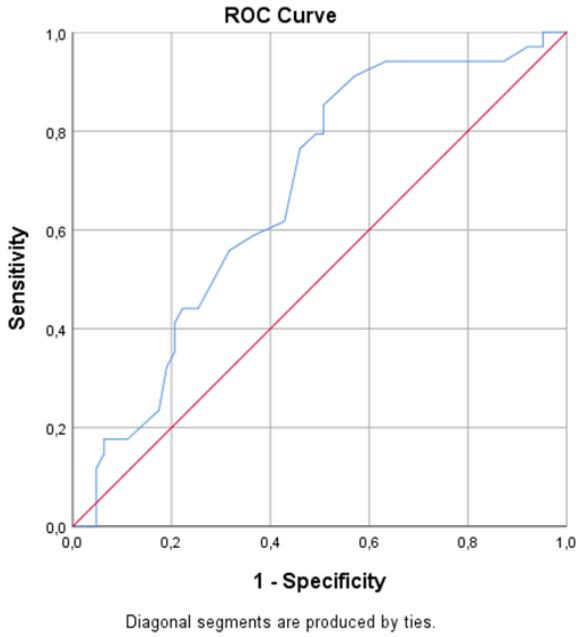

Figure 1: ROC curves and cutoff values of Hb level for NMNE risk. ROC receiver operating characteristic, AUC the area under the ROC curve

DISCUSSION

The pathogenesis and treatment of MNE and NMNE are different from each other. Some factors are implicated in the etiology of MNE. Increased urine output, low nocturnal bladder capacity, increased detrusor activity, and sleep-wake disorders are responsible etiological factors for MNE. On the other hand, NMNE represents a separate clinical entity such as lower urinary tract dysfunction (LUTD) (5,6).

We found that the NMNE patients were significantly younger than the MNE patients, as also shown in previous studies (7,8). This difference may stem from the fact that patients with NMNE seek medical care earlier due to the additive symptoms. The female preponderance in the NMNE group supports previous observations and findings suggesting a higher prevalence of LUTD among girls (9,10). Mota et al. (11) showed a LUTD prevalence of 24.2% in a study of 580 children aged between 3 and 9 years; Similar to our results, the disease had a higher prevalence in girls and younger children. These findings suggest a hormonal effect on bladder function. Estrogen receptors have been demonstrated in the urethra, bladder, and pelvic floor musculature so that estrogen has an important role in these pathways (12). Another explanation is that a slower maturation of boys than girls results in delayed

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voluntary urinary continence in boys compared to girls, which can explain the higher prevalence in girls (13).

Children with constipation or fecal incontinence often experience concomitant symptoms of LUT (22-34%) (14,15). Previous studies have shown that more than half of children with LUT dysfunction also have bowel dysfunction, with 30% of such patients presenting to the first visit with fecal impaction, and 80% with fecal incontinence (16,17). It has been observed that constipation is a risk factor for NMNE and lower urinary tract dysfunctions, but not MNE (18). Similarly, we found a higher rate of bowel dysfunction in NMNE.

The difference in urinary density is caused by the restriction of nocturnal water depletion in patients with MNE. The parental history of childhood enuresis is a risk factor for the offspring in MNE (19). Therefore, as expected, the MNE group had a higher rate of family history of childhood enuresis.

The rate of coexisting asthma (3,1-3.4%) was lower than the prevalence of the pediatric population (7.5-10.4%) (20,21). A significant proportion of patients delayed their follow-up; thus, the number of patients who subsequently developed asthma may have been overlooked. On the other hand, the rate of epilepsy in our study group was similar to those reported by previous studies (22).

A relatively low hemoglobin level was a novel risk factor for NMNE. There is no report in the literature investigating the effect of hemoglobin on enuresis. On the other hand, previous reports have shown that pediatric patients with sickle cell anemia may be at a higher risk of nocturnal enuresis than those with a normal hemoglobin (Hb) genotype (23,24). This is caused by a lower functional bladder capacity and a higher overnight urine volume to functional bladder capacity ratio in these patients (25). Studies with near infrared spectroscopy (NIRS) have shown that an abnormal hemodynamic response or the onset of oxygen debt during voiding causes underlying LUT, including detrusor dysfunction (26). Additionally impaired perfusion and low oxygen capacity due to low Hb may lead to oxidative stress of the bladder wall (27). Therefore, we suggest that the oxygen transfer capacity of Hb as well as the Hb level must have an effect on bladder function. It has been shown that chronic iron deficiency resulted in decreased MAO activity both in vitro and in vivo in rats, hence, reduced sympathetic activity may lead to urination (28). Anemia refers to a low red blood cell count or low serum iron level. The body will try to increase body fluid level to maintain the blood volume. An extra fluid volume can cause extra urination.

The lack of assessment of the iron status in our patients and the lack of comparison of the population with anemia were important limitations of our study. Another main limitation of the study is that there are no urodynamic studies in patients with NE due to the invasive characteristics of these tests.

Making the differential diagnosis of MNE and NMNE and determining the risk factors earlier in the disease course are essential tasks to be accomplished in the initial evaluation of patients with enuresis. Relatively low Hb levels may be a novel risk factor for NMNE. Additional studies are needed to determine whether hemoglobin and iron affect the pathogenesis of NMNE.

Conflict of Interest: The author has no conflict of interest to declare.

Researchers' Contribution Rate Statement:

Concept/Design: YK,ZA; Analysis/Interpretation: YK,ZA; Data Collection: ZA,AA,UK,SY; Writer: YK; Critical Review: YK,ZA; Approver : YK,ZA,AA,UK,SY

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