Characterization and treatment of enuresis in overactive bladder patients

B. Capdevila Vilaró[1], I. Casal-Beloy[2], F.N. Villalón Ferrero[4], O. Martín-Solé[3], M. Coronas Soucheiron[1], N. González-Temprano[4], L. Larreina De la Fuente[4], M. Carbonell Pradas[1], S. Pérez-Bertólez[3], X. Tarrado Castellarnau[1], L. García-Aparicio[3]

[1]Pediatric Surgery Department. Hospital Sant Joan de Déu. Barcelona (Spain). [2]Pediatric Urology Unit, Pediatric Surgery Department. Hospital Virgen del Rocío. Sevilla (Spain). [3]Pediatric Urology Unit, Pediatric Surgery Department. Hospital Sant Joan de Déu. Barcelona (Spain). [4]Pediatric Urology Unit, Pediatric Surgery Department. Hospital Universitario de Donostia. (Spain).

ABSTRACT

Objective. To define the types of overactive bladder (OAB) patient enuresis and study daytime bladder treatment response.

Materials and methods. A prospective, multi-center study of OAB patients with enuresis treated with anticholinergics or neuromodulation over 3 months from 2019 to 2021 was carried out. Variables achieved from the voiding calendar and PLUTSS (Pediatric Lower Urinary Tract Score System), as well as enuresis-related variables, were collected. Two study groups were created –primary enuresis (PE) and secondary enuresis (SE). Partial enuretic response (PER) was defined as a >50% reduction in baseline enuresis, and complete enuretic response (CER) as a 100% reduction. A multivariate analysis was eventually conducted to detect CER independent predictive factors.

Results. 152 OAB patients were included. 109 of them (71.7%) had enuresis –29 (26.7%) SE and 80 (73.3%) PE. PLUTSS score was higher in PE patients than in SE patients (20.8 vs. 17.2; p=0.001). PER and CER were significantly higher in the SE group (55.2% vs. 15%; p=0.000 in PER, and 48.3% vs. 5%; p=0.000 in CER). In the multivariate analysis, SE patients demonstrated to have a 50-fold increased probability of responding to daytime bladder treatment than PE patients (OR: 49.79; 95%CI: 6.73-36.8).

Conclusions. Most OAB children have PE and not SE, which explains why enuresis does not typically respond to daytime bladder treatment. Characterizing the type of enuresis in OAB children is important to adequately approach treatment.

KEY WORDS: Enuresis; Overactive bladder; Cholinergic antagonists; Transcutaneous electrical nerve stimulation.

CARACTERIZACIÓN Y TRATAMIENTO DE LA ENURESIS EN PACIENTES CON VEJIGA HIPERACTIVA

RESUMEN

Objetivos. Definir los tipos de enuresis de los pacientes con vejiga hiperactiva (VH) y estudiar su respuesta al tratamiento vesical diurno.

Material y métodos. Estudio prospectivo y multicéntrico: pacientes con VH y enuresis, tratados con anticolinérgicos o neuromodulación durante 3 meses (2019-2021). Recogimos variables obtenidas del calendario miccional, cuestionario PLUTSS (Pediatric Lower Urinary Tract Score System), y relacionadas con la enuresis. Generamos 2 grupos de estudio: enuresis primaria (EP) y enuresis secundaria (ES). Consideramos respuesta parcial enurética (RPE) a la reducción del valor de enuresis inicial en más de un 50% y respuesta completa (RCE) el 100%. Finalmente realizamos un análisis multivariante para detectar factores predictivos independientes de RCE.

Resultados. Incluimos 152 pacientes con VH, 109 de los cuales presentaban enuresis (71,7%): 29 ES (26,7%) y 80 EP (73,3%). El valor PLUTSS fue mayor en pacientes con EP que en ES (20,8 *vs.* 17,2, p=0,001.) La RPE y la RCE fueron significativamente mayores en el grupo de ES (55,2% vs. 15%, p=0,000 en RPE y 48,3% *vs.* 5%, p=0,000 en RCE). En el análisis multivariante se identificó que los pacientes con ES tienen una probabilidad de responder al tratamiento vesical diurno 50 veces superior que los pacientes con EP (OR 49,79, IC95% 6,73-36,8).

Conclusiones. La mayoría de niños con VH tienen una EP y no secundaria, por lo que generalmente la enuresis de estos pacientes no responde al tratamiento vesical diurno. Es importante caracterizar el tipo de enuresis de los niños con VH para plantear su tratamiento de forma adecuada.

PALABRAS CLAVE: Enuresis; Vejiga hiperactiva; Antagonistas colinérgicos; Estimulación eléctrica transcutánea sacra.

INTRODUCTION

5-7% of 7-year-old children have enuresis. According to the International Children's Continence Society (ICCS)[1], enuresis can be either monosymptomatic (ME) or non-monosymptomatic (NME). ME represents a clinical

DOI: 10.54847/cp.2024.01.14

Corresponding author: Dr. Blanca Capdevila Vilaró . Servicio de Cirugía Pediátrica. Hospital Sant Joan de Déu. Pg. De Sant Joan de Déu 2. 08950 Esplugues de Llobregat, Barcelona
E-mail address: blanca.capdevila@sjd.es

This work was presented at the 31st National Meeting of the Spanish Pediatric Urology Group held in 2022.

Date of submission: May 2023 *Date of acceptance:* October 2023

entity per se, with incontinence during sleep being the only symptom. NME is an additional symptom within lower urinary tract dysfunctions (LUTD). Enuresis can also be classified as primary –the patient has never achieved continence during sleep– or secondary –the patient remains dry during sleep for at least 6 months and then incontinence resumes.

Enuresis' physiopathology is different according to the aforementioned classification, which means the therapeutic approach should be individualized and adjusted on a case-by-case basis, according to whether it is ME or NME. In ME, recent studies suggest a sleep disorder could be the most frequent cause[2,3]. In NME, the mechanism varies according to the patient's LUTD. Therefore, in overactive bladder (OAB) patients, enuresis should occur as a result of the low bladder capacity of these individuals, along with the presence of bladder contractions during the bladder filling stage[4-6].

Enuresis is present in 40-70% of OAB children. The latest ICCS guidelines for the management of enuresis and for the management of pediatric daytime incontinence[1] establish daytime symptoms of OAB patients are to be treated first, since enuresis will parallelly resolve in most cases –enuresis being an additional symptom within their LUTD. However, clinical experience reveals that enuresis typically persists following complete daytime symptom resolution. This reduces hopes among parents and children regarding their dysfunction, thus increasing therapy dropout rates.

Today, literature references analyzing the characteristics of enuresis in OAB patients and its response to specific daytime treatment are scarce. Consequently, the first objective of our study was to characterize the enuresis of OAB patients. The second objective was to analyze enuresis' therapeutic response when following the ICCS recommendation of initially treating daytime symptoms.

MATERIALS AND METHODS

An observational, longitudinal, prospective, multi-center study of OAB patients was carried out. Patient follow-up was conducted at Sant Joan de Déu Hospital (Barcelona, Spain)'s and Donostia University Hospital (San Sebastián, Spain)'s pediatric urology consultations from 2019 to 2021.

Patient inclusion criteria were as follows: diagnosis of OAB according to the ICCS definition –urinary urgency, associated or not with pollakiuria and daytime urinary incontinence, in the absence of an active urinary tract infection or other detectable organic disease justifying the presence of these symptoms–, presence of a tower- or bell-shaped flowmeter curve without electromyographic activity or post-voiding residual urine before OAB specific treatment initiation, PLUTSS score over 8.5 points, and age range between 5 and 16 years old. Patient exclusion criteria were the following: patients receiving nocturnal incontinence treatment, changes in diagnosis along follow-up, diagnosis of mixed or combined LUTD, OAB patients with full symptom resolution or a < 8.5-point PLUTSS score following initial management measures –urotherapy and constipation management–, incomplete follow-up or lack of documents and complementary tests during data collection, patients whose parents or guardians were not willing to sign the informed consent forms to participate in the study, and patients lost during follow-up.

Once OAB diagnosis had been established, patients with concomitant enuresis were selected. Two primary study groups were created –the **PE group** (patients with primary enuresis who subsequently developed LUTD, namely OAB) and the **SE group** (patients with OAB and secondary enuresis, since the beginning of daytime symptoms). In all patients, management measures were aimed at targeting daytime symptoms. Patients initially received standard urotherapy[7] and constipation management measures in case symptoms were present for 2-3 months. After this initial period, all patients with persistent symptoms were eligible for transcutaneous electrical nerve stimulation (TENS) treatment or drug therapy (oxybutynin or solifenacin), at the physician's discretion. These therapies were administered for 3 months, with standard urotherapy or constipation management measures being maintained.

TENS treatment

Patients who received TENS treatment and their guardians were taught at the consultation how to use the system. The therapy was conducted at home under the supervision of the person in charge of the patient's care. Regarding the technique, it involves placing two electrodes at the cutaneous level, in the sacral region (S2-S3), through which the electric current is transmitted towards the sacral plexus. The parameters employed for pulse frequency and width were 10 Hz and 200 μseg, respectively. The intensity of the pulse wave –measured in milliamperes– was individually regulated according to the maximum intensity tolerated without pain by the patient, up to 40 milliamperes (mA). Sessions were held on a daily basis for 20 minutes, and at-home treatment was maintained for 3 months.

Drug therapy with oxybutynin

Patients under drug treatment with oxybutynin received the oral medication as a daily immediate liberation therapy. The dose was 0.5 mg/kg/day, distributed in 2 doses –in the morning and at noon.

Drug therapy with solifenacin

In this case, oral solifenacin syrup at a 1 mg/ml dose, administered once daily, was used. Dosage was determined according to weight as established by the package insert.

Patient follow-up was conducted at pediatric urology outpatient consultations, in a serial manner, over 6 months. The first consultation was held 3 months following initiation of standard urotherapy and constipation management measures. All patients were assessed, and in those with dysfunctional clinical signs, one of the three specific aforementioned therapies was introduced. The second consultation took place 3 months following specific treatment initiation –equivalent to 6 months since standard urotherapy had started. In this consultation, overall symptom therapeutic response, as well as enuresis itself, was assessed.

Demographic and clinical variables were collected. They were achieved from the voiding calendar –number of daytime urinations and bladder capacity– and the Spanish validated version of PLUTSS[8]. Enuresis-related variables –primary or secondary enuresis, number of wet nights per week over 1 month, and volume of losses– were also recorded.

PLUTSS was used to assess overall symptom therapeutic response –both daytime and nocturnal. Scores ≥ 8.5 points were considered diagnostic of LUTD (maximum score: 35 points), and the higher the score, the more severe the dysfunction. Enuresis therapeutic response was established using the score achieved through PLUTSS questions 3 and 4 –which assess enuresis frequency and volume–, with a 0-9 score range (0 = absence of nocturnal incontinence; 9 = maximum grade of enuresis). Partial enuretic response (PER) was defined as a > 50% reduction in baseline enuresis, and complete enuretic response (CER) was defined as a 100% reduction.

Once the study period was over, medical records were manually reviewed. The variables collected were transcribed on RedCap® (Vanderbilt University) platform and hosted in a safe server owned by Sant Joan de Déu Hospital, Barcelona (Spain) (https://apps.sjdhospitalbarcelona.org/redcap/).

Statistical analysis was carried out using the Stata 14.2® (StataCorp LLC, Texas, USA) software. Initially, a descriptive analysis of study variables was conducted. Quantitative variables were expressed as mean and standard deviation (SD), whereas qualitative variables were featured as absolute value and percentage. All variables recorded were compared between both study groups. Regarding quantitative variables, mean values were compared using Student's t-test or Mann-Whitney's U test, whereas qualitative variables were compared by means of the chi-squared test or Fisher's exact test. Finally, a multivariate logistic regression model was used to detect PER and CER independent predictive factors.

Ethical approval

Ethical approval was achieved from the relevant Clinical Research Ethics Committees (approval number: ICB-OXI-2018-01). Patient confidentiality was ensured according to the European Data Protection Regulation (EU 2016/679).

RESULTS

152 OAB patients (50.4% of whom were girls) were included. 109 (71.7%) of them had enuresis –80 (73.3%) in the PE group and 29 (26.7%) in the SE group (Figure 1).

The demographic and clinical characteristics of the various groups are featured in Table 1. PE was significantly higher in boys (61.2%; $p<0.001$), and SE in girls (87.8%; $p<0.005$). Bladder capacity was significantly lower in the PE group than in the SE group (191.3 ml vs. 284.1 ml; $p<0.05$).

The PLUTSS score was significantly higher in PE than in SE patients (20.8 vs. 17.2; $p<0.005$). When analyzing daytime symptoms (LUTS variable) only, there were no differences between the PE and SE groups (12.1 PE vs. 12.9 SE; $p>0.05$). In addition, LUTS score in the group of OAB patients without enuresis had no significant differences vs. the OAB + enuresis groups (14.5; $p>0.05$). This means OAB patients with enuresis had no statistically significant differences regarding symptomatic severity vs. OAB patients without enuresis, regardless of whether enuresis was PE or SE.

Both PER and CER rates were higher in the SE group (Fig. 1, Table 2). The type of treatment received (anticholinergics or electrotherapy) did not modify PER or CER.

Finally, a multivariate analysis was conducted to assess which factors were independently correlated with CER three months following treatment initiation. The only factor correlated with CER was having SE (OR: 49.79; $p<0.001$). This means that, in patients with OAB and SE, the possibility of full enuresis resolution with the targeted daytime treatment was 50-fold higher than in patients with OAB and PE.

DISCUSSION

There are very few articles in the scientific literature analyzing enuresis in OAB patients. However, it is one of the symptoms most commonly associated with OAB, and the most resistant to the currently proposed treatment[6]. According to the ICCS definition, all patients with enuresis associated with OAB should be regarded as non-monosymptomatic secondary enuretic individuals. However, in our study, two types of enuretic patients were detected. The first group consisted of patients who already had primary enuresis (PE) and subsequently developed LUTD in the form of overactive bladder, which means both dysfunctions were completely different but concomitant entities. This group had characteristics typical of patients with monosymptomatic enuresis –it was more

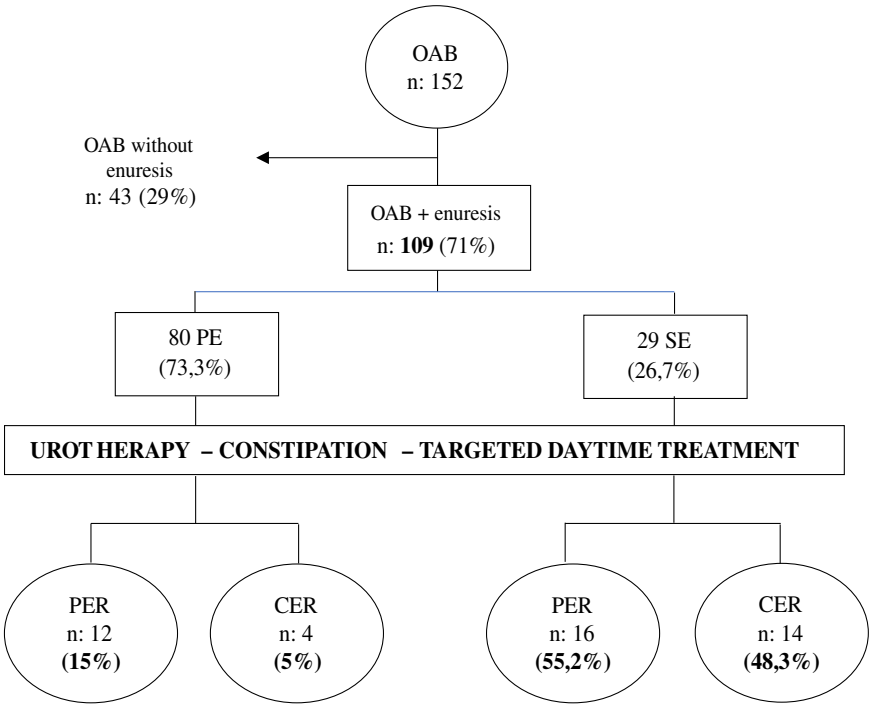

Figure 1. Patient flow diagram.

Table 1. Patient demographic and clinical characteristics, and comparison according to the study group.

	No enuresis (n = 43)	*PE group (n = 80)*	*SE group (n = 29)*	*p*
Age (years), mean (SD)	9.7 (3.1)	8.4 (2.6)	10.3 (2.6)	0.004
Sex (f/m), n (%)	29 (67.4%) / 14 (32.5%)	31 (38.7%) / 49 (61.2%)	24 (87.8%) / 5 (17.2%)	0.000
BMI (kg/m²), mean (SD)	18.4 (2.9)	18.9 (4.9)	19.2 (3.8)	0.062
PH (no/yes), n (%)	39 (90%) / 4 (10%)	58 (72%) / 22 (28%)	21 (72%) / 8 (28%)	0.042
BC (ml), mean (SD)	253.9 (123.2)	191.3 (82.8)	284.1 (138.9)	0.006
No. of urinations, mean (SD)	9 (3)	9.3 (2.7)	9.3 (4.6)	0.623
PLUTSS score, mean (SD)	14.6 (4.4)	20.9 (4.6)	17.3 (4.3)	0.001
LUTS score, mean (SD)	14.6 (4.4)	12.1 (4.6)	12.9 (3.7)	0.521
Enuresis score, mean (SD)	0	8.8 (0.9)	4.3 (1.7)	0.0001

PE = primary enuresis; SE = secondary enuresis; SD = standard deviation; f/m = female/male; BMI = body mass index; PH = pathological history; BC = bladder capacity; LUTS = PLUTSS score without enuresis questions (questions 3 and 4), maximum score: 26; Enuresis score = score of PLUTSS enuresis questions, maximum score: 9.

frequent in younger males, and it involved large daily wettings. The second group of enuretic patients was made up of overactive bladder patients with secondary enuresis (SE) as an additional symptom related to LUTD, and coincident with daytime symptom onset. When studying how enuresis works in OAB patients when LUTD is generally and specifically treated, fewer enuretic patients had enuresis resolution, contrarily to what has been reported in the latest enuresis management guidelines[7]. When analyzing enuretic response separately between both groups, secondary enuresis patients were 50-fold more likely to respond to daytime bladder treatment than primary enuresis patients.

This suggests and demonstrates that the underlying physiopathology of each enuresis type is different, which means the therapeutic approach should not be the same. The studies[6,9-11] analyzing the consequences of daytime bladder treatment (urotherapy, oxybutynin,

Table 2. Distribution of partial and complete enuretic response according to group distribution (PE vs. SE).

		PE (n = 80)	*SE (n = 29)*	*p*
PER, n (%)	No	68 (85%)	13 (44.8%)	< 0.001
	Yes	12 (15%)	16 (55.2%)	
CER, n (%)	No	76 (95%)	15 (51.7%)	< 0.001
	Yes	4 (5%)	14 (48.3%)	

PE = primary enuresis; SE = secondary enuresis; CER = complete enuretic response; PER = partial enuretic response.

solifenacin, and TENS) on enuresis available up until now have always grouped the total of enuretic patients together when assessing results, without considering the two groups identified in this study. When considering the two groups in terms of treatment response analysis, secondary enuresis acts as a factor associated with complete enuresis resolution, whereas primary enuresis acts as a lack-of-healing factor. In these cases, enuresis resolution is known to be delayed for months or years[6,12], thus reducing hopes among parents and patients, and increasing therapy dropout rates. Based on our results, we suggest enuresis management be initiated from the early stages by adding nighttime alarm to standard urotherapy in patients where primary enuresis is detected as an individual entity –present before daytime symptom onset– through relevant questionnaires.

Our study has a series of limitations. The main one is the low number of patients included in each group, which limits statistical power, especially when interpreting conclusions. However, given that this is the first study analyzing and characterizing enuresis in overactive bladder patients, it can be used as a reference in future studies. Another limitation lies in the subjective nature of the symptoms assessed for the clinical study of these patients, which may have led to interpretation mistakes. In an attempt to minimize this, validated questionnaires and specific data such as number of wet nights, volume of losses, etc. were used.

We believe our study results could have an impact on the daily clinical practice of the physicians dealing with lower urinary tract dysfunction patients. OAB patients who would clearly benefit from simultaneous enuresis treatment should be detected. This change in the therapeutic approach aims to reduce treatment resistance rates, while achieving better clinical results.

In conclusion, enuresis is frequently associated with overactive bladder –it is present in 70% of OAB patients. In our study, the enuresis most frequently associated with OAB was primary enuresis. In only 25% of OAB patients, enuresis was secondary to daytime symptoms. Less than half of enuresis patients had a complete response when daytime dysfunction was treated, and the enuresis type with the greatest treatment response was precisely secondary enuresis. This suggests it would be interesting to detect enuresis type and identify those patients who would benefit from a simultaneous enuresis treatment, in order to specifically focus treatment and achieve better clinical results.

ACKNOWLEDGEMENTS

We would like to thank all contributors to this article and to the research work. Each and every of them participated with their own skills and knowledge to achieve the final goal.

We would also like to thank the anonymous reviewers for their constructive remarks and suggestions.

Thank you all for your invaluable cooperation and support in this project.

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