

PRIMARY NOCTURNAL ENURESIS: A CLINICAL URODYNAMIC EVALUATION AND ANALYSIS OF THERAPEUTIC OPTIONS

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Objective To assess the clinical evaluation, urodynamic data and therapeutic options in patients with primary nocturnal enuresis.

Patients and Methods A total of 473 patients aged between 5 and 35 years were evaluated clinically and underwent urine analysis and cultures as well as plain radiography of the abdomen. Intravenous urography was done when indicated. A urodynamic study was done in patients with polysymptomatic enuresis, a failed previous therapy and enuresis in adults. Initially, patients with monosymptomatic enuresis and those who had polysymptomatic enuresis with a stable detrusor function were managed by conditioning therapy using a calendar. When urodynamic studies detected detrusor instability (DI), the patients were initially treated by antimuscarinics.

Results Monosymptomatic enuresis was diagnosed in 329 patients, while the remaining 144 patients had polysymptomatic enuresis. Detrusor instability was detected in 36% of the monosymptomatic patients and in 93% of the polysymptomatic patients. Bladder capacities at the first sensation (FS), at normal sensation and at

the maximum cystometric capacity (MCC) showed a statistically significant increase in patients with stable detrusor function compared to those with DI. The detrusor pressure (Pdet) was significantly higher at the first sensation and at the MCC in patients with DI than in patients with a stable detrusor. Conditioning therapy showed satisfactory results in 74% of the patients with a better outcome in those with monosymptomatic enuresis. Antimuscarinics treated 91% of both monosymptomatic and polysymptomatic enuretics with DI.

Conclusion Conditioning therapy using a calendar can offer a good therapeutic modality to most patients with primary nocturnal enuresis with stable detrusor function avoiding the costs and side effects of drugs. Pharmacotherapy should only be used when this conditioning therapy fails. Filling cystometry can detect detrusor instability as a cause of enuresis that helps in the proper choice of antimuscarinics as a primary line of treatment.

Keywords Enuresis, urodynamic, antimuscarinic, bladder, detrusor, instability

INTRODUCTION

Nocturnal enuresis is a widespread problem that can create tremendous social and emotional anxiety for patients and parents on a daily basis. It is defined as the involuntary voiding of urine on at least 2 nights per month continuing beyond the age of 5 years in the absence of congenital or acquired disease of the urinary tract¹. Many classifications have been used to define the types of nocturnal enuresis. Primary nocturnal enuresis is defined as nocturnal incontinence in a child who has never gained nocturnal urinary control. It accounts for 75-80% of the cases. Secondary enuresis is diagnosed when at least a 6-month

period of dryness has preceded the onset of bedwetting. Polysymptomatic nocturnal enuresis is defined as nocturnal incontinence that occurs in association with urinary urgency or/and urge incontinence, while the term monosymptomatic enuresis describes nocturnal enuresis that occurs without any other symptoms^{1,2}. The frequency of enuresis in children is age-dependent. It varies between 45% at age 3, to 23% at age 5, 6% at age 10, and 2% after age 15³. More than 1% of adults older than 20 years suffer from persistent nocturnal enuresis⁴. Fortunately, a spontaneous annual cure rate of 15% usually occurs^{5,6}. Daytime incontinence is present in 15-20% of patients with nocturnal enuresis⁷.

Table 1: Detailed Demographic Data of our Patient Population

	Age (years)			Total
	5 – 10	11 – 20	> 20	
Males	64 (31%)	133 (64.6%)	9 (4.4%)	206 (43.6%)
Females	91 (34%)	162 (60.7%)	14 (5.3%)	267 (56.4%)
Total	155 (32.8%)	295 (62.4%)	23 (4.8%)	473

Table 2: Data of 77 Patients Subjected to Urodynamic Studies

	Monosymptomatic		Polysymptomatic	
	Detrusor Instability	Stable Detrusor	Detrusor Instability	Stable Detrusor
<u>Age (years)</u>				
Range	6 – 30	10 – 35	6 – 29	15 & 19
Mean	16	16	14.3	
SD	6.6	5.3	5	
P Value	0.8		0.3	
<u>Gender</u>				
Males	8	16	7	0
Females	9	14	21	2
Total	17	30	28	2
	47		30	

This study attempts to determine the extent of the clinical evaluation required in patients with nocturnal enuresis to assess their current situation and the urodynamic evaluation, when indicated, and to determine and evaluate the choice of appropriate treatment.

PATIENTS AND METHODS

Between November 1997 and December 2001, 437 patients with primary nocturnal enuresis out of a group of 520 patients presenting to the Nocturnal Enuresis Clinic, Al-Hussien University Hospital, Cairo, Egypt,

were enrolled in this study. Their age ranged from 5 to 35 years (mean age 12.5 ± 4.6 years). There were 206 males (mean age 12.2 ± 4 years, range 5 to 29) and 267 females (mean age 12.7 ± 5 years, range 5 to 35).

The first step in the diagnostic process was the exclusion of any physical cause for this condition. All patients were evaluated with a complete medical history that also determined the pattern, frequency and duration of bed-wetting, and their sleeping pattern. A history of associated daytime voiding symptoms including frequency of micturition, urgency, daytime incontinence and weak stream was recorded,

Table 3: Bladder Capacity (ml) at First Sensation in Relation to Detrusor Instability (DI) vs. the Type of Enuresis

	No DI (total)	DI (total)	No DI, Mono	DI, Mono	DI, Poly
Mean	205.7	101.6	205.4	99.7	106.5
SD	128.8	61.3	133.6	44.5	79.7
min	45	6	45	27	6
max	526	252	526	179	252

mono = monosymptomatic; poly = polysymptomatic

Table 4: Bladder Capacity (ml) at Normal Sensation in Relation to Detrusor Instability (DI) vs. the Type of Enuresis

	No DI (total)	DI (total)	No DI, Mono	DI, Mono	DI, Poly
Mean	325.3	202.8	325.9	194.3	190.2
SD	127	97.3	132	81.5	124
min	106	23	106	88	23
max	551	430	551	338	430

Table 5: Bladder Capacity (ml) at Maximum Cystometric Capacity in Relation to Detrusor Instability (DI) vs. the Type of Enuresis

	No DI (total)	DI (total)	No DI, Mono	DI, Mono	DI, Poly
Mean	416	268	415.3	256.7	245.2
SD	152.3	119	157.4	116.7	135.8
min	52	23	181	180	23
max	951	530	951	441	460

together with a history of previous urinary tract infection and bowel habits, e.g. encopresis. A previous evaluation, attempts at therapy and its results, as well as the attitude of the patient and parents towards the problem were also taken into consideration. A psychosocial history and family history of enuresis in other family members such as parents or siblings were carefully evaluated. Physical examination was undertaken with focused neurological examination including observation of the gait, inspection and palpation of the lower back, peripheral reflexes, perineal sensation and

anal tone. Urine analysis and cultures were done to exclude urinary tract infection. Routine plain radiographs of the abdomen (KUB) were obtained. Intravenous urography (IVU) was done in polysymptomatic enuresis and before urodynamic studies to exclude associated upper urinary tract anomalies and to assess the bladder configuration.

Patients with organic urological diseases or abnormalities found on neurological examination, suspected diabetes insipidus, allergy, attention deficit disorder or radiological ab-

Table 6: Detrusor Pressure (Pdet) at First Sensation (FS) and Maximum Cystometric Capacity (MCC) in cmH₂O in Relation to Detrusor Instability (DI)

	No DI		DI	
	FS Pdet	MCC Pdet	FS Pdet	MCC Pdet
Mean	8.4	13.2	25	51.1
SD	6.6	10.2	22.3	34
min	1	2	6	10
max	30	38	92	151

normalities as shown by IVU were excluded from the study.

Urodynamic studies were advised only when the preliminary evaluation was abnormal like in cases with encopresis, polysymptomatic enuresis or failed previous therapy, and enuresis in adults. Cystometry was done in the sitting position using the Ellipes-4 Audcat machine, Andromeda, Munich, Germany. While the patient was sitting, artificial bladder filling was undertaken using 0.9% physiological sterile saline at room temperature in a medium filling rate of 25-50 ml/min by using a dual lumen 6 Fr. urethral urodynamic catheter (Porges). The abdominal pressure was measured by using a 10 Fr. ballooned rectal tube (Porges). Bladder volume (Vves) and detrusor pressure (Pdet) were documented at first sensation (FS) and at maximum cystometric capacity (MCC). Provocative tests such as cough and fast filling rate were done to uncover detrusor overactivity. Video urodynamics, under fluoroscopy, were done in patients with a dilated upper urinary tract or an opened bladder neck as seen on IVU. Bladder filling was continued until the patient experienced a desire to void or until maximum cystometric capacity. The expected bladder capacity was calculated according to the age based on the formula proposed by Hjalmas: "bladder capacity (mL) = (30xage[yrs])+30"⁸. Definitions and methods conform to the recommendations of the International Continence Society (ICS)^{9,10} and the International Children's Continence Society (ICCS)¹.

As a general advice, patients need to be made aware of the benefits of regulating and altering both the timing and type of fluid intake. Acidic drinks and caffeine-containing drinks are

good examples. All patients were instructed to refrain from all food and fluid intake one hour before bedtime and were encouraged to void before retiring. They were advised to wake up at least two times, first at midnight and again at dawn to go to the bathroom. Initially, they did not receive any other behavioural or pharmacological therapy. Only in cases where the patient failed conservative therapy, imipramine therapy was initiated. It was given orally 30 to 45 minutes before retiring at a dose of 1.5 mg/kg. When detrusor instability was detected on urodynamic studies the patients were initially treated with antimuscarinic drugs at an appropriate dose. Pro-Banthine was initially used and subsequently oxybutynin, in cases where intolerable antimuscarinic side effects occurred with pro-Banthine. The dose of oxybutynin for children younger than 7 years was 2.5 mg two times daily and for those older than 7 years it was 5 mg two to three times daily. Dosages were adjusted according to the response and with respect of the side effects. Follow-up urodynamic studies were repeated 3 to 6 months after the beginning of the treatment for an objective evaluation of its efficacy. The patient himself assessed the results by affixing the non-enuretic nights to a calendar, thereby re-enforcing his ability to remain dry. The patients were evaluated monthly depending on the decrease in the number of wet nights compared to their number at presentation. The results were considered excellent when the number of wet nights decreased by at least 75% at the first month, good when the decrease was at least 50%, and poor when it was less than 50%.

For the statistical analysis, the comparison between the groups was performed using unpaired t tests. A p value of <0.05 was

Table 7: Follow-Up of Conditioning Treatment in 89 Patients

Results	Monosymptomatic	Polysymptomatic
Excellent	39	9
Good	13	5
Poor	12	11
Total	64	25

considered significant. The results are presented as mean plus or minus standard deviation (SD).

RESULTS

The detailed demographic data of our patients are illustrated in Table 1.

The mean incidence of enuresis was 5 nights a week (range 3 to 7). Forty-nine patients had attempted previous enuresis treatment for more than one year, in the form of imipramine (24 patients), antimuscarinic drugs (4 patients), combined imipramine and antimuscarinics (19 patients), and desmopressin spray (2 patients). Many others had received pharmacological treatment for a short duration. Fifty-two patients had a positive family history of enuresis (11%).

Monosymptomatic enuresis was diagnosed in 329 patients (69.6%), 164 males and 165 females. Their mean age was 12.1 ± 4.5 years (range 5 to 35). The other 144 patients (42 males and 102 females) had polysymptomatic enuresis with daytime frequency, urgency, and/or urge incontinence. Their mean age was 13.2 ± 4.7 years (range 5 to 32). Most of the family members of the monosymptomatic enuretic patients (237 patients, 72%) were found to have a deep sleep. All the patients enrolled in the study were normal on clinical examination.

Spina bifida occulta was detected in 294 patients (62.2%) consisting of 115 males (39.1%) and 179 females (60.9%). In total, 193 (65.6%) suffered from monosymptomatic enuresis, while 101 patients (34.4%) had polysymptomatic enuresis. Seventy males

(39.1%) and 109 females (60.9%) had normal spines. Forty-one of them (23%) had monosymptomatic enuresis, while poly-symptomatic enuresis was found in 138 patients (77%).

Urodynamic studies were performed in only 77 patients (Table 2). The other patients refused to do the test. Pre-test free flowmetry was normal in all patients. Bladder capacities at the first sensation (FS), at normal sensation and at the maximum cystometric capacity (MCC) showed a statistically significant increase in patients with a stable detrusor compared to those with detrusor instability (DI) (p values 0.0004, 0.004 and, 0.04, respectively) (Tables 3, 4 and 5). They also showed a highly significant increase among patients with monosymptomatic enuresis and a stable detrusor compared to patients with DI (p values 0.016, 0.003 and 0.0005, respectively) (Tables 3, 4 and 5). However there was no statistically significant difference between the bladder capacities in patients with monosymptomatic and polysymptomatic enuresis with DI (p values 0.49, 0.095 and 0.215, respectively) (Tables 3, 4, and 5). The detrusor pressure (Pdet) was significantly higher at the first sensation and at the MCC in patients with DI compared to patients with a stable detrusor (p value 0.0000015 and 0.0003, respectively) (Table 6). Only two adult female patients with polysymptomatic enuresis had a stable detrusor. Voiding pressure flow studies revealed a normal detrusor power in all patients.

In total, 166 out of 473 (35%) patients in our study had a prolonged follow up of at least 12 months. The mean follow up duration was 8.6 ± 9.4 months (range 3-40). The remaining patients were either followed with a short duration or were lost to follow up. The treatment strategy for a total of 89 patients with monosymptomatic enuresis (64 patients) and polysymptomatic enuresis with stable detrusor (25 patients) was conservative management by conditioning therapy using a calendar. After 3 months, 48 patients (54%) had excellent results and 18 patients (20%) had good results. Eight of the latter group started imipramine that improved their results to an excellent level. In the remaining 23 patients (26%) the results were poor (Table 7). Twelve of them had polysymptomatic enuresis and improved on antimuscarinic drugs. The other 11, with monosymptomatic enuresis, were not cooperative and did not adhere to the instructions.

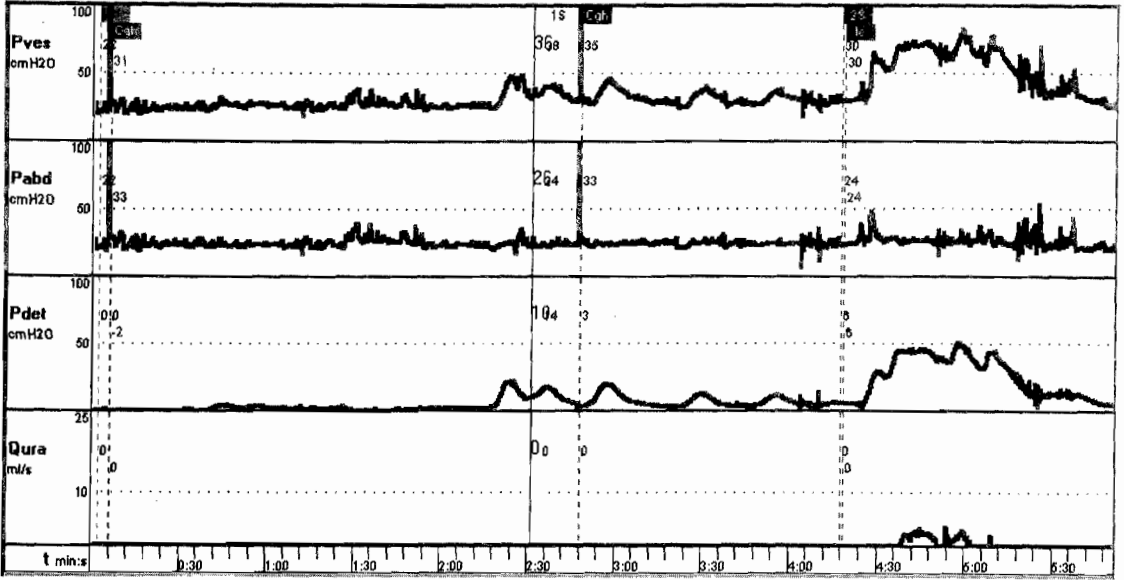


Fig. 1A: Filling cystometry in a 19-year-old lady with polysymptomatic enuresis showing an overactive detrusor with a maximum cystometric capacity of 218 ml. Voiding cystometry shows a normal voiding pattern in relation to the voiding volume.

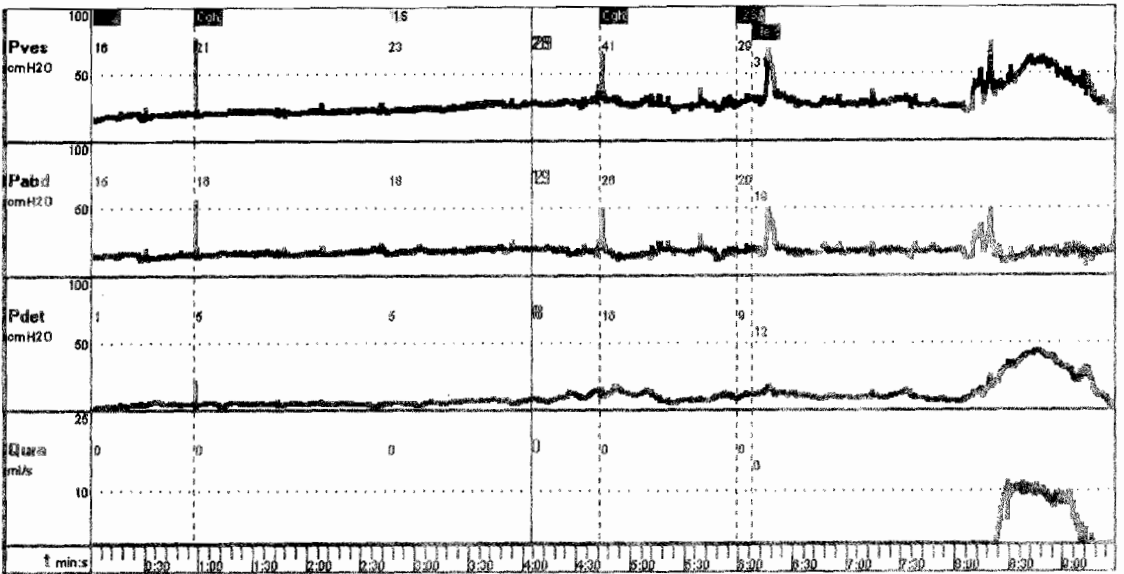


Fig. 1B: Filling cystometry of the same lady 6 months after treatment with oxybutynin showing a stable detrusor function with a maximum cystometric capacity of 400 ml. Voiding cystometry shows a normal voiding pattern in relation to the voiding volume.

Of the 77 patients with DI, 47 mono-symptomatic and 30 polysymptomatic enuretics, were treated with antimuscarinic drugs. During the first month of treatment the irritating bladder symptoms and enuresis improved in all but 7 patients. Therapy was discontinued due to intolerable anticholinergic side effects in 3 patients. They were treated with imipramine

and flavoxate with poor results. The other 4 patients treated with antimuscarinics and imipramine showed bad results with a persistent high-pressure detrusor instability (>80 cm H₂O) on follow-up cystometry. Augmented ileocystoplasty was performed in all of these 4 patients. Of the 70 patients on antimuscarinic treatment, 46 achieved continence

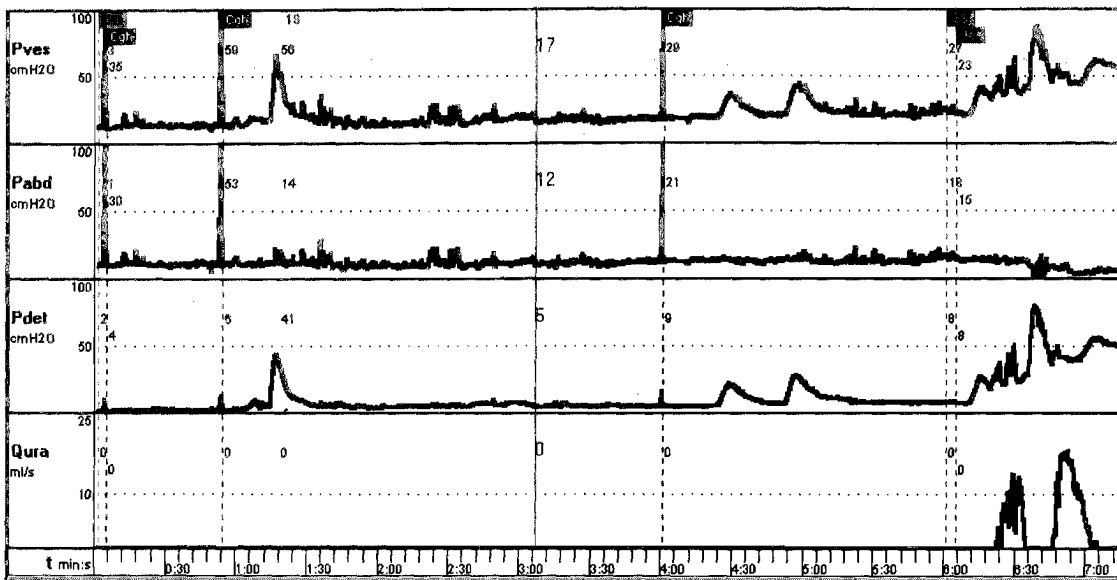


Fig. 2A: Filling cystometry in a 12-year-old girl with polysymptomatic enuresis showing an overactive detrusor with a maximum cystometric capacity of 300 ml. Voiding cystometry shows persistent postvoid tone detrusor contraction.

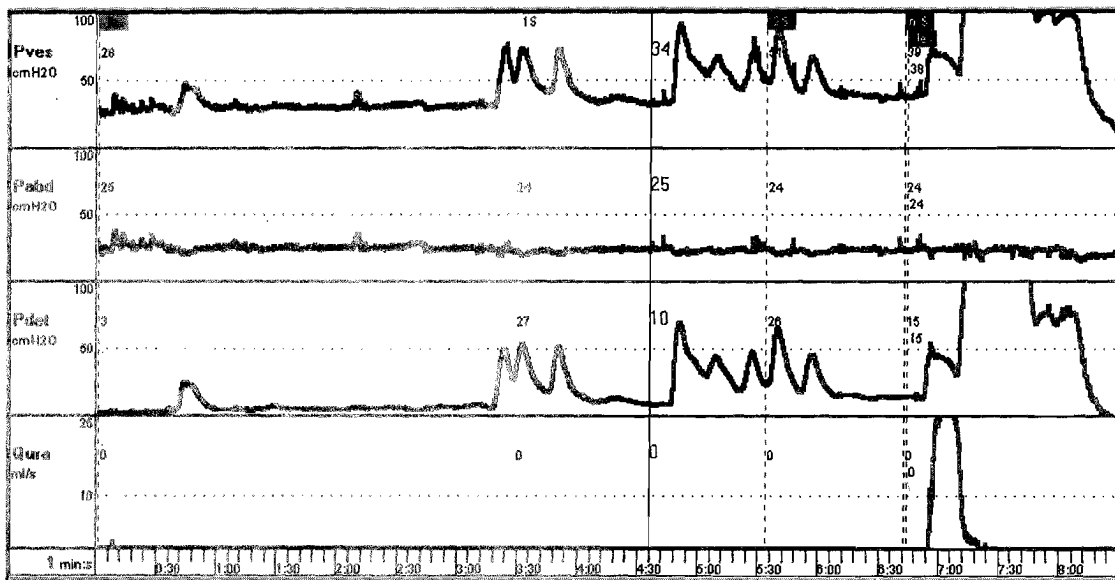


Fig. 2B: Filling cystometry of the same girl 6 months after treatment with pro-Banthine and then oxybutynin showing detrusor instability with a maximum cystometric capacity of 387 ml. Voiding cystometry shows persistent high pressure postvoid tonic detrusor contraction.

at night at 3 months and all of them were continent within 6 months. Follow-up CMG was done after 3 to 6 months of treatment in 29 patients. The mean bladder capacity at FS increased from 129 ± 105 to 261 ± 147 ml ($p < 0.014$) and the mean MCC increased from 218 ± 103 to 404 ± 148 ml ($p < 0.0017$) (Figure 1). Detrusor overactivity disappeared in 8 patients,

improved in its frequency, duration, and amplitude in 14 and persisted unchanged in the remaining 7 patients (Figure 2). The dose of oxybutynin was doubled and imipramine was added to the treatment regimen of the latter group. Relapse of enuresis only occurred in 2 females; in one it occurred when she got pregnant and in the other it was found 6

months after reducing the dose of oxybutynin to one tablet at night.

DISCUSSION

Historical reviews document the presence of bedwetting and its social dilemmas as far back as the Ebers papyrus of 1550 BC¹¹. Nevertheless, the aetiology of enuresis remains unknown in the majority of patients. The problem is considered multi-factorial, including developmental delay¹², genetic factors¹³, the lack of a normal diurnal rhythm of the anti-diuretic hormone¹⁴, sleep-arousal disorders¹⁵ and/or insufficient waking¹⁶, abnormal behavioural symptoms and environmental stress¹⁷. Therefore, no single treatment modality has proved to be efficacious for all enuretic patients. The aim of the Enuresis Clinic is to provide comprehensive health services to these patients and their families. An essential part of the treatment program is providing reassurance and emotional support to the patients and their families. Starting by telling them that many others share the same problem can dramatically improve the patients' self-confidence and reduce stress. It is important to emphasize that enuresis is a transitional condition in the vast majority of cases and does not represent a disease, but simply a delay in the maturational process. The objective of this effort is to develop a close collaborative relationship with the patient and his relatives to work together as a family to solve this problem. Not all patients require treatment for nocturnal enuresis. After evaluation and reassurance, some patients may improve with simple instructions and may not desire treatment with its possible morbidity and expenses. When needed, treatment should be individually judged and based on the patient's age and response. Marking the dry nights on a calendar may act as a visual symbol of appropriate response to the treatment. Although this method has the disadvantage of the lengthy instructions that must be given to the family, a close follow up and the necessity of co-operation among the doctor, patient and family, it has the advantage of a good success rate without side effects caused by drugs. In the present study the overall success rate in achieving a full or major improvement in monosymptomatic enuresis with a stable detrusor was 74% with the treatment strategy focussing on reassurance and conservative treatment. Restriction of fluid intake later in the day and awakening the patient during night

have proven helpful and were successful in many cases. However, the success depends upon sufficient motivation of the patient and eagerness of the parents to awaken and alert the patient. No form of therapy is successful in the absence of determination on the part of the patient to deal with enuresis. The patient should be bothered by the symptoms and see bedwetting as a problem that should be faced. This will encourage him to follow the instructions. In our study, the moisture alarm was not used because it awakens the patient from sleep after bedwetting. Moreover, there is a characteristic pattern of deep sleep from which the patients may tend to have difficulty in waking up on their own even after bedwetting.

Imipramine is a tricyclic antidepressant that was first used to treat enuresis in 1960¹⁸. It has demonstrated some efficacy in patients showing a poor response to the conservative management. However, the significant side effects of the drug have limited its use. Most of the patients complained of loss of concentration. Unfortunately, in most of the cases, the patients relapsed after drug withdrawal. This finding is consistent with previous studies, which have shown that treatment with imipramine results in a significant improvement of nocturnal enuresis; but stopping the medication causes relapse in a significant number of patients¹⁹.

Desmopressin was not used as a primary treatment modality in this study because it is an expensive drug and relapse occurs in 65-90% of cases after cessation of the drug^{20,21}. Desmopressin gives marginal or no better results than the spontaneous expected annual cure rate (15%)^{5,6}. Algallad, 1999, used desmopressin in patients with severe polyuria that was refractory to other forms of therapy and reported a cure rate of 50%²².

Urodynamic studies, particularly on children, are unpleasant due to the need for catheterization, which most children cannot accept. However, such studies confirmed an inadequate storage function in 45 out of 77 patients (58%). A relatively low incidence of detrusor instability during the filling CMG was seen in patients with monosymptomatic enuresis (36%) compared to those with polysymptomatic enuresis (93%). In a previous study, DI was noted in only 15% of the patients with monosymptomatic nocturnal enuresis compared to 97% with polysymptomatic enuresis²³. In accordance with other studies,

the current study shows that the cystometric capacity at normal sensation and the MCC are comparable to the age-expected capacity in monosymptomatic patients with a stable detrusor²⁴. Algallad, 1999, did urodynamic studies in patients with primary nocturnal enuresis that did not respond to pharmacotherapy. He detected a small bladder capacity in 37% of these patients and DI in 35%²². Khan and others found detrusor instability in 74% of 50 enuretic boys and girls by supine cystometry. The mean threshold volume at which detrusor instability was demonstrated was 200 ml. The mean bladder capacity of age-matched non-enuretic children was 325 ml. They considered detrusor instability at this reduced threshold volume to be the main cause of primary enuresis²⁵. Medel et al, detected detrusor instability in 49% of monosymptomatic and 79% of polysymptomatic enuresis²⁴. The use of ambulatory urodynamic studies provides continuous monitoring of the bladder function for a long duration that may yield more useful information in the detection of detrusor instability as a cause of lower urinary tract dysfunction²⁶. Treatment based on this information gives good results and may prevent years of unnecessary or inappropriate therapy, with subsequent psychological upset. The use of antimuscarinic drugs has proved helpful in the treatment of enuretic patients with detrusor instability. It also improves their daytime control by reducing the frequency of micturition, increases the voided volume and decreases nighttime wetting as well. Neveus, 2001, showed a good response of a single dose of oxybutynin at night in treating patients with monosymptomatic enuresis with a low spontaneous functional bladder capacity who did not respond to desmopressin. He considered detrusor overactivity a cause of their enuresis²⁷.

In summary, the present study reveals that the establishment of an Enuresis Clinic may be important for a proper diagnosis, management, and follow-up of enuretic patients. Reassurance and conservative treatment using a calendar can give good results in patients with primary nocturnal enuresis with a stable detrusor. Pharmacotherapy should only be used when this conditioning therapy fails. Patients with DI should be actively managed with antimuscarinic drugs. This indicates that although cystometry does not contribute to the diagnosis of enuresis, it helps to enlighten its physiopathology especially in polysymptomatic enuresis. When urodynamic studies are carried

out early in these cases, rather than as a last resort, the diagnosis, and thus the treatment regimen, can be established.

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RESUME

Enurésie Nocturne Primaire: Evaluation Clinique et Urodynamique et Analyse des Options Thérapeutiques

Objectif Evaluer les données cliniques et urodynamiques et les options thérapeutiques chez des patients présentant une énurésie nocturne primitive **Patients et Méthodes** Un total de 473 patients âgés de 5 à 35 ans ont été évalués cliniquement et ont bénéficié d'un examen cytobactériologique de urines et d'une radiographie de l'abdomen sans pré-paration. Une UIV a été réalisée lorsque nécessaire. Un bilan urodynamique a été fait chez les patients présentant une énurésie polysymptomatique et dans les cas d'échec d'un traitement antérieur chez l'adulte. Initialement, les patients ayant une énurésie mono-symptomatique et ceux qui étaient polysymptomatiques mais avec une fonction détrusorienne stable étaient pris en charge par traitement conditionné avec un calendrier mictionnel. Lorsque le bilan urodynamique avait détecté une instabilité vésicale, les patients recevaient un traitement initial à base d'anti-muscariniques. **Résultats** Une énurésie mono-symptomatique a été diagnostiquée chez 329 patients, tandis que les 144 patients restants avaient une forme poly-symptomatique. Une instabilité détrusorienne a été détectée dans 36% des formes mono-symptomatiques et dans 93% des patients polysymptomatiques. La capacité vésicale au premier besoin (B1), à B2 et à la capacité vésicale maximale montrait une augmentation statistiquement significative chez les patients à détrusor stable comparés à ceux qui avaient une instabilité vésicale. La pression détrusorienne était significativement plus élevée à B1 et à la capacité vésicale maximale chez les patients chez les patients avec une instabilité vésicale que chez avec une vessie stable. Le traitement conditionné a été satisfaisant chez 74% des patients et d'autant meilleur chez ceux avec une énurésie mono-symptomatique. Les anti-muscariniques ont traité 91% des formes aussi bien mono-symptomatiques que poly-symptomatiques associées à une instabilité vésicale. **Conclusion** Un traitement conditionné utilisant un calendrier mictionnel est une méthode efficace chez la plupart des patients présentant une énurésie primaire avec détrusor stable, évitant les coûts et les effets secondaires des médicaments. Le traitement pharmacologique doit être utilisé qu'en cas d'échec de cette méthode thérapeutique La cystomanométrie peut détecter une instabilité détrusorienne et peut aider dans le choix d'un traitement anti-muscarinique de première ligne.

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