

Enuresis: Recent Research and Options

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Enuresis is a multifactorial condition in which involuntary loss of urine occurs beyond the anticipated age of successful toilet training. This disorder has plagued humans for longer than its first description on the Ebers Papyrus in 1500 B.C. (6).

Treatment modalities have included various, mostly incredible, measures such as blistering of the buttocks, caustic agents injected into the genitalia, penile clamps, frogs tied to the genitalia and humiliation. Punishment is still employed by many parents (7,25).

Definition

Enuresis is defined as persistent bed-wetting more than twice a month after the age of 5 years (23). The term **primary nocturnal enuresis** describes patients who have never been dry, whereas **secondary enuresis** implies a previous dry period of more than 6 months. Bed-wetting occurs in 15 % of 5-year-old, 5 % of 10-year-old and 1 % of 15-year-old children. A spontaneous cure rate is expected in 15 % of the patients, so that by the age of 15 about 99 % are dry (9).

Diurnal enuresis is pertinent if there is daily leakage of urine beyond 5 years of age that occurs at least once a week, which makes it socially unacceptable. Leakage is large enough to cause social inconvenience (>1 ml) (8). Giggle or stress incontinence is also considered enuresis.

Bladder maturation

Emptying of the bladder in newborns is unconscious, uninhibited and frequent. The increasing filling of the bladder stimulates detrusor contractions and urination. At the age of 6 months an unconscious inhibition of micturition leads to greater

intervals between bladder emptying. Between 1 and 2 years of age the sensation of bladder filling and urge is developed. This is the first step towards voluntary control of bladder activity. In most children total voluntary control is achieved around the fourth year of life. Toilet training usually starts when bladder sensation is existent but voluntary control is incomplete. Urodynamically, this development can be detected by increasing contraction of the sphincter muscles. Simultaneously, a reduction of urine production during nighttime and concentration of urine under ADH influence is observed. The effect is a reduction from 20 micturitions in the newborn period to 1 or 2 at night in a 2-4 year-old child. Parallel to this somatic development, maturation of the individual personality and awareness of social structures occurs that may last through school age until puberty.

Disturbances of maturation

- If adequate sensation of bladder filling and the urge for micturition is delayed, deficient or absent, incontinence may result. In some cases this may last until adulthood and may persist as pollakisuria, imperative urge and enuresis.

- If bladder sensation exists but cortical control of the detrusor is deficient or absent, children try to avoid micturition with active contraction of the pelvic floor or by crossing their legs. This behavior may persist even after maturation of cortical control, leading to insufficient relaxation of the pelvic muscles.

Urodynamically, a functional obstruction combined with hyperactivity of the detrusor is observed. Clinically, changing amounts of residual urine and urinary tract infections (UTIs) may develop.

- Bladder control is adversely influenced by infections and malformations of the urinary system.

- Neurogenic defects (covered spina bifida) occasionally are responsible for absent bladder maturation.

- Polyuria as a manifestation of diabetes mellitus or insipidus or renal insufficiency consists of large amounts of urine even at night that may endanger bladder control.

- In some children a typical circadian rhythm of ADH production has not developed, and therefore the amount of nocturnal urine production is not reduced. This may cause polyuria early at night and may also be a factor for delayed maturation of bladder control.

- The development of the individual personality and social behavior is strongly dependent on parental influence. Prolonged enuresis in neglected children, especially of lower socio-economic classes, may be attributable to this factor.

Factors not responsible for enuresis

Several invasive urodynamic studies performed both at day- and nighttime in patients with monosymptomatic enuresis have been undertaken (15,16,17). The conclusions may be summarized:

1. The bladder capacity of enuretics lies within the normal range.
2. Enuresis takes place when the bladder has reached maximum capacity and not before.
3. Unstable bladder contractions are seen more frequently during sleep in enuretics, but are not causative in relation to the enuretic episode.
4. Enuretics have normally coordinated micturition in the awake state and during sleep.
5. Overnight bladder activity is rarely increased in enuretics.
6. Deep sleep is not responsible for altered bladder activity (3).
7. The sensory innervation in the lower urinary tract of children with bed-wetting is not disturbed (28).

The first question that arises is the appropriate time for evaluation of an enuretic child. The situation should always be considered important if enuresis is disturbing the patient or his social environment. This is usually relevant at the age of 5-7 years.

History

Besides a general pediatric history, a specific voiding history is taken. Was the patient ever dry?

Is he/she wetting during the day or nighttime?

Additional questions concentrate on

- Frequency of micturition during the day
- Pain or other disturbances during voiding
- Drinking behavior
- Constipation
- Earlier UTI
- Behavior of child and parents following a "wet night"
- Motivation towards changing the situation
- Psychosocial and intellectual status

Urological work-up

This should never be invasive during a first visit. It includes a urinalysis, bacterial cultures, ultrasonography of the kidneys, ureters and bladder, uroflowmetry and residual urine. Major malformations and disturbances of micturition can be detected.

Oetliker et al (18) insist on a "micturition protocol", which may give important additional information: During 1 week the amount of urine at each micturition, the drinking volume and the time are noted. The patient is awakened 3-5 times during 2 nights for voiding. For the second night no beverage is permitted from noon until the next morning (concentration test). The urine of both nights are analyzed.

This protocol gives information about drinking and voiding behavior, the bladder capacity and diurnal rhythm of the urine volume, as well as the ability of concentrating urine. Additional investigations (i.v. pyelography, voiding cystogram) should be undertaken in patients with a history of UTI. Some authors extend their investigations to children who are day and night wetters, those with daytime urgency and frequency and those with secondary enuresis (26). Vesicorenal reflux of grade I-IV has been found in one of six enuretic children by Sujka et al (26). They therefore recommend screening these children with a voiding cystourethrogram. Urodynamic studies are reserved for children with urge syndrome, staccato voiding, fractionated and incomplete voiding and lazy bladder syndrome (27) (Fig. 1).

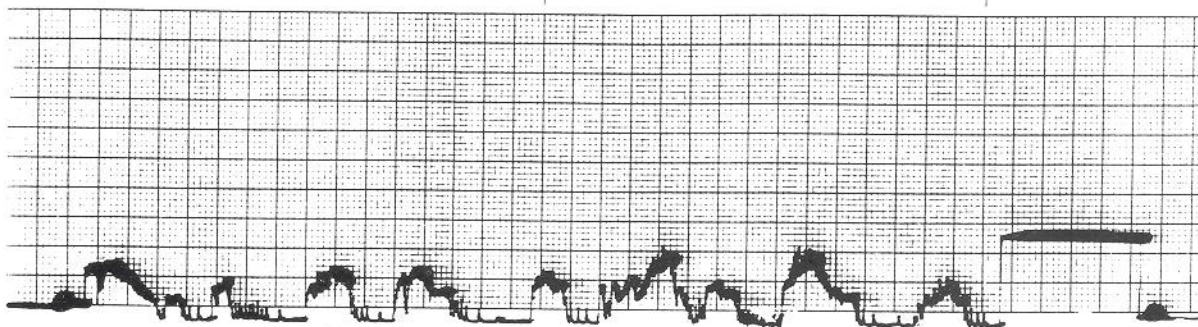


Figure 1. Staccato voiding in 12 year-old boy with nocturnal and diurnal enuresis (voiding time 55 sec, urine volume 100 ml).

Urge syndrome is characterized by uninhabitable detrusor contractions countered by pelvic floor contractions. The staccato voiding is caused by bursts of pelvic floor activity during voiding, resulting in peaks of bladder pressure. Flow time is prolonged and bladder emptying is often incomplete. In incomplete voiding, the detrusor muscle is hypoactive and urge is easily inhibited. Wetting occurs as a form of overflow incontinence. Lazy bladder syndrome is the result of long-standing fractionated and incomplete voiding. Micturition is postponed as long as possible, until the urge is so imperative that voiding irrevocably takes place, even in the pants.

Genetic component

The genetic component to enuresis is irrefutable. If both parents were enuretic, the incidence of enuresis occurring in the family is 77.3 %. If only one parent was enuretic the incidence is 44 %, and if neither parent was enuretic, the incidence is 15 %⁽⁴⁾. A genetic predisposition is usually not coupled with developmental or maturational factors⁽²³⁾.

Therapeutic measures (Table 1)

General approaches

Most parents primarily seek advice in order to be sure that there is no organic defect in their child and that they are not "missing something". Counseling parents also means that any type of punishment should be prevented. More than 25 % of enuretic children are punished for bed wetting⁽⁷⁾. In addition, it is important to avoid any feelings of guilt.

Drinking and voiding behavior can easily be changed, especially if children are in the habit of

drinking large amounts of fluid during the second half of the day. Voiding should not be suppressed if the sensation of bladder fullness occurs.

UTIs may influence the dynamics of micturition. The infection and its underlying malformations must be treated prior to any attempt to treat enuresis (i.e., antireflux procedures, correction of bladder diverticula or bladder outlet obstruction).

Alterations of kidney function (renal insufficiency) or metabolic disorders (diabetes insipidus or mellitus) demand specific treatment. The same applies for constipation, oxyuriasis or neurogenic disorders of the pelvic floor muscles (spina bifida).

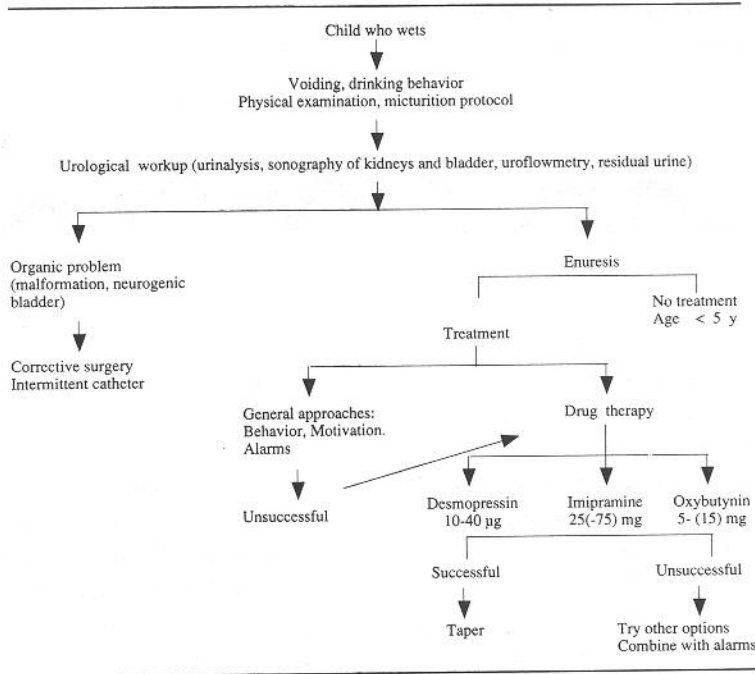
As far as true enuresis is concerned, various approaches have been tried with no/minimal success:

- Avoidance of fluid in the evening hours has not led to cure in most instances.
- Scheduled awakening only rarely improves bed wetting. Many children are found already wet when awakened during the night.
- Psychotherapy: This treatment has been offered in the past because wetting has been viewed as a symptom of psychopathology. There is little evidence that enuresis stems from psychologic issues and psychoanalytic causes. It is therefore not surprising that the results of psychodynamic treatment are no different from those of no-treatment control groups⁽¹⁰⁾. As a rule, enuresis is not a psychiatric disorder, but rather an expression of a learning deficit.

Conditioning alarms

Such alarms require the child to sleep on a mattress pad or a sensor placed in the underwear. When the sensor is moistened by urine, an electrical circuit

Table 1. Algorithm for enuretics



is closed and a bell rings. According to conditioning theories, it is expected that the child will wake up and inhibit urination.

This concept suffers because many children may not really wake up from their deep sleep. It is ultimately the parents' responsibility to transport the child to the toilet.

This means in many instances the entire family is awake except for the enuretic child. Nevertheless, we have used the alarm in over 100 patients with an immediate success rate of 55 % and a permanent success rate of 35 % within 3 months of treatment. In combination with imipramine, about 50 % achieved complete success.

3. Drug therapy (Table 2)

3.1. Tricyclic antidepressants

Of this pharmacological group, particularly imipramine has been used extensively since 1960 (11). Although its exact action is not clear, four mechanisms have been claimed:

- antidepressant effect
- anticholinergic and antispasmodic effect
- alterations in sleep
- adrenergic neurotransmitter reuptake blockade (5).

The antienuretic effect precedes the antidepressant effect by 10 days (21) and sleep studies have failed to prove an association between sleep and enuresis (15,16,17), but bladder capacity increases by up to 35 % (23). Therefore, the antienuretic effect is likely due to an adrenergic effect. There is some evidence that imipramine increases the antidiuretic hormone ADH (vasopressin) (20).

Imipramine is not given to children under the age of 5 years. As a starting dose, we recommend 25 mg (0.9-1.5 mg/kg) 1-2 hours before sleep. The dosage may be increased in older children to 50-70 mg/day. The drug is given for 2 months, and after tapering off it may be repeated after 1 month for another period of 2 months.

Independent of plasma concentrations, the long-term success is 25 % (12). Imipramine is potentially toxic. In the UK it is the most common cause of poisoning in children aged under 5 years. It may cause behavioral changes (irritability, lethargy, ano-

Table 2. Drug therapy of nocturnal enuresis

Drug	Recommended dosage	Duration
Tricyclic antidepressants:	Age 5-8: 25 mg/day 2 hours before sleep	2 months, then taper Second course possible after 1-2 months
Imipramine	Age 9-15: 50-75 mg/day	
Anticholinergic agents:	Age 5-8: 5 mg twice daily	
Oxybutynin	Age 9-15: 5 mg three times daily	2 months, then taper
ADH analogues:	Starting with 1 µg, then 20-40 µg intranasally	Adjust dosage weekly
Desmopressin		

rexia), cardiovascular disturbances and hepatic failure (2,23,24). Furthermore, the drug should not be abruptly stopped, but continuously tapered.

3.2. Anticholinergic agents

These drugs (oxybutynin, propantheline) act by reducing uninhibited bladder contractions. They are beneficial for patients with diurnal enuresis, urinary frequency and urgency. They may enlarge bladder capacity and reduce bladder spasms. Maizels et al (12) found oxybutynin a helpful adjunct to the treatment of nocturnal enuresis with reduced functional bladder capacity when used in conjunction with an alarm. Persson et al (19) have found the drug to be very effective in cases with inadequate bladder storage and uninhibited contractions in combination with enuresis. Its effect was doubtful in cases with normal urodynamic findings. Children with reduced bladder capacity receive 2.5 mg in the morning and 2.5-5 mg before sleep. Side effects are rare; they include headache, blurred vision, constipation or altered behavior.

3.3. Desmopressin

Desmopressin acetate, a synthetic analogue of the posterior pituitary hormone arginine vasopressin, acts as an antidiuretic agent in the kidney. The rationale for desmopressin treatment is based on the observation that many enuretics show nocturnal polyuria. According to Ritig et al (22), the nightly urine production may exceed functional bladder capacity by as much as four times.

Normally, nocturnal urine production is less than half the daytime rate (12). Nørgaard (15,16,17) and Ritig (22) observed that enuretics do not have circadian vasopressin release leading to a reduction in urine volume at night, with a simultaneous increase in urine osmolarity.

To date, over 30 reports on the effect of desmopressin have been published. Every study has established that this agent is efficacious during the time of administration, but only a small number of children become permanently dry, and most will relapse when treatment is stopped.

Desmopressin is administered by nasal spray, usually at a dosage of 40 µg. Children who show increased osmolarity predictably respond well, whereas patients with reduced bladder capacity or those younger than 9 years are unfavorable responders. Except for some cases with headache and nasal irritation, no side effects have been reported so far.

Despite the magnitude of information on desmopressin in bed-wetting, we still do not know whether the circadian patterns of urine volume, urine osmolarity and vasopressin concentration are normalized. It is also not known why children with a smaller urine volume at night should become continent. At present, desmopressin is especially useful if conditioning has failed or if nighttime polyuria exists.

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