Monosymptomatic Enuresis

17

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17.1 Definitions

Enuresis is defined as an intermittent urinary incontinence that occurs exclusively during sleeping periods after the age of 5 years, when the volitional control of micturition is expected [1]. The condition can be both a social and psychological distress for the child, and it requires effort and attention from the parents [2]. Its high prevalence and psychosocial effects validate the importance of the subject.

Monosymptomatic enuresis (MNE) is a subgroup of enuresis. MNE occurs without any other lower urinary tract (LUT) symptoms (nocturia excluded) and bladder dysfunction. Children with MNE can comfortably control the urine when awake. Children with enuresis and any LUT symptoms are said to suffer from *non-monosymptomatic enuresis* [1]. This classification is of utmost importance to guide the need for further investigation and best treatment option.

In accordance to its onset, enuresis can be also classified as primary or secondary enuresis. The term secondary enuresis should be reserved for those children who have had a previous dry period, which exceeds 6 months. If this is not the case, the term primary enuresis should be used. Primary enuresis occurs in 75–90% of children with enuresis, whereas secondary enuresis occurs in 10–25% and is associated with behavioral comorbidities that necessitate investigation [1].

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17.2   Epidemiology

Studies in different countries show a prevalence of enuresis of around 10% among children and adolescents and of 10–15% at the age of 7 years [3, 4]. It has an annual spontaneous resolution rate of approximately 10–15%, but not all cases resolve spontaneously. Nocturnal enuresis persists in up to 3% of adolescents and 1% of untreated adults [5, 6]. It is more common in boys than in girls. Family history is often positive in these children. If one parent is enuretic, the risk that the child develops the condition is of 44%; if both parents are enuretic, the risk rises to 77% [7]. This inheritance is important in the different types of enuresis, and there is no good correlation between phenotype (MNE or NMNE) and genotype [8].

Currently, there are changing views regarding how many children with enuresis are truly monosymptomatic. The first epidemiological studies on enuresis often fail to identify the presence of LUTS and to differentiate between monosymptomatic and non-monosymptomatic nocturnal enuresis, showing an overestimated MNE prevalence [9]. In the last decade, the greater awareness about the importance of bladder function alongside ICCC's LUTS standardization [10] has highlighted this issue, resulting in an increase in the identification of children with LUTS and NMNE. Daytime incontinence was found to be associated with nocturnal enuresis [11–15], and MNE was found to represent less than half of all children with nocturnal enuresis [14, 16–18]. Many of these children were previously considered to have MNE due to a superficial evaluation [9, 11]. A detailed evaluation is very important for a good treatment result and will be further explored in the clinical evaluation section of this chapter.

17.3   Pathology

Monosymptomatic enuresis is a multifactorial condition. Three major pathogenic mechanisms are well accepted as crucial, with a varying degree of influence in each child: nocturnal polyuria, detrusor overactivity, and an increased arousal threshold or sleep disorder.

Nocturnal polyuria is related to a lack of the normal nocturnal increase in vasopressin secretion and, as a result, an exaggerated urine production [19]. Other renal circadian rhythms, such as solute handling and glomerular filtration rate, might also be disturbed [20, 21]. Although nocturnal polyuria is common in children with MNE, not all of them have polyuria [22], and not all patients with polyuria have vasopressin deficiency [23].

Bladder overactivity is clinically evident in children with NMNE, but it also has a subclinical role in an MNE subgroup with detrusor contractions and decrease in bladder capacity. This means that the bladder tends to contract before it is full, or to become full before morning, or even both. Bladder dysfunction is related to inappropriate central nervous system control of the detrusor muscle [24, 25].

Neither polyuria mechanism nor nocturnal detrusor overactivity explains why children do not awake when the bladder is full. An **increased arousal threshold** is considered to be the reason for enuretic children difficulties to wake up despite the signals from the bladder. This disorder in the arousal mechanisms could be

secondary to a disturbance in the area around locus coeruleus [26]. Yeung et al. demonstrated, by polysomnography and continuous cystometry, an interaction between bladder overactivity and cortical arousability, which was defined as a "bladder–brain dialogue." The authors suggested that the transition from light sleep to awakening was suppressed by long-term overstimulation caused by signals from the bladder to the brain [27]. In addition, sleep fragmentation caused by increased cortical arousals was demonstrated in children with refractory nocturnal enuresis, using video polysomnography [28]. It is clear from the literature that fragmented sleep is less restorative than consolidated sleep and leads to sleepiness-related daytime impairment [29]. Sleep fragmentation can lead to sleep deprivation in children with nocturnal enuresis, influencing the endocrine, metabolic, immune, inflammatory, and cardiovascular regulation. A substantial increase in diuresis, a higher heart rate, and higher blood pressure with suppressed plasma levels of all sodium-retaining hormones have been demonstrated [30].

Enuresis may also be caused by obstructive sleep apneas due to adenotonsillar hypertrophy. It is considered to be a symptom of sleep-disordered breathing. There are two, nonexclusive, possible explanations for this: first, the constant arousal stimuli from the obstructed airways cause paradoxically high arousal thresholds, and, second, the negative intrathoracic pressure causes polyuria via increased secretion of the atrial natriuretic peptide [26, 31].

Comorbid conditions also have a central role in the pathogenesis and treatment of enuresis. Among these conditions, constipation and neuropsychiatric disorders, such as attention-deficit hyperactivity disorder, are common comorbidities.

Epidemiological studies show that 20–30% of all children with enuresis present clinically relevant behavioral problems at rates, which are two to four times higher than in children with no enuresis. Psychological disorders are more frequent in children with secondary enuresis (up to 75%) and non-monosymptomatic subgroups. The children with monosymptomatic nocturnal enuresis are the subgroup with the lowest comorbidity rates. Attention-deficit hyperactivity disorder (ADHD) is the most specific comorbid disorder with enuresis, with a comorbidity rate of 28.3%. ODD and conduct disorders as well as emotional disorders, such as depressive and anxiety disorders, can also coexist with enuresis. These comorbidities have a negative effect on compliance and outcome if not addressed and left untreated [32].

Constipation associated with nocturnal enuresis, especially non-monosymptomatic constipation, is quite frequent. The gastrointestinal and genitourinary tracts have the same embryological origin, the same innervation (sacropelvic plexus), and the same anatomical location. Different studies have shown the improvement and resolution of enuresis with the proper treatment of constipation [33, 34].

17.4 Psychosocial Impact of Enuresis

Enuresis and delayed bladder control are common sources of psychosocial problems for both parents and children. Nocturnal enuresis is associated with poor school performance and can cause loss of self-esteem, social isolation, stress, and family violence during childhood and adolescence. In addition to work overload with pajamas, bedlinen, and mattresses because of nocturnal urinary loss, there is

also a significant monetary cost associated with diapers, a new mattress, and a new sofa, to name but a few.

The results of researches carried out in different countries have shown violence against enuretic children. The conviction that a child wets the bed on purpose increases the risk of punishment [2, 35]. The reported rates of punishment vary in the different cultures. Fonseca et al., in a population-based study with 296 children and adolescents, found out that 53.3% of enuretics felt excluded or had been ridiculed because of bedwetting and that 46.7% had been punished. It is noteworthy that 42.9% of those punished for bedwetting were children of parents who also often wet their beds when children. Although most enuretics felt excluded, were ridiculed, and had already been physically punished for bedwetting, only one received treatment for bedwetting [14]. Can et al. studied the physical abuse of children with enuresis and found that 42.1% of enuretic children were spanked, 12.8% were beaten, and 40.6% of children were medically neglected [36]. Karaman et al. found at least one punishment method was applied to 291 (58.1%) of children with NE. Punishment methods of parents were detected as child's condemnation (257 patients, 51.3%), child's craving deprivation (120 patients, 23.9%), child's humiliation in the presence of other children (113 patients, 22.6%), and child's reprimand threat of punishment (203 patients, 40.5%) [35]. Alpaslan AH et al. reported a case of death as a result of physical violence during toilet training [37].

The reasons for the non-treatment were fourfold: (1) enuresis was not considered a problem to take the child to the doctor; (2) those responsible did not know there were treatments for bedwetting; (3) the child itself was found guilty of bedwetting; and (4) socioeconomic difficulties [14]. These data highlight the psychosocial impact of enuresis, lack of knowledge on the subject, and scarce access to treatment.

17.5 Clinical Assessment

Enuresis is a symptom and may be a condition of intermittent incontinence that occurs exclusively during sleeping periods. As a symptom, it should always be assessed. The complaint of "wetting the bed" should always be valued and initially investigated by history and physical examination. This initial evaluation has to identify both the enuretic child due to underlying medical conditions and the child with relevant comorbid conditions, as well as to indicate whether further investigations are needed (Table 17.1) and what the best treatment option is.

A good history taking is the mainstay of the enuretic child evaluation. This should include a detailed bladder- and bowel-oriented history and also questions about psychological or neuropsychiatric comorbidities, upper airway obstruction, and systemic diseases. The following topics should be included:

1. **Bedwetting features**: Is it a primary or secondary enuresis? How often does it occur? How many nights in a week or month? How many incontinence episodes per night? Does the child also have nocturia? Is there any difficulty to wake up?

Table 17.1 Warning findings that indicate the need of additional investigation before enuresis treatment

During history taking:
– Daytime urinary incontinence
– Continuous urinary incontinence
– Straining, weak stream, or drip
– Urgency, holding maneuvers
– Urinary tract infection
– Constipation and/or fecal incontinence
– Low concentrated urine, polyuria
– Excessive thirst, need to drink during the night
– Nausea, weight loss, fatigue
– History of gestational diabetes and neonatal asphyxia
During physical examination:
– Neurocutaneous stigmata in the back (lumbosacral region)
– Intergluteous groove: short or asymmetric
– Abnormality in the neurological examination
– Orthopedic changes of lower limbs and/or spine
– Abdominal mass palpation
– Growth deficit
Initial investigation:
– Glucosuria
– Proteinuria
– Leukocyturia or nitrite test positive
– Hematuria
– Bladder wall thickness, post void residual urine, hydronephrosis, and kidney cysts found on kidney and urinary tract ultrasound

More than one enuretic episode per night indicates detrusor overactivity. Frequent bedwetting indicates detrusor overactivity and a poor prognostic [6, 11]. Nocturia indicates that the child is not extremely difficult to arouse from sleep. Comorbid conditions are more common in children who were previously dry than in those with primary MNE. In addition, it is relevant to ask about previous treatment. Has the child been treated for bedwetting? What is the treatment being used? Has it been done correctly? What are the results?

2. **Lower urinary tract symptoms (LUTS):** Relevant LUTS are: voiding frequency smaller than or equal to three or greater than or equal to 8×/day, current or previous daytime incontinence, urgency, hesitancy, straining, intermittency (interrupted micturition), holding maneuvers, weak stream, feeling of incomplete emptying, post-micturition dribble and genital or LUT pain. The child with monosymptomatic nocturnal enuresis—the focus of this chapter—does not show other lower urinary tract symptom and his or her physical examination is normal. Concomitant daytime bladder symptoms mean that the child has NMNE. Urgency, usually accompanied by frequency and nocturia, with or without urinary incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology is indicative of overactive bladder (OAB). It is important to distinguish children

who void with a weak or interrupted stream and must use abdominal pressure to pass urine. The latter must be sent to a specialized center without delay because these signals are suggestive of anatomical bladder outlet obstruction. The history of recurrent urinary tract infection (UTI) and vesicoureteral reflux should also alert to the possibility of lower urinary tract dysfunction. UTI and recurrent bacteriuria often have residual urine. If the child presents continuous incontinence, i.e., drip loss between the normal voiding 24 h/day, it is mostly always caused by ectopic ureter.

The systematic search for lower urinary tract symptoms during anamnesis should always be emphasized. Parents often do not spontaneously report, due to their ignorance, or consider them to be normal. Other times, parents consider the urgency and incontinence as a result of the child's laziness, which would rather play until the last minute instead of going to the bathroom as soon as he or she feels the urge to.

3. **Constipation and fecal incontinence** should always be investigated. Constipation often leads to detrusor overactivity and/or residual urine. Constipation is often overlooked, and if it is not treated, it may be difficult to get the child dry. Constipation manifests by difficulty in defecation, stool frequency of less than three times per week, pain and abdomen bloating, painful defecation, fecal soiling, hard consistency of stool, and history of large diameter stools which may obstruct the toilet. ROME IV criteria are widely accepted in the diagnosis of constipation (Table 17.2) [38], and the use of Bristol stool scale facilitates the identification of the appearance of the stool [39]. Aspects 1 and 2 are characteristic of intestinal constipation.
4. **Behavioral and psychosocial problems** should be investigated: Problems at home or school. What is the impact of bedwetting? If the child shows significant difficulty to socialize, it is necessary to consider the possibility of psychiatric illness.
5. **Upper airway obstruction:** Children with heavy snoring or nocturnal apneas should be seen by an otorhinolaryngologist for a possible surgical correction.
6. **Diabetes mellitus or diabetes insipidus** should be suspected in case of a history of weight loss, thirst, polyuria, and secondary enuresis. Short stature, fatigue, polyuria, and dehydration suggest **underlying kidney disease**. Although these diagnoses correspond to a small percentage of cases of enuresis, they are important in order to discard them.

Table 17.2 Roma IV diagnose criteria of functional constipation

Diagnostic criteria must include 1 month of at least two of the following in children of a developmental age of at least 4 years:
1. Two or fewer defecations in the toilet per week
2. At least one episode of fecal incontinence per week
3. History of retentive posturing or excessive volitional stool retention
4. History of painful or hard bowel movements
5. Presence of a large fecal mass in the rectum
6. History of large diameter stools which may obstruct the toilet
After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

7. In the **history of pregnancy, labor, and birth**, risk factors should be investigated for perinatal anoxia, including prematurity, cyanosis, respiratory distress, congenital infections, and sepsis. These conditions are associated with lower urinary tract dysfunction, often without any other apparent neurological signs. History of gestational diabetes relates to sacral agenesis and neurogenic bladder. History of delayed psychomotor development may indicate a dysfunction of the central nervous system (CNS) which also affects the urinary tract. This is often not perceived or valued.

8. **Family history** of enuresis, incontinence, or kidney disease should be investigated.

Physical examination should focus on weight, height, blood pressure, abdominal mass palpation, genitalia, neurological examination, orthopedic changes of lower limbs and/or spine, and inspection of the lumbosacral region for cutaneous stigmas—hair tufts, cutaneous appendices, hemangiomas, hypo- or hyperchromic spots, dimples, lipoma, and intergluteous groove, short, or asymmetric. These signals in the lumbosacral region suggest a possible occult dysraphism and neurogenic bladder secondary to this. This is because of common embryonic origin of the skin and CNS.

After history taking and physical examination have excluded any of the aforementioned changes, the child can be classified as having monosymptomatic nocturnal enuresis and treated at primary level. This will be addressed below.

17.6   Additional Examination

17.6.1 Bladder Diary

Notes of frequency and of urine output are recommended in nocturnal enuresis to exclude the possibility of reduced bladder capacity. The highest urinated volume (excluding first morning urine) should be compared to the estimated bladder capacity (EBC) for the age. The latter shall be calculated by the following formula: BC = 30 × age + 30 or BC = (age + 1) × 30. The bladder capacity is considered low when it is smaller than or equal to 65% of the estimated value, and is considered increased when greater than or equal to 130% of the estimated value [1, 10]. Frequent, small voiding and urgency indicate reduced bladder capacity and detrusor overactivity. Infrequent voiding and holding maneuvers indicate voiding postponement.

In non-monosymptomatic nocturnal enuresis and enuresis resistant to first-line treatment, the record of urine volume is essential. The diary should also include a note of fluid intake and the presence of other urinary symptoms, such as urgency, incontinence, and hesitation. This intake note can contribute to the diagnosis of polydipsia. The full bladder diary consists of a seven-night recording of incontinence episodes and nighttime urine measurements to evaluate volume enuresis and 48 h daytime frequency and chart volume (which do not need to be recorded on two consecutive days) to evaluate for LUT dysfunction [1].

Nocturnal urine output excludes the last voiding before sleep but includes the first voiding in the morning. In enuretic children, urine voided during sleep should be collected in diapers and the change of diaper weight be measured. **Nocturnal polyuria** is a term relevant mainly in children suffering from enuresis and is defined as a nocturnal urine output exceeding 130% of estimated bladder capacity for the child's age [1].

The ability of the child and family to fill the bladder diary gives a good indication of their future compliance to the treatment.

17.6.2 Bowel Diary

A 7-day bowel diary is advisable to help to diagnose constipation and should include the Bristol stool form scale.

17.6.3 Urine Dipstick Test

Urine dipstick test is used to search the presence of glucose, leukocytes, protein, erythrocytes and bacteria in urine. Diabetes should be considered in the presence of glycosuria, and kidney disease, in the presence of proteinuria.

17.6.4 Ultrasound

Ultrasound measurement of bladder wall thickness, post void residual urine, and rectal diameter can be useful to indicate voiding dysfunction and occult constipation [40, 41]. Hydronephrosis and kidney cysts can eventually be found, although usually no abnormalities are seen in patients with MNE.

17.6.5 Blood Tests, X-Rays, and Invasive Urodynamics

There is no indication of blood tests, X-rays, and invasive urodynamic in patients with monosymptomatic nocturnal enuresis. In case the previously mentioned evaluations are changed, evaluation should be individualized. Uroflowmetry and measurement of residual urine can be helpful when voiding dysfunction or bladder outlet obstruction is suspected.

17.7 Treatment

Enuresis tends to disappear spontaneously as the child grows, with 15% of resolution rate by year, but a significant proportion of patients continue to wet the beds into adolescence or adulthood. Many adults with LUTS were enuretic children.

17.7.1 General Measures

The treatment of nocturnal enuresis always needs to start with a clear explanation of the condition and its mechanisms to the parents and patients. It is imperative to clarify the fact that enuresis is involuntary and that the child does not lose urine intentionally. Thus, neither patient nor his or her parents are to blame. Knowing that enuresis has a high frequency as well as the enuresis history of the parents and/or family helps to reassure the child, to lessen his or her embarrassment and to strengthen self-esteem.

It is necessary to provide guidance on the importance of the regular trip to the bathroom. The child should void regularly every second or third hour, and its postponement should be avoided. Yet, fluid intake needs to be sufficient during the day and reduced at night. At least half of the day's fluid intake needs to be before the afternoon. The diet should be low in caffeine and rich in fiber, and the excess of sodium should be avoided. If there is constipation, this needs to be treated with diet, regular trip to the bathroom (preferably after meals), developing the habit of going straight to the bathroom upon the first sensation of rectal filling (not postponing), and osmotic laxatives and enemas, if necessary.

17.7.2 Active Treatment

The active treatment for nocturnal enuresis shall be offered to children over the age of 6 who feel disturbed by the condition and are willing to undergo treatment. The International Children's Continence Society (ICCS) recommends using the alarm as the first nondrug option and desmopressin as the first drug option for medical treatment for monosymptomatic enuresis [42]. The cases of reduced bladder capacity can better respond to treatment with alarm. The cases of nocturnal polyuria can better respond to desmopressin. The therapeutic options should be presented to the child and family with their pros and cons so that they can decide upon the best treatment for them.

17.7.3 Alarm

The use of the alarm in the treatment of enuresis has an evidence level IA and results in continence in up to 70% of cases. It is believed to act by the arousal response and/or the increase in bladder capacity. Its use is safe and with great healing potential but requires time, commitment, and motivation of both child and family. The alarm consists of a moisture sensor to be placed in the underwear connected to an audible or vibrating alarm. Moisture detection causes the alarm to go off. Parents need to participate actively, helping to wake up the child in the first 2 weeks. The child ought to maintain the continued use of the alarm and go to the bathroom whenever the alarm goes off. In the case of enuresis, the child ought to complete urination in the toilet, changing his pajamas and resetting the alarm. The child's difficulty to

wake up to the alarm in the first 2 weeks of use shall be anticipated at the time the treatment is indicated so that parents do not give up on the treatment by thinking it has not worked. The result is not immediate, and the use shall be discontinued after 2–3 months without response. Difficulties relate to the discomfort often caused to brothers and family. Some children can turn off the alarm after some time, so it is important for parents to make sure that the child wakes up whenever the alarm goes off.

17.7.4 Desmopressin

Desmopressin is an analogue of the antidiuretic hormone (ADH). Desmopressin works by mimicking the action of ADH, which causes the urine to become concentrated in a smaller volume overnight, which allows the majority of children to sleep through the night without needing to pass urine. It is a therapy with level of evidence IA. Around 30% of patients show a complete response whereas 40% of patients a partial one. The curative potential is low. The best result is obtained in children with nocturnal polyuria and normal bladder capacity. Reduced bladder capacity indicates poor response.

Desmopressin is an easy-to-use medication with a quick effect and can be used in children older than 5 years. It is given either as oral tablets or in MELT (MELT oral lyophilisate) presentation. But MELT is not yet available in all countries. The nasal spray is not recommended for bedwetting owing to an increased incidence of serious side effects. Younger children often prefer MELT since it avoids the swallowing of tablets. Desmopressin in either form should be taken before bedtime.

Given its antidiuretic effect, the use cannot be associated with an excessive fluid intake because of the risk of water intoxication and hyponatremia. Children should restrict their fluid intake from 1 h before taking the medicine to 8 h afterward so as to avoid this serious side effect. If the family needs a general recommendation about fluid intake, a good rule is an evening intake of 200 mL (6 oz) or less and then no intake until the next morning [42]. Desmopressin should be avoided in children who have fluid control problems, such as in heart failure, and if the child is likely to find difficulty in complying with fluid restriction requirements.

Desmopressin tablets should be taken at least 1 h before going to sleep, since the maximum renal concentrating effect and minimal diuresis are attained after 1–2 h. Oral MELT tablets should be taken 30–60 min before bedtime. The ordinary dose of the tablets and MELT formulation is 0.2–0.4 mg and 120–240 mcg, respectively. This dose is not influenced by body weight or age. The beginning of the desmopressin effect is perceived immediately. If after 2 weeks there is no effect, treatment shall be discontinued. In children with a good response to treatment, this can be maintained with daily administration or be used in special situations, such as trips and nights away from home, according to the family's choice. In the first option, medication-free intervals are required every 3 months in order to verify if medication is still needed. If during this period the child presented enuresis, treatment may be restarted for another 3 months [43].

17.7.5 Enuresis Resistant to First-Line Treatment

The child who does not respond to treatment with desmopressin and/or alarm should be evaluated by a specialist. History needs to be remade, and it is necessary to check whether previous treatment was done correctly. Constipation and severe respiratory obstruction shall be excluded. The evaluation of these patients shall include voiding diary, measurement of nighttime urine production, ultrasound of the urinary tract, and uroflowmetry [42, 44].

The first-line treatment of resistant enuresis includes the possibility of alarm association with desmopressin, constipation treatment, and correction of airway obstruction. The second-line treatment includes the use of anticholinergics, with or without desmopressin. The anticholinergics should not be used with the child who presents UTI and residual urine >20 mL once or >10 mL in more than one examination. Constipation should also be ruled out before the anticholinergic treatment is started. The third-line treatment includes the use of imipramine, with or without desmopressin. There is a risk of overdosage and cardiotoxicity when imipramine is used. Imipramine should only be considered if the child has no history of syncope or palpitations, and there are no cases of sudden cardiac death or unstable arrhythmias in the family. If there is any doubt, an ECG should be performed to exclude long QT syndrome. There are reports of cardiotoxicity and death by accidental ingestion of younger siblings. The family should be informed to keep the pills securely locked [42, 44].

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