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Etiology and evaluation of nocturnal enuresis in children

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INTRODUCTION — Urinary incontinence is a common problem in children. At five years of age, 15 percent of children are incompletely continent of urine. Most of these children have isolated nocturnal enuresis (monosymptomatic nocturnal enuresis).

An overview of the causes and evaluation of nocturnal enuresis in children will be presented here. The management of nocturnal enuresis and dysfunctional voiding are discussed separately. (See "Management of nocturnal enuresis in children" and "Etiology and clinical features of voiding dysfunction in children" and "Evaluation and diagnosis of voiding dysfunction in children" and "Management of voiding dysfunction in children".)

TERMINOLOGY — The International Children's Continence Society (ICCS) has developed standardized terminology for lower urinary tract function and malfunction in children [1].

Enuresis (synonymous with intermittent nocturnal incontinence) refers to discrete episodes of urinary incontinence during sleep in children ≥5 years of age [1]. Enuresis is divided into monosymptomatic and non-monosymptomatic forms.

Monosymptomatic enuresis is defined as enuresis in children without any other lower urinary tract symptoms and without a history of bladder dysfunction [1]. Monosymptomatic nocturnal enuresis usually is divided into primary and secondary forms. Children who have never achieved a satisfactory period of nighttime dryness have **primary enuresis**. An estimated 80 percent of children with nocturnal

enuresis have this form. Children who develop enuresis after a dry period of at least six months have **secondary enuresis** [2]. Secondary enuresis often is ascribed to an unusually stressful event (eg, parental divorce, birth of a sibling) at a time of vulnerability in a child's life. However, the exact cause of secondary enuresis remains unknown.

Non-monosymptomatic enuresis is defined as enuresis in children with other lower urinary tract symptoms, including [1]:

- Consistently increased (≥8 times/day) or decreased (≤3 times/day) voiding frequency
- Daytime incontinence
- Urgency
- Hesitancy (difficulty initiating voiding)
- Straining (application of abdominal pressure to initiate and maintain voiding)
- A weak stream
- Intermittency (micturition occurs in several discrete spurts)
- Holding maneuvers (strategies used to postpone voiding)
- A feeling of incomplete emptying
- Postmicturation dribble
- Genital or lower urinary tract pain

The pathogenesis, evaluation, and treatment of monosymptomatic nocturnal enuresis and non-monosymptomatic nocturnal enuresis overlap [3]. Approximately 20 percent of children who have nighttime wetting also have significant daytime symptoms [4]. Patients who have nocturnal enuresis with daytime symptoms are described as having **dysfunctional voiding** (also called complex or complicated enuresis). The daytime symptoms may be limited to urgency and frequency, but often include incontinence. Urologic (eg, detrusor instability, recurrent urinary tract infection) and neurologic disorders (eg, spinal dysraphism) are more common among children with daytime symptoms than those with monosymptomatic enuresis [5]. Approximately 15 percent of children with nighttime wetting also have troublesome encopresis [5]. Children who have associated urinary and bowel symptoms often are described as having **dysfunctional elimination syndrome** [6] **or bladder bowel dysfunction** (BBD).

This topic review will focus on the causes and evaluation of monosymptomatic enuresis in children. Dysfunctional voiding is discussed separately. (See "Etiology and clinical features of voiding dysfunction in children" and "Evaluation and diagnosis of voiding dysfunction in children" and "Management of voiding dysfunction in children".)

EPIDEMIOLOGY AND NATURAL HISTORY — Monosymptomatic nocturnal enuresis is common in children. The prevalence varies according to age (graph 1) [7-9]:

- 5 years: 16 percent
- 6 years: 13 percent
- 7 years: 10 percent
- 8 years: 7 percent
- 10 years: 5 percent
- 12 to 14 years: 2 to 3 percent
- ≥15 years: 1 to 2 percent

Monosymptomatic nocturnal enuresis is twice as common among boys as girls. It resolves spontaneously at a rate of approximately 15 percent per year [10,11]. The longer the enuresis persists, the lower the probability that it will spontaneously resolve [8,10].

BLADDER MATURATION — Normal bladder function depends upon a complex interrelationship between autonomic and somatic nerves, which are integrated at various sites in the spinal cord, brainstem, midbrain, and higher cortical centers (figure 1). The complex coordination permits urine storage at low pressure with high outlet resistance and voiding with low outlet resistance and sustained detrusor (bladder wall muscle) contraction.

At birth, bladder function is thought to be coordinated through the lower spinal cord and/or primitive brain centers. Voiding at this stage is efficient but uncontrolled: uninhibited contraction is caused by progressive and sustained bladder filling. Voiding in the newborn also may be initiated by neurologically stimulating activities, such as feeding, bathing, tickling, etc.

During the first three years of life, bladder capacity increases disproportionately relative to body surface area. By four years of age, most children void five to six times per day [12,13].

Development of bladder control appears to follow a progressive maturation whereby the child first becomes aware of bladder filling, then develops the ability to suppress detrusor contractions voluntarily and, finally, learns to coordinate sphincter and detrusor function. These skills usually are achieved, at least during the day, by approximately four years of age. Nighttime bladder control is achieved months to years after daytime control, but is not expected until five to seven years of age [14,15].

Incomplete development of bladder control results in more complex wetting problems that almost always are associated with daytime incontinence. These

include dysfunctional voiding, overactive bladder, underactive bladder, recurrent urinary tract infections, and some cases of vesicoureteral reflux. (See "Etiology and clinical features of voiding dysfunction in children", section on 'Daytime urinary incontinence' and "Etiology and clinical features of voiding dysfunction in children", section on 'Associated conditions'.)

CAUSES — Monosymptomatic nocturnal enuresis may result from one or a combination of several possible factors in a given child [16-18]. The major pathogenetic mechanisms include nocturnal polyuria, detrusor overactivity, and disturbed sleep [3]. Other factors that are believed to contribute include maturational delay, genetics, and abnormal secretion of antidiuretic hormone (ADH, vasopressin). Psychologic and behavioral abnormalities appear to be a result, rather than a cause, of enuresis [19-21]. (See 'Associated conditions' below.)

Maturational delay — In almost all cases, monosymptomatic nocturnal enuresis resolves spontaneously (graph 1). This observation suggests that delayed maturation of a normal developmental process plays a role in nocturnal enuresis [22-24]. Some studies have demonstrated an increased incidence of delayed language and gross motor development and slowed motor performance among children with enuresis [25,26]. The hypothesis that there is a difference in the central nervous system maturation in children with primary enuresis compared with controls is supported by neurophysiologic data [27-29].

Enuretic episodes are associated with characteristic urodynamic and electroencephalographic (EEG) findings. Many children who have enuresis are noted to have progressive maturation of bladder stability in conjunction with EEG findings that suggest increased central nervous system recognition of bladder fullness and the ultimate ability to suppress the onset of bladder contraction [29]. These findings support the hypothesis that delayed maturation of bladder control plays a role in monosymptomatic nocturnal enuresis.

Genetics — There is a genetic tendency toward nocturnal enuresis. The concordance among monozygotic twins is almost twice that among dizygotic twins (68 versus 36 percent) [30]. When one or both parents have a history of prolonged nighttime wetting, approximately one-half and three-quarters, respectively, of the offspring are affected [31]. On the other hand, when neither parent has a history of nocturnal enuresis, only 15 percent of offspring are affected. An autosomal dominant form of primary nocturnal enuresis with a penetrance greater than 90 percent has been identified in Danish families and linked to a locus on chromosome 13q13-q14.3 (MIM %600631) [32]. Additional genetic loci for enuresis have been identified on chromosomes 12q13-q21 (MIM %600808) and 22q11 [33].

Parents who experienced nocturnal enuresis as children may derive some reassurance from the knowledge of the role of genetics in enuresis, which may help

them to understand that their child's problem will resolve as their own did. However, data from genetic studies have not yet been helpful in the development of treatment strategies.

Small bladder capacity — At birth, bladder volume is approximately 60 mL; bladder volume increases with age at a relatively steady rate of approximately 30 mL per year. Normal bladder capacity (in ounces) can be estimated by adding 2 to the child's age in years, until 10 years of age [34]. Children with nocturnal enuresis, even those who do not have daytime symptoms, have been noted to have a smaller bladder capacity than age-matched children who do not have nocturnal enuresis [35-39]. Clinical findings suggestive of reduced bladder capacity include urinary frequency, and associated constipation or cystitis [40].

The reduced bladder capacity appears to be functional rather than anatomical. This was illustrated by a study in which bladder capacity was measured in the awake state as well as under general anesthesia in children with nocturnal enuresis, and compared with functional bladder capacity among controls [41]. Compared with control children, the average volume of urine voided by enuretic children in the awake state was reduced: 135 versus 180, 165 versus 240, and 180 versus 360 among children aged four to six years, seven to eight years, and 9 to 11 years, respectively. However, the average bladder volume measured during general anesthesia in the enuretic children was 206 mL, 229 mL, and 283 mL in the respective age groups.

In another study, the maximal endurable bladder capacity during the daytime was similar between children with enuresis and controls [42]. However, among children with enuresis, the maximal voided volume during the night was significantly smaller than the maximal daytime bladder capacity, suggesting that inability to hold urine during sleep plays a role in nocturnal enuresis.

Nocturnal polyuria — Increased nighttime urine output appears to play an important role in nocturnal enuresis [3,43,44]. Mechanisms for increased nighttime urine output may include increased fluid intake before bedtime [40], reduced response to antidiuretic hormone (ADH, vasopressin), and decreased secretion of ADH [45-49]. Clinical findings suggestive of or associated with nocturnal polyuria include majority of fluid intake during the late afternoon and evening; soaking of or through absorbent underpants; and large-volume first morning void despite nocturnal enuresis [40]

Role of ADH — In children who do not have enuresis, urine output decreases during the night because the secretion of ADH and other regulatory hormones follows a circadian pattern, with increased secretion at night [50-52].

The relationship between ADH secretion and nighttime urinary flow rates remains controversial. Abnormalities in ADH secretion appear to play a role in at least some patients with nocturnal enuresis. However, whether these abnormalities are primary or secondary (eg, to bladder capacity or maturational delay) is not clear.

Various observations regarding ADH secretion in enuretic children have been used to explain nocturnal enuresis:

- Initial studies in enuretic children suggested that they had a blunted response to vasopressin compared with age-matched controls. It was postulated that this abnormality might permit urinary flow rates at night sufficiently high to exceed bladder capacity, resulting in enuresis. Subsequent studies failed to reproduce this observation.
- Other studies have indicated that children with nocturnal enuresis have decreased nocturnal secretion of ADH [45-49], which also would cause increased nocturnal urine output. One of the reasons may be small bladder capacity, since ADH secretion is thought to increase with bladder distension [53].

Neither of these observations (blunted response to ADH or decreased nocturnal secretion of ADH) explains why the children do not wake to void. However, the observations that the urine osmolality of enuretic and nonenuretic children is similar, and that early morning osmolality tends to increase with age, suggest that the ADH secretion response may be a maturational one [54]. (See 'Maturational delay' above.)

Detrusor overactivity — Urodynamic testing in children who have daytime incontinence demonstrates a variety of significant functional detrusor abnormalities. In contrast, no clear pattern of urodynamic abnormality has been demonstrated in children with primary monosymptomatic nocturnal enuresis. Nonetheless, bladder dysfunction should be considered in children who have refractory monosymptomatic primary nocturnal enuresis [55]. (See "Etiology and clinical features of voiding dysfunction in children", section on 'Daytime urinary incontinence'.)

Most studies suggest that the incidence of uninhibited bladder activity in children with primary monosymptomatic nocturnal enuresis is similar to the incidence of uninhibited activity in normal children (between 3 and 5 percent) [56-58]. However, children with monosymptomatic nocturnal enuresis may have a defect in the circadian rhythm of detrusor inhibition [59].

When urodynamic studies are performed during sleep, the only difference between enuretic and non-enuretic children is the increased rate of bladder contractions that occur in association with the enuretic episode [60]. In addition, urodynamic studies

during sleep demonstrate a relationship between nocturnal enuresis and pelvic floor activity. When pelvic floor activity increased in association with detrusor contractions, wetting was usually avoided, and the patient would often awaken subsequently to void. In contrast, when pelvic floor activity did not increase, the detrusor contraction usually was associated with a wetting episode [61,62].

Disturbed sleep — Whether abnormally deep sleep contributes to enuresis is controversial. Parents often describe their children with enuresis as excessively deep sleepers [63,64]. This may be a bias of observation, since parents rarely attempt to wake non-enuretic children. Nonetheless, in one sleep laboratory study of 33 boys aged 7 to 12 years (15 with enuresis and 18 age-matched controls), attempts at arousal were more often successful in control subjects than in boys with enuresis (40 versus 9 percent) [65]. Excessively deep sleep also appears to contribute to nocturnal enuresis in adolescents and adults [66].

Another sleep study found that children with severe and refractory enuresis (≥5 wet nights/week) slept more lightly than controls but did not wake before voiding [67]. Enuretic subjects had frequent cortical arousals but inability to waken completely. The cortical arousals were associated with unstable bladder contractions, suggesting to the authors that the arousal center may be paradoxically suppressed by signals from the bladder.

Other sleep studies show that sleep patterns among children with and without enuresis are similar [68,69]. These studies indicate that enuretic episodes may occur at random throughout the night, but primarily during nonrapid eye movement (non-REM) sleep [70]. However, some children wet during phases of early awakening.

Psychologic — Although psychologic abnormalities have been considered to play a role in nocturnal enuresis, this relationship has not been proven. Children whose enuresis has resolved do not develop substitute symptoms, which would be expected if there was ongoing psychopathology [19,20,71]. In addition, perceived adjustment problems tend to improve after resolution of enuresis, suggesting that the behavioral abnormalities are a result, rather than a cause, of the enuresis [19-21].

ASSOCIATED CONDITIONS — Nocturnal enuresis may be associated with neuropsychiatric problems, including cognitive problems, low self-esteem, and attention deficit hyperactivity disorder [72-74]. Disturbed sleep may contribute to or exacerbate these problems [75]. (See "Evaluation of suspected obstructive sleep apnea in children", section on 'Daytime'.)

DIFFERENTIAL DIAGNOSIS — Other causes of nocturnal enuresis that may require additional evaluation and/or treatment should be considered in children with enuresis. These include [38,76-78]:

- Unrecognized underlying medical disorders (eg, sickle cell disease, seizures, diabetes mellitus, diabetes insipidus, hyperthyroidism) (see appropriate topic reviews)
- Encopresis or constipation (see "Definition, clinical manifestations, and evaluation of functional fecal incontinence in infants and children", section on 'Clinical manifestations' and "Constipation in children: Etiology and diagnosis", section on 'Constipation and enuresis')
- Dysfunctional voiding (usually associated with daytime symptoms) (see "Etiology and clinical features of voiding dysfunction in children", section on 'Daytime urinary incontinence')
- Urinary tract infection (see "Clinical features and diagnosis of urinary tract infections in children", section on 'Clinical presentation')
- Chronic kidney disease (see "Clinical presentation and evaluation of chronic kidney disease in children", section on 'Clinical presentation')
- Spinal dysraphism (see "Pathophysiology and clinical manifestations of myelomeningocele (spina bifida)", section on 'Spinal cord')
- Upper airway obstruction (ie, obstructive sleep apnea) [79-82] (see "Evaluation of suspected obstructive sleep apnea in children", section on 'Diagnostic evaluation')
- Pinworms [83,84] (see "Enterobiasis and trichuriasis", section on 'Clinical manifestations' and "Enterobiasis and trichuriasis", section on 'Diagnosis')
- Psychogenic polydipsia (see "Diagnosis of polyuria and diabetes insipidus", section on 'Primary polydipsia')

EVALUATION — The evaluation of the child with monosymptomatic nocturnal enuresis includes history, physical examination, and urinalysis. The history, including a voiding diary, is the mainstay of the evaluation [3,40,85].

The main goal of the evaluation is to determine whether the child has dysfunctional voiding or enuresis as a manifestation of an underlying medical problem (eg, posterior urethral valves or other anatomic abnormality, spinal dysraphism, diabetes, etc.) [3]. Additional evaluation may be necessary to exclude these disorders. (See 'Differential diagnosis' above.)

History — Important issues to be considered in the history include (table 1) [3,38,40,76,85]:

- Presence of daytime wetting or symptoms, including urgency, holding maneuvers, interrupted micturition, weak stream, and straining (see 'Terminology' above); urologic and neurologic disorders are more common among children with daytime symptoms
- Any prolonged period of dryness
- Frequency and trend of nocturnal enuresis (eg, number of wet nights per week or month, number of episodes per night, time of episodes, approximate volume of each episode)
- Fluid intake diary (does the majority of fluid intake occur during the late afternoon and evening?); this may help to identify children with diabetes, kidney disease, or psychogenic polydipsia
- Stooling history and history of soiling (to determine whether there is associated constipation or encopresis, an important cause of secondary enuresis) (see "Constipation in children: Etiology and diagnosis")
- Determination of which interventions the family has tried
- Medical history (eg, review of systems for symptoms of sleep apnea, diabetes, sickle cell disease or trait, urinary tract infection, gait or neurologic abnormalities)
- Family history of nocturnal enuresis
- Social history (particularly important in secondary enuresis because somatic and psychologic comorbidities are more common among children with secondary enuresis) [2,86]
- Assessment of how the problem has affected the child and family; the risk of treatment resistance is increased in children who are not bothered by their enuresis. Postponement of therapy until the child is motivated may be warranted.
- Behavioral history or behavior screening questionnaire (to screen for psychiatric comorbidity) (see "Developmental and behavioral screening tests in primary care", section on 'Behavioral screening tests')

Voiding diary — A voiding diary is helpful in identifying children with non-monosymptomatic enuresis or other conditions that may require additional evaluation or referral. The diary should include [3,40]:

- The number of daytime voids
- Usual volume of voided urine (to estimate bladder capacity)
- Maximum length of time between voids
- Lower urinary tract symptoms (eg, difficulty starting or stopping stream; dribbling; sensation of incomplete emptying)
- Timing of voids in relation to events such as meals, school breaks, play activities, etc.

Sample frequency-volume charts are available from the International Children's Continence Society.

Physical examination — The physical examination of the child with primary monosymptomatic nocturnal enuresis usually is normal. Aspects of the physical examination that may indicate an underlying medical etiology for enuresis include (table 2) [3,40]:

- Poor growth and/or hypertension (calculator 1 and calculator 2) may indicate renal disease.
- Detection of wetness in the undergarments is a sign of daytime incontinence.
- Palpation of stool in the abdomen suggests constipation or encopresis.
- Perianal excoriation or vulvovaginitis may indicate pinworm infection. (See "Enterobiasis and trichuriasis".)
- Presence of abnormalities of the lumbosacral spine (eg, abnormal tuft of hair or an abnormality in the gluteal fold) and/or abnormalities on neurologic examination of the perineum and lower extremities may indicate occult spinal cord abnormalities. (See "Pathophysiology and clinical manifestations of myelomeningocele (spina bifida)".)
- Detection of incomplete bladder emptying by percussion and/or palpation or observation of voiding that demonstrates slow urinary stream, dribbling, or intermittent stream may indicate urologic abnormalities (eg, posterior urethral valves, ectopic ureter). (See "Clinical presentation and diagnosis of posterior urethral valves", section on 'Clinical manifestations' and "Ectopic ureter", section on 'Clinical presentation'.)
- Undescended testicles, underdeveloped scrotum, and abnormal location or characteristics of the urethral meatus also may indicate urologic abnormalities. (See "Undescended testes (cryptorchidism) in children and adolescents" and "Hypospadias".)

Urinalysis — Urinalysis should be performed in all children with monosymptomatic enuresis [3]. The urinalysis (including specific gravity) is obtained as a screen for diabetic ketoacidosis, diabetes insipidus, water intoxication, and/or occult urinary tract infection [40]. Urine culture is not necessary unless indicated by the presence of white blood cells or nitrites on urinalysis. (See appropriate topic reviews).

Imaging — Urologic imaging (renal sonogram and voiding cystourethrogram) is reserved for children who have significant daytime complaints, a history of urinary tract infection(s) not previously evaluated, and/or signs and symptoms of structural urologic abnormalities [3,40,87]. Ultrasonography may be helpful in estimating bladder capacity, post-void residual volume, and bladder wall thickness.

Neurologic imaging (usually magnetic resonance imaging of the spine) is indicated in children who are noted to have abnormalities of the lower lumbosacral spine on neurologic examination of the perineum and lower extremities [88].

REFERRAL — Children who have clinical or radiographic findings suggestive of renal/urologic abnormality or bladder overactivity should be referred to a pediatric nephrologist/urologist for further evaluation. Such findings include [3]:

- Daytime incontinence; urgency; holding measures; increased (≥8 times/day) or decreased (≤3 times/day) voiding frequency (possible voiding dysfunction)
- Weak stream, use of abdominal pressure, continuous incontinence, micturition in more than one phase (possible neurogenic bladder or anatomic abnormalities)
- Proteinuria, nausea, weight loss, or fatigue (possible kidney disease)
- Excessive thirst, need for nighttime drinking (possible polydipsia or kidney disease)

Referral to an enuresis specialist may be warranted for children who have nightly enuresis since the prognosis in such children is unfavorable [3,89].

Referral to a pediatric neurosurgeon may be warranted for children with clinical or radiographic findings suggestive of occult spinal dysraphism (eg, abnormalities of the lower lumbosacral spine).

RESOURCES — The International Children's Continence Society provides guidelines for the evaluation and treatment of monosymptomatic enuresis, as well as information for the general public.

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient information: Bedwetting (The Basics)")
- Beyond the Basics topics (see "Patient information: Bedwetting in children")

SUMMARY AND RECOMMENDATIONS

- Enuresis refers to discrete episodes of urinary incontinence during sleep in children who are ≥5 years of age. Monosymptomatic enuresis refers to enuresis in children without any other lower urinary tract symptoms and without a history of bladder dysfunction. (See 'Terminology' above.)
- Monosymptomatic nocturnal enuresis has a high rate of spontaneous resolution: the prevalence decreases from 15 percent among five-year-old children to 1 to 2 percent among those ≥15 years (graph 1). (See 'Epidemiology and natural history' above.)
- Monosymptomatic nocturnal enuresis may result from one or a combination of several possible factors. The major pathogenetic mechanisms include nocturnal polyuria, detrusor overactivity, and disturbed sleep. Other factors may include maturational delay, genetics, and abnormal secretion of antidiuretic hormone. (See 'Causes' above.)
- The evaluation of children with nocturnal enuresis should include a complete history (table 1), voiding diary, physical examination (table 2), and urinalysis. The main purpose of the evaluation is to determine whether the child has complex enuresis or enuresis as a manifestation of an underlying medical problem. (See 'Differential diagnosis' above and 'Evaluation' above.)
- Children who have clinical or radiographic findings suggestive of renal/urologic abnormality or bladder overactivity should be referred to a pediatric nephrologist/urologist for further evaluation. Referral to a pediatric neurosurgeon may be warranted for children with clinical or radiographic findings suggestive of occult spinal dysraphism. (See 'Referral' above.)

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