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Review Article

# Investigating Enuresis in Children: A Review Article

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## ABSTRACT

Nocturnal enuresis is defined as a wetting episode at nighttime in children over 5 years of age and it is divided into primary and secondary types. Primary nocturnal enuresis refers to cases who had never had a dry bed with a prevalence from 1.6% to 15% and it may continue to adolescence. Ignoring the problem has some psychological consequences and a significant impact on the quality of life. Conservative therapy and active intervention have been proposed as the modality of treatment. This review address on the assessment of nocturnal enuresis, sleep disorder, psychological impact, and the management of enuresis by considering the causes of resistance to treatment.

**Keywords:** Enuresis, Primary care, Incontinence, Overactive bladder, Treatment, Desmopressin, Child

## Introduction

Nocturnal enuresis (NE) is the most prevalent and fearful chronic condition among families. The prevalence of this disorder varies in different countries ranging from 2.3% to 25%. A recent systematic review estimated that the prevalence of NE in Iranian children is 10.2% (95% confidence interval (CI), 7%-14.8%) [1].

Daytime incontinence is more common in females and night bedwetting is more observed in male children. This review address on the assessment of NE, sleep disorder, psychological impact, and management of enuresis by considering the causes of resistance to treatment.

### Definitions

NE is more common among children with urinary tract infections, positive history in relatives, water consumption before bedtime, and child punishment [1]. NE refers to episodes of urinary incontinence during sleep in children over the age of 5 years. There are several subtypes of this disorder, including a) Monosymptomatic enuresis (bedwetting during sleep without any lower urinary tract symptoms); b) Non-monosymptomatic enuresis (when NE is associated with increased frequency, daytime incontinence, urgency, or lower urinary tract pain); c) Primary enuresis (children who have never achieved satisfactory dry nights); and d) Enuresis that occurs after a dry period of at least 6 months and is referred to as

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secondary enuresis. The majority of secondary enuresis cases in children have no known cause [2].

### Assessment

Warning Sign: individuals should observe the warning signs, including a history of urinary tract infection; chronic constipation; severe daytime symptoms, such as weak urine stream and straining that suggest posterior urethral valve in boys; and recent onset of secondary enuresis that might be due to pathological condition, such as diabetes mellitus.

### The evaluation of the child with monosymptomatic enuresis

The evaluation of monosymptomatic enuresis includes considering a history comprising voiding diary, and bowel habits, through physical examination, and urinalysis [3, 4]. The historical assessment should explore the presence of daytime wetting or symptoms, covering urgency, holding maneuvers, interrupted micturition, weak stream, and straining. Urologic and neurologic disorders are more common among children with daytime symptoms and any prolonged period of dryness. The frequency and trend of nocturnal enuresis (e.g. number of wet nights per week or month, number of episodes per night, time of episodes) [3], fluid intake diary (does the majority of fluid intake occur during the late afternoon and evening?) may help to identify children with diabetes, kidney disease, or psychogenic polydipsia, in addition to determining the applied interventions by the family, medical history (e.g. review of systems for symptoms of sleep apnea, diabetes, sickle cell disease or trait, urinary tract infection [UTI], gait or neurologic abnormalities), family history of nocturnal enuresis, social history (particularly important in secondary enuresis as somatic and psychologic comorbidities are more common among children with secondary enuresis), and the 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. The postponement of therapy until the child is motivated may be warranted, along with behavioral history or behavior screening questionnaire to screen for psychiatric comorbidity.

### Bladder Capacity

The bladder capacity is determined as follows:

- The observed maximal voided volume (MVV) is compared with age-expected bladder capacity (EBC) (valid until age 12 or a maximum of 400 mL)

- Using the following Equation (Equation 1) [2, 5]:

1. • EBC=(age in years+1)×30 mL

• Reduced MVV, defined as MVV <65% of EBC.

### Nocturnal polyuria (2, 5)

Nocturnal polyuria is observed as follows:

- One week of home recording based on diaper weights and first morning voided volume

• (Nocturnal urine volume=diaper weight before sleep - diaper weight after sleep+first morning void);

- Definition:

• Nocturnal urine volume on a night with enuresis exceeding 130% of EBC of the child;

• Urine volume exceeding 20×(age in years)+9) mL

Physical examination: The physical examination should evaluate general health, and genital examination, and look for signs of occult spinal dysraphism, such as lumbosacral findings, leg, and gluteal cleft asymmetries, and abnormal neurology of lower extremities.

### Laboratory and imaging study

All cases should do urine analysis and ultrasound determination of rectal diameter. Filling NE clinical management tool (CMT) may be useful. In specific patients, ultrasound of kidneys and urinary tract, voiding-cysto-urethrography, magnetic resonance imaging of the lower back, and urodynamic investigations might be requested [6-8].

### Enuresis and sleep disorders

The prevalence of NE decreases with age as the voiding control and bladder-brain relationship improve [9]. Some possible organic causes are mentioned as the pathogenesis of NE. Diuresis during sleep is normally reduced because of a circadian rhythm of the antidiuretic hormone arginine-vasopressin (AVP). This hormone is secreted from the posterior part of hypophysis at a higher level at night and decreases urine production. It seems that children with NE and nocturnal polyuria have lower levels of AVP at night compared to non-enuretic cases. Sometimes

there is resistance to AVP [10]. Other factors which may have a role in NE are overactivity, decreased capacity, and delay awaking on the fullness of the bladder [10, 11].

Some studies have demonstrated a tight relationship between sleep and NE. Sleep is under control of microstructures and neurotransmitters in the brain stem, hypothalamus, and cortex. γ-Aminobutyric acid (GABA), an inhibitory neurotransmitter, and adenosine have an important role in promoting sleep, and acetylcholine, norepinephrine, serotonin, and histamine maintain wakefulness [12].

Human sleep cycles have two phases, including rapid eye movement (REM) with lower muscle tone and non-rapid eye movement (NREM), a deeper sleep, and includes three stages of N1, N2, and N3. More than 3 quarter of sleep is spent in the NREM sleep, especially during the N2 stage. Each sleep cycle lasts an average of 90 min and is repeated 4 to 6 times during the night [13]. NE often occurs early at night and in NREM sleep, stages N2 and N1. Polysomnography analysis in NE cases has shown changes in these sleep stages and can prone subjects to more sleep fragmentation and delayed arousability [13, 14].

Sleep-disordered breathing (SDB), such as sleep apnea-may contribute to NE in different ways. SDB can lead to the fragmentation of child sleep and distract the awakening. It may change natriuretic peptides, and antidiuretic hormone levels, and lead to overactivity of a sympathetic system that finally provides more chance for NE. When respiration is performed against a partial obstruction of the airway, such as large tonsils, cardiac dilatation, and then atrial natriuretic peptide secretion occurs and interferes with the water volume, AVP and the renin–angiotensin–aldosterone axis [10]. The removal of large tonsils as a common treatment of SBD has dramatically declined refractory NE [15, 16].

Periodic limb movement syndrome is a disorder leading to leg involuntary movements through sleep with a frequency of 20 to 40 s. It results in cortical arousal and can disturb sleep. Studies suggest that periodic limb movement syndrome has a higher rate in children with refractory NE [17].

An observational study on 116 children with NE compared to 58 healthy children y performance on the Pittsburgh sleep quality index test. Cases with NE slept shorter hours at night, require the presence of parents or toys more, have a higher rate of eating and drinking before bedtime, and are more frequently suffering from sleep apnea compared to healthy children [18].

## Enuresis and psychiatric comorbidities

Although most children with enuresis do not have comorbid psychiatric disorders, comorbidities are more common in children with enuresis than in the general population [19, 20].

Attention deficit/hyperactivity disorder (ADHD) is the most common psychiatric comorbidity in enuresis [21, 22]. ADHD is not secondary to enuresis and the presence of enuresis does not increase the risk of psychopathology in ADHD; however, enuresis is associated with a higher rate of learning disorders, oppositional defiant disorder (ODD), encopresis, sleepwalking, and sleep terror in normal children [23, 24].

Enuresis with a history of at least 1 dry year (secondary enuresis) is more frequently associated with a concomitant psychiatric difficulty than primary enuresis [19, 25]. It can have a link with generalized developmental delay, including speech, language, learning, and motor skills delays, as well as an autism spectrum disorder [26]. In up to 20% of young children, enuresis may be precipitated by psychosocial stressors (e.g. the birth of a sibling, hospitalization, the start of school, separation of a family due to divorce, or a move to a new environment) [23, 25]. The relation between unintentional wetting and psychological problems is still unclear; however, ODD or a psychotic disorder may be the most likely underlying problem in voluntary enuresis. Daytime wetting in children with ADHD may be due to delays in going to the bathroom. A careful interview is important in exploring possible environmental and psychological contributions [19, 20].

## Psychiatric consequences

Enuresis is troubling to children and their caregivers. Although most cases do not wet intentionally, it is often misunderstood as voluntary misbehavior. It can lead to punishment, domestic violence, and a reduction in quality of life [27]. Although the nature of the behavioral disturbances in children with enuresis is broad and nonspecific, the link between enuresis and developmental delays, which are also linked to psychopathology, would suggest the presence of a common underlying maturational factor that predisposes vulnerable children to both behavioral disturbances and enuresis [26]. Children with enuresis may have behavioral disturbances which may be because of comorbid psychiatric disorders or may be an emotional reaction to having enuresis [25, 27]. The correlation with behavioral disturbances increases with age and is more pronounced in secondary enuresis, children with older age, and adolescents [28].

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Compared to children suffering from other chronic illnesses, children with enuresis have more negative feelings about their problems [29]. Primary enuresis, male gender, and a greater frequency of wet nights are factors related to negative self-image [30, 31]. Most children gain self-esteem and improved social confidence when they become content [32]; therefore, poor self-image, decreased self-esteem, social embarrassment, social restriction, poor school performance, and interfamilial conflict, are among their significant primary psychological and social difficulties, can often improve with effective treatment [30, 33].

## Treatment

Determining whether the child is mature enough to take responsibility for the treatment is important. If the caregivers appear to be more interested in treatment than the child, and the child is unwilling or unable to take responsibility for the treatment program, treatment should probably be delayed. A child must be highly motivated to participate in a treatment program that may take months to achieve successful results. Children younger than 6 years can usually be managed with motivational education and therapy [8]; however, age should not be the only criterion for starting active treatment.

Consumption of drinks containing high sugar and caffeine should be avoided. Patients with NE were given the advice to drink 40% of their total daily fluids in the morning (7:00 AM to 12:00 PM), 40% in the afternoon (12:00 to 5:00 PM), and only 20% drink in the evening (after 5:00 PM) [34].

Active treatments include nocturnal alarms and desmopressin [8, 35-37] that are suggested to individuals who do not improve after 3 to 6 months of initial treatment, based on family preferences.

Desmopressin has a higher rate of relapse but is more quickly effective than alarms and requires less caregiver supervision and time commitment [8, 38, 39]. It is most suitable for children with nocturnal polyuria and normal bladder capacity [8, 38, 40, 41]. Responses should be evaluated within 1 to 2 weeks. If signs of response are observed, treatment should be continued for 3 months. If desmopressin is given daily, it should be discontinued for a week every 3 months to determine if continued dosing is necessary.

Desmopressin is administered orally 60 min before bedtime. The initial dose of the oral melt tablet is 120 µg. If necessary, it can be increased to 240 µg after 7 days. To prevent dilution hyponatremia, fluid intake should be limited to 200 mL from 1 h before to 8 h after prescribing.

Failure to respond to desmopressin within 1 to 2 weeks may be due to decreased nocturnal bladder capacity, persistent nocturnal polyuria related to increased fluid intake in the evening, increased nocturnal solute excretion, or decreased pharmacodynamics effect of desmopressin.

The alarm should be shown to the child and family before use. Every night before going to sleep, the child should test the alarm. Considering the sound (or vibration), the child must imagine in detail for 1 to 2 min the sequence of events that will occur when the bedtime alarm sounds (or vibrates). The sequence is as follows [42]:

1. The child turns off the alarm, gets up, and urinates in the toilet (only the child should turn off the alarm). The child needs to be fully awake and aware of what is happening for the success of alarm therapy; however, at the start of alarm therapy, caregivers may need to wake the child by ringing the bell.

2. The child returns to the bedroom.

3. The child changes his bedding and clothes (with careful supervision). Changing the bed and clothes should be near the bed.

4. The child wipes the sensor with a wet cloth and then a dry cloth (or replaces the sensor if it is disposable).

5. The child resets the alarm clock and goes back to sleep.

Bedwetting continues until the child is dry for at least 14 consecutive nights [43]. This usually lasts between 12 and 16 weeks, with a range of 5 to 24 weeks [43]. If after a 3-month trial period, the child has more dry nights per week, even if they have not achieved more than 14 consecutive dry nights, alarm therapy should be continued. If improvement is not achieved after 3 months of therapeutic alarm, alternative interventions may be required.

## Refractory enuresis

The lack of response to active intervention is defined by a <50 percent improvement in the baseline frequency of enuresis [43]. At this stage, it is necessary to obtain a detailed history, re-examination, record of voiding and fluid intake diary, and re-check the method of taking alarm and desmopressin [44]. In case of treatment resistance without obvious reason, bladder function disorders and neurogenic bladder should be suspected.

Indications for referral to a specialist in the management of recurrent or persistent bedwetting include the following items [8]:

a) Suspicion of structural or anatomical abnormalities;

b) NMEN;

c) Developmental, attention, or learning problems;

d) Behavioral or emotional problems;

e) Known or suspected physical or neurological problems;

f) Caregivers who have difficulty coping with enuresis or who express anger, denial, or guilt towards the child - these caregivers may need extra support;

g) Refractory enuresis.

## Conclusion

Simple MSE needs clinical and a brief investigation; accordingly, NMSE and resistant cases to treatment require more study. Regarding frequency, a volume chart helps to decide which therapy to choose. Sleep disorders and NE have a reciprocal relationship. It is recommended to evaluate and treat sleep disorders in every child with refractory NE.

The course of children with enuresis can be influenced by careful evaluation and providing appropriate treatment for comorbid disorders (especially ADHD) since comorbidities can reduce compliance and treatment outcomes. Relapses may occur both in subjects who are in treatment and individuals who are becoming dry spontaneously.

## Ethical Considerations

### Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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### Authors' contributions

All authors contributed equally to the conceptualization, writing the draft, reviewing, and editing of the article.

### Conflict of interest

The authors declared no conflict of interest.

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## Quiz:

**1. Which sleep stage may be related to enuresis?**

a. Early sleep stage as drowsiness

b. Rapid eye movement sleep

c. Non rapid eye movement sleep

d. All sleep stages

**2. Which one is definition of MSEN?**

a. Wetting at day and night while sleeping

b. Unconscious wetting at the age of 3.5 years

c. Involuntary incontinency while waking

d. Inability to toilet trained after 2 years old

**3. Which sleep disorder is more related to enuresis?**

a. Sleep apnea

b. Restless leg syndrome

c. Snoring

d. All choices

**4. Which item does have a role in the pathogenesis of enuresis?**

a. Low capacity of bladder

b. Non-arousal response to bladder fullness

c. Abnormal AVP secretion rhythm

d. All choices

**5. Which one is the most common psychiatric comorbidity in enuresis?**

a. Encopresis

b. Learning disorder

c. ADHD

d. Sleepwalking

**6. Which type of enuresis is more frequently associated with concomitant psychiatric difficulty?**

a. Primary enuresis

b. Secondary enuresis

c. Mixed enuresis

d. There is no relation between the type of enuresis and psychiatric difficulties.

**7. Which one is related to negative self-image in children with enuresis?**

a. Female gender

b. Secondary enuresis

c. Greater frequency of wet nights

d. Younger age

**8. Which one of the following statements is true?**

a. Most children with enuresis have comorbid psychiatric disorders.

b. ADHD is secondary to enuresis.

c. In the majority of young children, enuresis is precipitated by psychosocial stressors.

d. Psychiatric comorbidities can reduce compliance and treatment outcomes.

**9. Which one of the following statements is false?**

a. Enuresis is often understood as a nonvoluntary misbehavior.

b. Psychological consequences of enuresis, can often improve with effective treatment.

c. Relapses may occur in those who are in treatment.

d. Relapses may occur in those who are becoming dry spontaneously.

**10. Enuresis requires referral to a specialist in all of the following cases except?**

a. Anatomical abnormalities

b. MSEN

c. Neurological problems

d. Behavioral problems

**11. Which of the following is essential in the treatment of MSE?**

a. Restrict fluid intake in the evening

b. Nocturnal alarms

c. Desmopressin

d. Oxybutynin

**12. When is an active treatment for MSEN recommended?**

a. Children who have no improvement after 3 to 6 months of initial treatment

b. At the beginning of the disease diagnosis

c. After one month from the onset of the disease

d. Active therapy has no role in the treatment of MSEN

**13. Failure to respond to desmopressin could not be due to which of the following?**

a. Decreased nocturnal bladder capacity

b. Increased fluid intake in the evening

c. Nocturnal polyuria

d. Decreased pharmacodynamic effect

**14. Which of the following can cause refractory enuresis?**

a. Diabetes mellitus

b. Urinary tract infection

c. Occult constipation

d. All items

**15. What is the Earliest step for assessment of a child with enuresis?**

a. Measure urine calcium to creatinine

b. Uroflowmetry

c. Urine analysis

d. Voiding diary

**16. Which item is a warning sign in enuresis?**

a. Weak urine stream

b. Drinking fluid before bedtime

c. Going to bed late

d. Prolong sleep

**17. Which statement defines nocturnal polyuria?**

a. Urine volume on a night exceeding 130% EBC

b. Urine volume exceeding 400 mL at night

c. Urine volume exceeding (age in years + 20 mL)

d. Urine volume of more than 4 mL/kg/h

**18. What is the prevalence of NE in Iranian children?**

a. 2.5%

b. 5%

c. 10%

d. 25%