

REVIEW ARTICLE

Enuresis

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Abstract: Nocturnal enuresis is not at all unusual in pediatric population. This article aims at presenting a review of the current information on nocturnal enuresis, including definition, causes and the available therapeutic modes, keeping the main focus on primary nocturnal enuresis. The possible mechanisms for primary nocturnal enuresis include-Genetic Factors, Maturational Delay, Sleep Disorders, Psychological Causes, and Small Bladder capacity. Treatment of primary nocturnal enuresis can be divided into two major categories: pharmacological and Non-pharmacological. There is no consensus about continuous medication. Children who have frequent episodes of enuresis should use a combination of a drug and an enuresis alarm. Relapse rate is very high with drug. After evaluating the cost, efficacy, side effects and the relapse rates associated with various treatments, Behavior Therapy, Parent awakening & the enuresis alarms seem to be most efficacious. Psychosocial and family histories are important to assess the attitude of parents and the child, in order to select a proper therapy. Organic cause of nocturnal enuresis may be elicitable in only 2-3% of the patients. Proper examination & investigation is needed to evaluate organic cause. Management of secondary nocturnal enuresis depends on cause.

Keywords: Enuresis, Genetic Factors, Maturational Delay, Sleep Disorders. Psychological Causes..., Behavior Therapy, Enuresis alarms, Drugs.

Wet child and nocturnal enuresis is not uncommon in pediatric population. This problem many times overlooked by the treating pediatrician, but is a source of psychological stress for the affected child as well as the parents.

I. Definitions

Nocturnal enuresis defines as a *repeated* discharge of urine into clothes or bed after a developmental age when bladder control should be established. *Repeated* means twice a week for 3 consecutive months. The American Psychiatry Association has defined bed wetting as children older than age five who are incontinent of urine at night [1]. Diurnal enuresis is defines as Wetting that occurs during waking hours (daytime incontinence) whereas nocturnal enuresis is the bed wetting that occurs during sleep. Uncomplicated enuresis is that type of nocturnal enuresis in which physical examination, is normal and urine analysis and urine culture is normal. In complicated enuresis onset of enuresis is secondary, there is history of urinary tract infection(s), abnormal neurological examination, and a history of voiding dysfunction. Some investigators make a distinction between primary and secondary incontinence. Primary incontinence is bed-wetting since birth without any significant periods of dryness whereas secondary enuresis occurs when continence is lost after

having been dry for more than six months. Secondary enuresis often implies loss of normal continence mechanisms and suggests that underlying disease may be present. Another classification of nocturnal enuresis is based on the presence or absence of other bladder symptoms. Mono symptomatic nocturnal enuresis is associated with normal daytime urination and is easier to treat, as compared to the former. Polysymptomatic nocturnal enuresis is bed-wetting associated with severe urgency, severe frequency, or other signs of an unstable bladder.

II. At what age do children achieve bladder control?

Children achieve bladder control at different ages. During the first two to three years of life bed-wetting at night is normal and expected. Thirty per cent of children at the age of four years still wet the bed, by the age of 5 years most children no longer urinate in their sleep. Bed-wetting up to the age of 5 is not unusual, even though it may be frustrating to parents. Treating a child for bed-wetting before the age of 5 is not necessary and may even be harmful to the child. . Ten per cent of children at the age of five to six years wet the bed and a little less than five per cent still do so at the age of 10 years. One per cent still wet the bed by the age of 18. One should take child to doctor when--(1)Child is older than 5 years and still wets the bed, (2) Child was once dry at night and then began wetting the bed again, (3) Bed wetting upsets your child or (4) child Wets or soils his or her pants during the day.

III. Epidemiology

The prevalence of nocturnal enuresis has been difficult to estimate because of variations in definition and in social standards [2-3].15-20% of children have some degree of bedwetting at five years of age, with a spontaneous resolution rate of 15% per year Bedwetting has been reported to be higher in males – 60% of bedwetters and more than 90% of nightly bedwetters are males. However this finding has been disputed by other reports [4].

IV. Causes of Primary Nocturnal Enuresis

The etiology of primary nocturnal enuresis has been widely debated but is still not completely understood. The final common pathway for all affected children is an inability to recognize the sensation of a full bladder during sleep and to awaken from sleep to go to the toilet. Another etiologic requirement is that the bladder reaches capacity during the night. The possible mechanisms include---

1. Genetic Factors
2. Maturational Delay
3. Sleep Disorders
4. Psychological Causes
5. Small Bladder

1. Genetic Factors: A Family history of nocturnal enuresis is found in most children. There is marked familial pattern. If one parent was a bed wetter the probability of having enuresis in the child is 45%; if both parents were bedwetters the probability increases to 77%. On the other hand only 15% will be affected if neither parent had enuresis [5]. But exact pattern of transmission not clear.

The concordance for identical twins (68%) has also been shown to be higher as compared to fraternal twins (36%) [6]. The frequency and duration of enuresis may also be similar in family members. Heredity as a causative factor has been confirmed by the identification of a major dominant gene for primary nocturnal enuresis on chromosome 13 [7]. Linkage studies show genes on Chromosome 22 is also implicated.

2. Maturational Delay: Although the most common accepted cause of primary nocturnal enuresis, it is the most difficult to prove. It is postulated that functional immaturity of the central nervous system results in decreased sensory perception of bladder filling, inability to inhibit bladder emptying and poor arousal mechanisms.

3 Sleep Disorders: The sleep patterns of patients with enuresis have varied widely and are difficult to interpret. Parents generally report that bedwetters are 'sound sleepers'. This observation is supported by Wolfish who used tones of increasing intensity, delivered through earphones, and observed that those who had enuresis woke 8.5% of the times compared with 40% of the time for controls [8]. Sleep EEG studies have also reported an association of nocturnal enuresis with slow brain-wave activity in children [9]. On the contrary other investigators have demonstrated that bedwetting may occur at different stages of sleep [10] and children who wet the bed have normal sleep patterns. The controversy on this topic continues till date and awaits a verdict. Nocturnal enuresis is also associated with episodes of obstructive sleep apnea in children with upper airway obstruction and surgical correction in such cases (viz. tonsillectomy, adenoidectomy etc.) diminishes the episodes of bedwetting [11].

4. Psychological Causes: The role of psychological disorders in the causation of nocturnal enuresis is primarily a myth, which, unfortunately, has been propagated by the general pediatricians themselves. Children with primary enuresis have essentially the same behavior pattern as normal children [12]. If a child develops secondary enuresis after a psychological event it is usually a relapse physiologic enuresis, and is usually also accompanied with daytime symptoms.

5. Small Bladder Capacity: Some studies [13-14] have found functional bladder capacity to be low in patients with nocturnal enuresis. These findings have been questioned by other investigators [15]. If the bladder is small, the patient would also manifest accompanying symptoms, such as daytime frequency, wetness every night, occasional wetness several times in a night and the problem being primary

V. Organic Cause of Nocturnal Enuresis

Organic cause to nocturnal enuresis may be elicitable in only 2-3% of the patients. Other 5-10% children have polysymptomatic enuresis which requires specific therapy. For control his or her urination, 3 mechanisms need to work together:-- The kidneys need to make the right amount of urine. Urine is stored in the bladder. In the bladder there is a muscle, which holds the urine in the bladder. So bladder has to hold the urine. The brain tells the muscle to stay closed until the child opens it (when on the toilet).

1. *Causes related to more urine production (Polyuria)* are diabetes Mellitus, diabetes insipidus, sickle cell disease (Isothenuria), alcohol, caffeine intake, drugs, habit polydipsia, and redistribution of mild edema & nocturnal ADH deficit (highly controversial)

2. *Related to bladder:* Bladder irritability, incomplete bladder filling & emptying can give rise to enuresis causes of Bladder irritability are urinary tract Infection, food allergies, Constipation, bladder calculi & hypercalciuria. Fecal impaction can lead to incomplete bladder filling. Lower Urinary Tract Infection, neurogenic bladder & dysfunctional voiding are the possible cause of incomplete bladder emptying.

VI. Causes of Diurnal Enuresis

Micturition deferral: child waits until last minute to void urine (as busy playing), urinary Tract Infection & Constipation can lead to diurnal enuresis.

VII. Causes of Secondary Nocturnal Enuresis

Psychosocial Stress: e.g. Child insecure after birth of younger sib, Family quarrels, Academic stress (school failure, does not like class room, teacher) Urinary Tract Infection Juvenile Diabetes Mellitus & Other cause of polyuria

VIII. Evaluation of Enuresis

1. *History:* Psychosocial and family histories are important to assess the attitude of parents and the child, in order to select a proper therapy. For detection of organic enuresis—a history of dysuria, intermittent daytime wetness, polydipsia, polyuria, CNS trauma, constipation and encopresis point to medically treatable conditions. Surgical management may be needed in patient with Constant wetness (.ectopic ureter), Abnormal urine stream with hesitancy or dribbling (posterior urethral valve), Snoring (adenoid hypertrophy).

2. *Physical Examination:* The physical exam will check the child's general health. An abdominal, genital-urinary, and neurological exam has to be performed to evaluate the child.

- i) *Genital-urinary:* Genitals examination for meatitis, vulvitis, labial adhesions or examination for signs of sexual abuse is also important. Distended bladder and bowel (fecal impaction) may be the cause for enuresis.
- ii) *Neurological system:* Alteration in gait may occur in spinal cord neoplasm led to enuresis. Muscle tone strength & Deep tendon reflexes in the lower extremity—may reveal a CNS etiology. Examination of the lumbosacral area may disclose an overlying midline defect

It is also important to check the patient for obligatory mouth breathing as children with adenoid hypertrophy may wet themselves during sleep apnea and the problem is alleviated by adenoidectomy

3. Investigations: i) Urinalysis

- a) Specific gravity (e.g.>1.015 rules out diabetes insipidus)
- b) Glucose (for diabetes mellitus)
- c) Urine culture-- if symptoms of urinary tract infection are present or if there is past history of urinary tract infection.

ii). Radiological studies are not necessary in all children with straightforward primary nocturnal enuresis. Radiological studies are also done in infant and young children with U.T.I to rule out structural abnormalities.

- a) Maturating cystourethrogram (MCU) is required in children with symptoms of urinary tract obstruction or a neurogenic bladder.
- b) Bladder ultrasonography (pre- and post-voiding) is indicated in children with diurnal enuresis, unresponsive to therapy, to rule out partial emptying.

iii) Determination of Bladder Capacity: This is an extremely important part of the evaluation of a child with bedwetting that is often overlooked. Ask the child to drink 12 oz. of water in the OPD and measure the volume of urine when the child voids. The normal bladder capacity, in ounce, is age (in years) + 2 (the normal adult bladder capacity is 12-16oz.). This helps in better understanding of the child's problems among the two primary etiologies-small bladder and inability to awaken. If the bladder capacity is normal the condition is more amenable to motivational therapy. If the bladder capacity is low, treatment is more difficult.

IX. Management

1. *Non-Pharmacologic Methods: This include Behavior Therapy, Awakening Programs, Enuresis Alarms Bladder Training Exercises, Hypnotherapy, diet therapy and physiotherapy*

Behavior Therapy &Awakening Programs for Nocturnal Enuresis: Parents counseled to encourage child to win cooperation. Never humiliate or punish child. Children should be encouraged to drink seven to eight cups of fluid, spaced out throughout the day. It's best to avoid drinks that contain caffeine because they have a diuretic (urine-producing) effect. Make sure your child doesn't have a drink within two to three hours of bedtime Ensure child doesn't drink fluids after 7 pm; sleeps by 10 pm after voiding urine& Wake up child at 12 midnight (2 hrs after falling asleep) to void urine. Parents sometimes lift a sleeping child to the toilet before they themselves go to bed. However, this may encourage a child to wet the bed because their bladder does not feel full before they pass urine. Generally enuresis subsides in a few months. Make it easy for your child to reach the toilet - perhaps leave a light on. Encourage your child to return to her own bed after it has been changed. Record wet and dry nights & reward child for being dry at night (Positive reinforcement). The child is to be reminded that enuresis is not the parents' or the physician's problem but something which they can

What doesn't help in Motivational therapy?: Punishments, Humiliation (The child is not doing it on purpose), Teaching the child to "hold it till morning", Keeping the child thirsty, Diapers---They give the wrong message. Motivational therapy is a good

first-line approach, especially in younger children. The resolution rate with this form of therapy has been estimated to be only 25%; however 70% of children show marked improvement [16].

Enuresis Alarms: If behavior therapy fails or if parents want prompt response: Bell and pad alarm system (conditioning device) used. These are signal alarm devices that consist of a moisture sensing device placed near the genitals that is activated when the child voids in bed. For Alarm therapy a motivation of child and family is required. Use of a reward system for positive reinforcement with alarms may help attain the desired results. Alarms are effective in about 70% of children [17-18]. But in 10-15% relapse of bedwetting can occur. Continuing to use the alarm for at least 3 weeks after the child's last wet night can reduce the chance relapse. A child will usually need an alarm for between three and five months.

2. Drug Therapy: i. **Tricyclic Antidepressants:** Tricyclic antidepressants such as Imipramine have been used extensively in the treatment of primary nocturnal enuresis. Probable mechanism of action includes alteration of sleep and arousal mechanism [19], effect on the sympathetic innervations to the bladder and altered secretion of Anti diuretic Hormone (ADH) [20], most plausible and accepted mode of action is anti cholinergic effect to increase bladder capacity and noradrenergic effect that decreases bladder excitability. Imipramine is taken 1 hour before bedtime with duration of action of 8-12 hours. Initial dose is 25 mg, if response is not satisfactory after 1-2 weeks; the dosage can be increased to 50 mg in children 7-12 years of age and 75 mg in older. Eight double blind controlled trials shows cure rate from 10-60 % [21] with a very high relapse rate off drugs (up to 90%). The optimal duration of therapy not determined. Empiric approach is to treat for 3-6 months, then taper in decrements of 25 mg over 3-4 weeks. The lower toxic/therapeutic ratio has raised concerns; side effects include anxiety, nervousness, constipation, personality changes, ventricular tachycardia, coma and seizures.

ii. **Anticholinergic Drugs:** Hyoscamine and oxybutinin: provide an anti cholinergic, antispasmodic effect causing smooth muscle relaxation and decreasing bladder's ability to contract. Oxybutinin not effective significantly in primary nocturnal enuresis [22]. However it has shown good results in children with polysymptomatic nocturnal enuresis [23]. Oxybutinin is given in doses of 5-10mg in children greater than 5 years of age, the drug being given at bedtime. Side effects include dry mouth, flushing, drowsiness and constipation. To date no RCTs using hyoscamine have been published; anecdotal reports indicate a favorable response [24].

iii. **Desmopressin Acetate (DDAVP):** It is a synthetic analog of Arginine Vasopressin (anti diuretic hormone). The drug is tasteless, and well absorbed from the nasal mucosa. The drug is administered intranasally using unit dose, spray pump delivery system. It is rapidly absorbed achieving peak levels in 45 minutes and has a half life of 4-6 hours [22]. Desmopressin is especially useful in patients who lack the normal diurnal rhythm of ADH production (normal children show a night-time increase in ADH production allowing the child to sleep for an extended period). Starting dose for all ages is 20 mcg (one spray into each nostril). Response to therapy is evaluated

after 2 weeks and dose can be increased 10mcg weekly to a maximum of 40 mcg. If more than 12 years of age up to 60 mcg of DDAVP can be administered safely. For any patient who remains dry on given dose, a dose of 10 mcg less should be tried. The subsequent therapy should be continued for at least 3-4 months. Abrupt stoppage of therapy is associated with a high incidence of relapse; therefore it is preferable to taper the dose slowly in decrements of 10mcg per month. Side effects are negligible and include headache, abdominal pain, nausea and nasal discomfort, rarely symptomatic hyponatremia. It is recommended that serum electrolyte levels of patients on this drug should be monitored periodically. Long term therapy with DDAVP has been shown to be safe .now there is switch from spray to tablet from where hyponatremia chance is less. Drug is contraindicated in patients with habit polydipsia, hypertension or heart disease. Several double blinded RCTs shows its efficacy has varied from 10-70 % [25-26]. The major limiting factor for the use of desmopressin is its prohibitive cost & increased relapse rate.

Comparison of treatments for bed wetting [27]:

Modality	Cure rate	Relapse rate	Risks
Alarms	70%	10%	None
Parent Awakening	Up to 90%	20%	None
Imipramine	10-60%	90%	Serious
Desmopressin	12-65%	90%	Mild

Choice of Treatment Modality:

After evaluating the cost, efficacy, side effects and the relapse rates associated with various treatments, the enuresis alarms seem to be most efficacious. Drugs are useful for short term use and it is considered appropriate to use drugs

intermittently in children older than 8 years of age. There is no consensus about which children should be put on continuous medication. After repeated attempts the child does not learn to self awaken then the physician has the option of continued symptomatic cure with drugs, after discussing the potential adverse effects with the parents. Some authors advise that it should be prescribed in older patients who have refractory enuresis and whose parents are unwilling to awaken the children at night. Children who have frequent episodes of enuresis should use a combination of a drug and an enuresis alarm. Combination drug therapy may be tried in patients with refractory primary nocturnal enuresis when neither alarm nor pharmacologic therapy is effective. In such cases combination therapy using 2 or more drugs has been shown to be effective.

X. Conclusions

Repeated (twice a week for 3 consecutive months) discharge of urine into clothes or bed after a developmental age (generally 5 year) when bladder control should be established is known as enuresis. The possible mechanisms include---Genetic Factors, Maturational Delay, Sleep Disorders, Psychological Causes, and Small Bladder. Psychosocial and family histories are important to assess the attitude of parents and the child, in order to select a proper therapy. The physical exam will check the child's general health. An abdominal, genital-urinary, and neurological

exam has to be performed. Treatment of primary nocturnal enuresis can be divided into two major categories: pharmacological and Non-pharmacological. After evaluating the cost, efficacy, side effects and the relapse rates associated with various treatments, Parent awakening & the enuresis alarms seem to be most efficacious. Encourage and support your child. Give praise for things your child does well. Do not punish or make fun of your child for this problem. Involve your child in the treatment plan and give lots of encouragement. Let your child know that other children have this problem too and that there are things that can be done to help. Make sure your child doesn't have a drink within two to three hours of bedtime. Make sure your child visits the toilet just before going to bed. Get your child up at night to go to the bathroom. Avoid chocolate or caffeine. An alarm is used to waken the child when he or she wets the bed. This trains the brain and the bladder to work together so that your child will either hold urine or wake up to pass it. There is no consensus about which children should be put on continuous medication. Sometimes medicine is used to reduce the amount of urine produced at night or to help the bladder hold more urine but relapse rate is very high with drug. Management of secondary nocturnal enuresis depends on cause.

References

1. Allen TD: The non-neurogenic neurogenic bladder. *J Urol* 1977;117: 232-238.
2. Fergusson DM, Horwood LJ, Shannon FT. Factors related to the age of attainment of nocturnal bladder control: an 8-year longitudinal study. *Pediatrics* 1986; 78(5):884-890.
3. Rushton HG. Nocturnal enuresis: epidemiology, evaluation, and currently available treatment options. *J Pediatr* 1989; 114(4 Pt 2):691-696.
4. Rittig S, Knudsen UB, Norgaard JP, Petersen EB, Djurhuus JC. Abnormal diurnal rhythm of plasma vasopressin and urinary output in patients with enuresis. *Am J Physiol* 1989;256(4 Pt 2):664-671.
5. Backwin H. The genetics of enuresis. In: Colvin I, McKeith, RC, Meadow, SR, eds. Philadelphia: Lippincott, 1973.
6. Schmitt BD. Nocturnal Enuresis. *Peds Rev* 1997; 18(6): 183-190.
7. Eiberg H, Berendt I, Mohr J. Assignment of dominant inherited nocturnal enuresis (ENURI) to chromosome 13q. *Nature Genet* 1995; 10:354-356.
8. Wolfish N, et al. Elevated sleep arousal patterns in enuretic boys: clinical implication. *Acta Paediatr Scand*. Accepted for publication.
9. Watanabe H, Azuma Y. A proposal for a classification system of enuresis based on overnight simultaneous monitoring of electroencephalography and cystometry. *Sleep* 1989;12:257-264.
10. Bhatia MS, Kaur N. The problem of bed-wetting. *Nurs J India* 1989;80(7):193.
11. Weider DJ, Sateia MJ, West RP. Nocturnal enuresis in children with upper airway obstruction. *Otolaryngol Head Neck Surg* 1991;105:427-432.
12. Feehan M, McGee R, Stanton W, Silva PA. A six-year follow-up of childhood enuresis: prevalence in adolescence and consequences for mental health. *J Paediatr Child Health* 1990;26:75-79.
13. Mayo ME, Burns MW. Urodynamic studies in children who wet. *Br J Urol* 1990; 65: 641-645.
14. Weerasinghe N, Malone PS. The value of videourodynamics in the investigation of neurologically normal children who wet. *Br J Urol* 1993;71:539-542.

15. Whiteside CG, Arnold EP. Persistent primary enuresis: a urodynamic assessment. *Br Med J* 1975;1:364-367.
16. Marshall S, Marshall HH, Lyon RP. Enuresis: an analysis of various therapeutic approaches. *Pediatrics* 1973;52:813-817.
17. Schmitt BD. Nocturnal enuresis. An update on treatment. *Pediatr Clin North Am* 1982;29:21-36.
18. Parang Mehta - Treatment of Bed Wetting (Nocturnal Enuresis)-www.mehtachildcare.com/misc/enuresis2.htm
19. Kales A, Kales JD, Jacobson A, et al. Effect of imipramine on enuretic frequency and sleep stages. *Pediatrics* 1977; 60:431-436.
20. Rapoport JL, Mikkelsen EJ, Zavadil A, Nee L, Gruenau C, Mendelson W, et al. Childhood enuresis. II. Psychopathology, tricyclic concentration in plasma and anti-enuretic effect. *Arch Gen Psychiatry* 1980;37:1146-1152.
21. Monda JM, Husmann DA. Primary nocturnal enuresis: a comparison among observation, imipramine, desmopressin acetate, and bed-wetting alarm systems. *J Urol*. 1995; 54:745-748
22. Richardson DW, Robinson AG. Desmopressin. *Ann Intern Med* 1985;103: 228-239.
23. Husmann D. Enuresis. *Urology* 1996; 48:184-193
24. Bamford MF, Cruickshank G. Dangers of intranasal desmopressin for nocturnal enuresis [Letter]. *J Royal Coll Gen Pract* 1989;39:345-346.
25. Rittig S, Knudsen UB, Sorensen S, et al. Long-term double-blind crossover study of desmopressin intranasal spray in the management of nocturnal enuresis. In: Meadows SR, ed. Desmopressin in nocturnal enuresis: proceedings of an international symposium. Sutton Coldfield, England: Horus Medical Publications, 1988:43-55.
26. Miller K, Klauber GT. Desmopressin acetate in children with severe primary nocturnal enuresis. *Clin Ther* 1990;12:357-66.
27. Terho P. Desmopressin in nocturnal enuresis. *J Urol* 1991;145(4):818-820

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