

Nocturnal Enuresis In Children

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Abstract

A myriad of disorders lead to a wet child and nocturnal enuresis is not at all unusual in pediatric population. It is a problem that is often ignored by the treating paediatrician, but is a source of psychological stress for the affected child as well as the parents. Increasing attention is now being focussed on the problem but a number of questions regarding the etiology and the management still elude an answer. This article aims at presenting a review of the current information on nocturnal enuresis, including the mechanisms for urinary continence, the etiopathogenesis and the available therapeutic modes, keeping the main focus on primary nocturnal enuresis.

DEFINITIONS

Nocturnal enuresis refers to involuntary passage of urine during sleep by a child old enough to have gained urinary control. The American Psychiatry Association has defined bed wetting as children older than age five who are incontinent of urine at night (1). Some investigators make a distinction between primary and secondary incontinence. Primary incontinence is lifelong bed wetting 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. Polysymptomatic nocturnal enuresis is bed-wetting associated with severe urgency, severe frequency, or other signs of an unstable bladder. Monosymptomatic nocturnal enuresis is associated with normal daytime urination and is easier to treat, as compared to the former.

DEVELOPMENT OF URINARY CONTINENCE

Urinary continence is a normal process of maturation. During the infantile period voiding is a spinal reflex with coordination of the sphincter (2). The bladder fills at low pressure, but not necessarily to capacity and empties in a coordinated manner at the time of voiding with simultaneous contraction of the detrusor and relaxation of the pelvic floor (3). The reflex is coordinated at the level of pontine mesencephalic reticular formation with no voluntary control

or modulation of the process.

Between 2-4 years the children exhibit a transit in period of voiding. During this period toilet training is also initiated leading to creation of a "social awareness" of acceptable time and place for toileting. However the conscious modulation of voiding remains deficient as uninhibited bladder contractions still occur and may produce voiding at less than capacity and at socially inappropriate times. At times the child postpones micturition by contracting the pelvic floor to produce bladder outlet obstruction until the urge to void is suppressed. This attempt to achieve social continence is a voluntary mechanism of vesicosphincter discoordination and is soon abandoned. Abnormal persistence of this voiding pattern beyond this age may lead to dysfunctional voiding (4).

With neurological and behavioural maturation the older child is able to void at less than capacity or postpone voiding until absolute capacity is reached. There are no uninhibited contractions and the voiding is well coordinated with simultaneous pelvic floor relaxation and detrusor contraction.

EPIDEMIOLOGY

The prevalence of nocturnal enuresis has been difficult to estimate because of variations in definition and in social standards (5,6). It is estimated that 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 (7).

ETIOLOGY

ORGANIC ENURESIS

An organic cause to nocturnal enuresis may be elicitable in only 2-3% of the patients. Another 5-10% children have polysymptomatic enuresis which requires specific therapy. The causes of organic enuresis are listed in Table 1.

Figure 1

Table 1: Important Mechanisms and Causes of Enuresis

Polyuria	
1.	Diabetes insipidus
2.	Diabetes mellitus
3.	Sickle cell disease (isotheruria)
4.	Drugs
5.	Alcohol, caffeine intake
6.	Habit polydipsia
7.	Redistribution of mild edema
Nocturnal ADH Deficit	
Highly controversial	
Bladder Irritability	
1.	Urinary tract infection
2.	Food allergies
3.	Constipation
4.	Bladder calculi
5.	Hypercalciuria
Incomplete Bladder Filling	
1.	Fecal impaction
Incomplete Bladder Emptying	
1.	Lower urinary tract obstruction
2.	Neurogenic bladder
3.	Dysfunctional voiding

PHYSIOLOGIC OR PRIMARY NOCTURNAL ENURESIS

It is vital to remember that primary nocturnal enuresis is a diagnosis of exclusion and other causes of bed-wetting must be ruled out. 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 recognise 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 are discussed in detail below:

1. Genetic Factors: A Family history of nocturnal enuresis is found in most children. If one parent was a bedwetter 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 (8). The concordance for identical twins (68%) has also been shown to be higher as compared to fraternal twins (36%) (9). 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 (10).

2. Maturation 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. The proponents of this theory cite the spontaneous cure with increasing age as evidence in support of their postulate.

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 (11). Sleep EEG studies have also reported an association of nocturnal enuresis with slow brain-wave activity in children (12). On the contrary other investigators have demonstrated that bedwetting may occur at different stages of sleep (13) 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 (14).

4. Psychologic 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 behaviour pattern as normal children (15). 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.

The impact of psychological problems primarily manifests as poor compliance with the treatment regime. Also enuresis itself may lead to lowered self-esteem and psychological problems in the 'wet' child.

5. Small Bladder Capacity: Some studies (16, 17) have found functional bladder capacity to be low in patients with nocturnal enuresis. These findings have been questioned by other investigators (18). 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.

OFFICE EVALUATION OF A WET CHILD

The evaluation is aimed at detection of organic enuresis. It is also important to consider the patient's age, the severity of the problem, the perception of seriousness of illness by the family and the acceptability of treatment.

1. Urinalysis

- a) Specific gravity (s.g.>1.015 rules out diabetes insipidus)
- b) Glucose (for diabetes mellitus)
- c) Urine culture, if symptoms of urinary tract infection are present, or the patient has had a UTI in the past.

2. Radiologic studies are not necessary in all children with straightforward primary nocturnal enuresis.

- a) Micturating 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.

Radiologic studies are also done in infant and young children with UTI to rule out structural abnormalities.

MANAGEMENT

Before starting management the physician should keep in mind that children younger than six years with enuresis and

other urologic problems do not require an evaluation. However parents need to be reassured that bedwetting is due to maturational delay and any punishment is unwarranted. Treatment modalities require consistent support and cooperation from the child and the family and are unlikely to succeed in their absence.

It is also important to preserve the child's self esteem till appropriate therapy is established.

Consistent follow up is essential to assess the results of the intervention. Improvement is defined as a 50% reduction in the number of nights that bedwetting occurs. Resolution is defined as only one or two wet nights over a three-month period, and documentation that the child wakes up spontaneously to void.

TREATMENT FOR ORGANIC ENURESIS

Diurnal enuresis deserves a detailed evaluation. Children with recurrent UTIs are given prophylactic antibiotics. Children with chemical urethritis must be advised to avoid soaps and other irritants. In atopic patients with diuresis, the aggravating food allergies should be eliminated from the diet. Children who have associated constipation need this symptom treated first.

Treatment of primary nocturnal enuresis can be divided into two major categories: pharmacological and non-pharmacological.

NON-PHARMACOLOGIC METHODS

This includes motivational therapy, behaviour modification, bladder training exercises, diet therapy and hydrotherapy.

Motivational Therapy: This involves reassuring the child and the parents and providing them emotional support. The child is to be reminded that enuresis is not the parents' or the physician's problem but something which they can solve. Positive reinforcement with a reward system for each dry night should be instituted. 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 (19).

Awakening Programs: Older children should be made to understand that every wet night represents a night that they should have got up to void. One technique of self awakening is to rehearse a sequence of events before going to sleep where the child pretends to be fast asleep in the middle of the night and the full bladder starts to hurt. The child then

gets up to empty the bladder. A similar approach can be adopted for a daytime rehearsal. Another approach uses self hypnosis with the suggestion that the child wake up to use the bathroom in the night. Investigators have reported upto a 77% cure rate with this approach (20). If self awakening fails, parent awakening is indicated. However it should be emphasized that the parent must not carry the child to the toilet but the child must be awakened and made to locate the bathroom. Azun and Thienes (21) have described a laborious technique in which the child is woken up at hourly interval on the first day until 1 AM. If the child is dry he/she is praised and enquired about the need to void on each awakening. A wet child is asked to change the bedclothes and pyjamas. On the last awakening (at 1AM) the child is asked to try to void even if dry. The next night the child is woken up only once, 3 hours after falling asleep. This interval is gradually decreased till the child is woken up 1 hour after falling asleep. After the sixth night the child is left to self awaken. The authors of this technique have reported a cure rate of 92% in wet children.

Enuresis Alarms: 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. Alarm therapy requires a motivated child and family. Use of a reward system for positive reinforcement with alarms may help attain the desired results. Long term success rate using alarm devices has been reported to be 70% (22). The alarm devices must be used until the child experiences at least 3 weeks of complete dryness for lower relapse rate.

Bladder Training Exercises: In children with a small bladder capacity the use of bladder retention training by asking the child to hold his urine for increasing periods of time during daytime may help increase the bladder capacity at night (23).

Hypnotherapy, diet therapy and physiotherapy have not been extensively used. Hypnotherapy and psychotherapy has been successful in limited trials. Diet therapy has been successful in some patients. Enuresis inducing food agents include caffeine containing products, dairy products, chocolates, citrus fruits and juices (24).

DRUG THERAPY

Several drugs have been used for the treatment of nocturnal enuresis. None of these agents offer a definitive cure but may provide a stopgap measure until the child is able to wake up in the night to void. Drug therapy is often reserved for children who have not responded to other treatment options.

1. **Tricyclic Antidepressants:** Tricyclic antidepressants such as Imipramine have been used extensively in the treatment of primary nocturnal enuresis. The postulated mechanism of action includes alteration of sleep and arousal mechanism (25), effect on the sympathetic innervation to the bladder and altered secretion of Antidiuretic Hormone (ADH) (26). The most plausible and accepted mode of action is anticholinergic effect to increase bladder capacity and noradrenergic effect that decreases bladder excitability. Imipramine is taken 1 hour before bedtime with a duration of action of 8-12 hours. The initial dose is 25 mg and if response is not satisfactory after one or two weeks the dosage can be increased to 50 mg in children 7-12 years of age and 75 mg in older children. Eight double blind controlled trials using imipramine have reported a cure rate from 10-60% (27) with a very high relapse rate off drugs (upto 90%). The optimal duration of therapy has not been determined but the empiric approach is to treat children for 3-6 months and then taper the drug in decrements of 25 mg over 3-4 weeks. The lower toxic/therapeutic ratio of imipramine has raised concerns; side effects include anxiety, nervousness, constipation, personality changes, ventricular tachycardia, coma and seizures.

2. **Anticholinergic Drugs:** Drugs such as hyoscamine and oxybutinin provide an anticholinergic, antispasmodic effect causing smooth muscle relaxation and decreasing bladder's ability to contract. Hyoscamine is available in timed release capsules which are effective for 8 weeks. To date no RCTs using hyoscamine have been published; anecdotal reports indicate a favourable response (28). The dose of the extended release form is 0.375 mg, to be given at bedtime. Oxybutinin is given in doses of 5-10mg in children greater than 5 years of age, the drug being given at bedtime. Oxybutinin in recent controlled trials did not increase the number of dry nights significantly in children with primary nocturnal enuresis (29). However it has shown good results in children with polysymptomatic nocturnal enuresis (30). Side effects include dry mouth, flushing, drowsiness and constipation.

3. **Desmopressin Acetate (DDAVP):** It is a synthetic analog of Arginine Vasopressin (antidiuretic hormone) with a specific antidiuretic effect on the distal tubules, and an extended duration of action. 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 (29). 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).

The starting dose for all ages is 20 mcg (one spray into each nostril). The response to therapy is evaluated after 2 weeks and the dose can be increased by 10mcg weekly to a maximum of 40 mcg. In patients 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.

The side effects of desmopressin are negligible and include headache, abdominal pain, nausea and nasal discomfort. Two cases of symptomatic hyponatremia on DDAVP therapy have been reported (28, 31); hence it is recommended that serum electrolyte levels of patients on this drug should be monitored periodically. The drug is contraindicated in patients with habit polydipsia, hypertension or heart disease. Long term therapy with DDAVP has been shown to be safe. The efficacy of desmopressin in several double blinded RCTs has varied from 10-70% (32, 33, 34). Desmopressin may be used on as-needed basis in patients who have responded to it and need temporary relief to overcome difficult psychological situations. The major limiting factor for the use of desmopressin is its prohibitive cost.

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 because the cure is permanent, cost is low with no significant side effects. Drugs are useful for short term use and it is considered appropriate to use drugs intermittently in children older than 8 years of age.

Children who have frequent episodes of enuresis should use a combination of a drug and an enuresis alarm. The drug reduces the necessity of awakening at night and alarm provides the backup. After the child is dry for more than 3 weeks the drug can be tapered gradually.

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.

There is no consensus about which children should be put on continuous medication. 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. The duration of therapy in such cases presents a dilemma because most of such patients tend to relapse when medication is stopped. Such patients are advised to reinstate alarm therapy every 6 months and attempt to taper the medication. If even 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.

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