REVIEW ARTICLES

NOCTURNAL ENURESIS

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INTRODUCTION

Enuresis, from the greek word 'enourein', to void urine,is the involuntary discharge of urine. Enuresis refers to the persistence of inappropriate voiding of urine beyond the age of anticipated bladder control (age 4 to 5 years at the latest). Diurnal enuresis is involuntary leaking of urine during waking hours. Nocturnal enuresis refers to involuntary passage of urine during sleep and is classified as primary (no prior period of sustained dryness) or secondary (recurrence of nighttime wetting after 6 months or longer of dryness) [1]. Recent urology literature describes another classification of nocturnal enuresis based on the presence or absence of other bladder symptoms. Monosymptomatic nocturnal enuresis (MNE) is defined as a normal void occurring at night in bed in the absence of any other symptoms referable to the urogenital tract, and it precludes any daytime symptomatology. Polysymptomatic nocturnal enuresis (PNE) is bed-wetting associated with other bladder symptoms such as urgency, frequency, instability, or voiding dysfunction. Investigations of patients who have MNE reveal that they are clearly different from patients who have PNE [2-4].

Epidemiology

Parents may become concerned about nocturnal enuresis when their child reaches 5 to 6 years of age and is preparing to enter school. Most children are not concerned until 7 to 8 years of age. Approximately 80% to 85% of children who have nocturnal enuresis have MNE [4]. Another 5% to 10% of cases meet the definition of PNE, with daytime wetting or other bladder symptoms. Organic causes are responsible for nocturnal enuresis in fewer than 5% of cases. Such organic causes must be searched for and ruled out if the history suggests their presence. There is a slight male predominance (about 60% overall) for nocturnal enuresis [1]. Etiologic factors contributing to MNE include genetics, sleep arousal dysfunction, urodynamics, nocturnal polyuria, psychological components, and maturational delay. That the condition probably is multifactorial, with various contributing factors in any one patient, confounds attempts to base therapeutic approaches on etiology. Approximately 25% to 30% of children with bed wetting are "secondary" enuretics who achieved a dry interval of at least several months and then reverted back to bed wetting [5].

Many old books and articles define enuresis in children at age 5 years, which means 15% or more would need evaluation and treatment, which is not practical. Most of the children at this age spontaneously resolve their bed wetting by age 8 years. Moffat concludes that enuresis does not interfere with socialization until age 7 years. Anxious parents of 4 and 5 year-old can be assured.Children who remains enuretic past the age of 8 years have a significant risk of never resolving their symptoms [6].

Genetics

A hereditary basis for nocturnal enuresis has been suspected for years. Studies of twins show a concordance rate of 43% to 68% for monozygotic and 19% to 36% for dizygotic twins [7]. Seventy percent of children who have enuresis have a parent who has a history of the disorder. Studies indicate that if one parent had enuresis, the probability of a child having it is approximately 40% to 45% [7]. If both parents were affected, the probability of a child having the condition increases to 70%

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to 77%. If neither parent had enuresis, only 15% of offspring will have enuresis [8]. Chromosomes 12q, 13q, and 22 all have been named as possible locations of a gene(s) resulting in enuresis, but a specific mechanism for enuresis related to a gene locus is not known.

Normal Bladder and Continence Development

Central to any discussion of enuresis is an understanding of development of continence. Bladder storage and evacuation require the activity of sympathetic, parasympathetic, and somatic voluntary nerves coordinated by the spinal cord, brainstem, midbrain and higher cortical centers. Infant empty their bladders about 20 times per day, roughly 40% of which occurs during sleep [9]. Infants aged 6 months feature a decrease in frequency of micturition and an increase in voided volumes. Between 1 and 2 years of age, children achieve conscious sensation of bladder fullness, and ability to inhibit voiding voluntarily is achieved in second or third year of life. By 4 years of age, most children have achieved an adult pattern of micturition [10].

Causes of Enuresis

Children with nocturnal enuresis are similar to healthy children except that they involuntary void without waking. There are many proposed causes for enuresis, and the condition may be multifactorial in any child.

Caffeine

The diuretic activity of caffeine is well documented. Consumption of caffeinated soft drinks has grown more than 500% since 1950. Most marketed drinks contain between 2.5 and 5.0 mg/fl oz. A typical 12 oz can thus contains 30 to 60 mg, with a maximum of 72 mg of caffeine per can (e.g., Mountain Dew). A pharmacologic dose of caffeine is approximately 2 mg/ kg. Thus a 30-kg child receives a pharmacologic dose of caffeine in each 12 oz can of soft drink. Chocolate and cocoa also contains caffeine. Most patients who failed previous treatments state that they have not been advised medically to give up caffeine [11].

Functional Bladder Capacity

Bladder capacity in children is related to age and it increases as children grow. Functional bladder capacity in children may be estimated by the formula: age in years plus 2, which gives bladder capacity in ounces [12]. By adolescence, this no longer applies; adult bladder capacity is approximately 10 to 15 oz. Children who have small bladder capacities probably represent a subgroup of patients who have MNE and presumably cannot hold the normal amount of urine produced at night. They are more likely to report frequent daytime voiding, some nights with multiple episodes of enuresis per night, and no history of attaining dryness. Low functional bladder capacity occurs in almost all enuretic children [13,14]. Increasing functional bladder capacity is, therefore, a committed therapeutic goal.

Dysfunctional Voiding

Children with functional voiding disorders typically see a doctor because of complaints related to incontinence, usually diurnal or infection. Bed-wetting children who are dysfunctional voiders often have other signs and symptoms [11].

Relative Nocturnal Polyuria and Antidiuretic Hormone Secretion

Poulton, proposed relative nocturnal polyuria as a factor in enuresis [15]. It has long been observed that less urine is secreted at night than during the day. ADH is secreted in the hypothalamus, stored in posterior pituitary, and released by factors such as elevated serum osmotic pressure and low fluid volume. The altered circadian ADH expression does seem to play a causative role in some children with enuresis [15-17].

Infection

It has been found that relapsed enuretics, particularly girls, are more likely to have a significantly irritated bladder secondary to cystitis cystica [18]. In this scenario, the urine culture is commonly negative and, therefore misleading. Pinworm is an important cause associated with sudden onset enuresis, which in this setting readily responds to antihelminthic therapy [19].

Maturational Lag, Delayed Development and Psychological Factors

Achieving nocturnal urinary control is a normal part of child's development and may be delayed by nonorganic internal or external factors. Enuresis, therefore, can be thought of as a maturational arrest. Bed-wetting is more common in lower socioeconomic groups. Children in families subject to stressful circumstances have a three fold high risk for enuresis [20]. The second through fourth years are a particularly sensitive time for the development of nocturnal bladder control, and anxiety-producing episodes during this time increase the risk for enuresis.

Although children with enuresis do not exhibit evidence of neurologic disease and their neuroanatomic pathways are considered intact, there is subtle evidence of maturational lag separate from enuresis. There may be evidence of passivity, late walking, delayed speech, and general clumsiness.

Psychopathology is uncommon among enuretic children. These children may be subject to abuse and wrongfully punished. Shame and embarrassment are important elements in the lives of enuretic children [21].

Sleep Disorders

The relationship of sleep patterns with enuresis is an area of active research. In some studies, the enuretic event seemed to occur during nonREM sleep and could occur during any part of the night. In others, enuresis reportedly was caused by a mild disturbance in arousal, based on the finding that activation of the arousal center preceded correctly, but the transition from light sleep to complete awakening was not achieved properly. In a subset of patients, the arousal center in the brain failed to activate, despite proper full bladder sensation [22]. There is conflicting evidence that children who have enuresis may exhibit other parasomnias, such as sleepwalking and night terrors. A recurrent theme in sleep research is the child's inability to recognize the sensation of a full bladder during sleep and failure to awaken from sleep to urinate in an appropriate place. There appears to be a maturational pattern of progressive central nervous system "recognition" of bladder fullness and control over the micturition reflex.

EVALUATION

History

In addition to a detailed toilet training history, a family history of enuresis should be sought because it rarely is volunteered, even when known by a parent. Other pertinent details of a history include the onset and pattern of wetting, voiding behavior, sleep pattern, parasomnias, medical conditions, daytime urinary symptoms, bowel habits, and psychosocial factors. It also is important to assess both the family's and the patient's attitude toward the bed-wetting and their readiness to initiate and continue treatment. Questions about voiding patterns may reveal urgency or a history of small, frequent voids that suggests bladder instability or small bladder capacity. Organic causes of enuresis may be apparent by a history of dysuria (urinary tract infection), polyuria and polydipsia (diabetes insipidus or mellitus), encopresis (constipation), abnormal urine stream (lower obstructive lesions), gait disturbances (spinal cord pathology), or nighttime snoring (adenoidal hypertrophy). A thorough and thoughtful history is the means by which the infrequent organic causes of

enuresis are separated from the majority of cases that have no organic etiology.

Physical Examination

Most children who have nocturnal enuresis will have normal findings on physical examination. In addition to assessing the child's height, weight and blood pressure, perform a complete examination, paying careful attention to the urogenital, neurologic, and gastrointestinal systems. A palpable bladder or palpable stool may be present on abdominal examination, ectopic ureter or signs of sexual abuse on urogenital examination, or abnormal gait apparent during neurologic examination. Cremasteric, anal, abdominal, and deep tendon reflexes that reflect spinal cord function all should be tested. The skin of the lower back should be inspected for the presence of a sacral dimple, hair patches, or vascular birthmarks, which can be clues to spinal dysraphism. Mouth breathing may suggest sleep apnea with associated enuresis due to adenoidal hypertrophy. Direct observation of the urinary stream in the office is important, especially if findings on the history suggest an abnormality. The family can measure bladder capacity at home prior to the initial evaluation or it can be measured in the office by having the child drink 12 oz of fluid on arrival, then voiding into a calibrated cup.

Laboratory and Radiographic Testing

All children who have enuresis should have urinalysis of a clean-catch midstream urine specimen. The ability to concentrate urine to 1.015 or greater rules out diabetes insipidus and the absence of glucose rules out diabetes mellitus as causes of nocturnal enuresis. A urine culture should be obtained for symptoms suggestive of urinary tract infection on history or findings on urinalysis. Bladder sonography to measure post void residual urine. PNE may require further evaluation with voiding cystourethrography (VCUG), renal and bladder ultrasonography, or urodynamic testing. When enuresis is resistant to treatment and the history suggests a sleep disorder, a sleep study may be useful to look for sleep apnea or parasomnias.

Treatment

Treating enuresis can be frustrating for parents and children and taxing on physicians. Parents need to be made to understand that the problem of bed-wetting may resolve with time and that their children are not at fault for wet episodes. All parties are dismayed if a child relapses after treatment, but parents must be made aware of the significant rate of it before initiating treatment. An important factor in any pediatric treatment is the child's motivation and acceptance. Parents also must support the child and the treatment program for maximal effectiveness. The child's age is a critical factor when formulating a treatment plan [23].

BEHAVIOR MODIFICATION

Responsibility Reinforcement

Motivational therapy promotes behavior modification by making the child responsible for his or her enuresis and crediting for successful dry nights. To initiate motivational therapy, a number of interviews are necessary to counsel the child to become an active participant in the treatment program. A record of child's progress is kept with a gold star or some other motivational reward given for each dry night. The success rate of motivational therapy is estimated to be as high as 25%. Responsibility reinforcement is a useful part of multicomponent treatment programs [24].

Fluid Intake Programs

Out of desperation, parents may attempt to limit fluids, which is often ineffective and may create hostility between the parent and child. The child's fluid requirements are calculated, and the parents and child are instructed to achieve the fluid requirement in the following way: 40% of fluid intake in the morning, 40% in the afternoon and 20% in the evening. This distribution helps to promote

healthy drinking habits while seeking to decrease urine production at night time and therefore decrease wet episodes [23,24].

Bladder Training

Retention-control training exploits the observation that many children with enuresis have decreased functional bladder capacity. Bladder retention training therefore proposes to affect enuresis by increasing bladder capacity, which is achieved by asking to hold urine for successively longer intervals after first sensing an urge to void. Caffeinated beverages and certain foods (e.g., dairy products, citrus juices, chocolate) should be restricted as much as possible especially during evenings and night.

Arousal Systems

Bladder alarms first were used by Pfaundler in 1902. Current models use transistor technology and a few drops of urine are all that is required to activate the system. Ideally the child then awakens, inhibits voiding, gets out of bed, and goes to toilet to complete voiding. Controlled trials have shown the alarm system to be effective in 40% to 70% of children. Relapse occurs in as many as 20% to 30% of patients [25]. It is recommended that treatment should continue until 4 dry weeks are achieved. Success requires a child to be motivated and parents to be willing to get up with their children several times per night [26]. Depending on the model it costs between $30 and $60, but its availability in Pakistan is not assured. Several studies comparing alarm systems with medical therapy have been performed, and the conditioning therapy is reported to be more effective [26].

DRUG THERAPY

Antibiotics

Girls older than 5 years of age may have resolution of enuresis after treatment with antibiotics for any detected UTI or bacteriuria [18]. Any boy in this age group with an infection warrants further evaluation for a cause of infection. A small group of patients with symptoms of bladder instability and no evidence of infection may respond to antibiotic therapy. It is thought that these patients (usually girls) may suffer from cystitis cystica.

Tricyclic Antidepressants

Tricyclic antidepressants have been used to treat enuresis since the effect of Imipramine on bed-wetting was observed in 1960 by MacLean. It appears to increase bladder capacity through a weak anticholinergic effect and also may decrease detrusor muscle contractions via noradrenergic effects. The starting dose is 25 mg taken 1 hour before bedtime for children ages 6 to 8 years and 50 to 75 mg for older children and adolescents. The duration of action is 8 to 12 hours. The dose may be increased in 25-mg increments weekly up to 75 mg. Therapy may continue from 3 to 9 months, with a slow tapering of medication recommended over 3 to 4 weeks in 25-mg decrements. Imipramine is relatively inexpensive, and the clinical response is usually apparent during the first week of treatment. The initial success rate (dry at 6 months post treatment) is reported to be 15% to 50%, but the relapse rate is high following drug discontinuation [27,30]. When used at the recommended dosage, mild side effects include irritability, dry mouth, decreased appetite, headaches, and sleep disturbances. An accidental or intentional overdose, however, can have serious and potentially lethal effects, including ventricular dysarrhythmias, seizures, and coma. Because of its narrow toxic/therapeutic ratio, some clinicians are understandably reluctant to use imipramine to treat a relatively benign condition such as nocturnal enuresis in young children. If imipramine therapy is selected, physician must counsel the family carefully about the dangerous potential of its accidental ingestion, safe storage of the drug, and supervision of the child taking the medication.

Desmopressin Acetate (DDAVP)

DDAVP is a synthetic analog of arginine vasopressin (ADH). Acting on the distal tubules of the kidney, it increases water reabsorption in the collecting ducts, producing a more concentrated, lower volume of urine. The use of DDAVP to treat nocturnal enuresis is based on the observation that some children who have enuresis do not have the normal nocturnal rise in ADH production, potentially leading to polyuria. DDAVP theoretically reduces urine volume at night in such children, who thereby can avoid a full bladder at night. DDAVP is available in an oral form and a nasal spray. The bioavailability is only 1% for the tablet and 10% for the nasal spray. Its duration of action is extended (approximately 10 to 12 h) and it is rapidly absorbed from the nasal mucosa. The initial dose of DDAVP is 20 mcg or one 10-mcg puff in each nostril within 2 hours of bedtime, regardless of the patient's age. The dose may be increased in increments of 10 mcg every 1 or 2 weeks up to a maximum dose of 40 mcg. The response to DDAVP usually can be evaluated within a few days of starting therapy. Patients may remain on medication for 3 to 6 months and then should begin a slow decrease of the dose by 10 mcg/mo. If a child remains enuretic after 6 months of therapy, combination therapy may be considered [28]. Side effects of DDAVP are rare and include abdominal discomfort, nausea, headache and epistaxis. Symptomatic hyponatremia with seizures has been reported very rarely, usually in the context of exceeding the recommended dosage. Nonetheless, nighttime fluid restriction is a reasonable recommendation for those receiving DDAVP. Various studies show immediate response rates as high as 70% and relapse rates as high as 95%. Moffat et al reviewed 18 controlled studies of DDAVP and found overall that only 25% of children were completely dry on the medicine, with a relapse rate similar to that noted previously [29-31]. The main limiting factor in using this drug is it's high cost which may exceed Rs.3000.00 a month.

Anticholinergics

Anticholinergic drugs have been found to be largely ineffective in children monosymptomatic primary nocturnal enuresis. The effectiveness in anticholinergic drug therapy has been reported to range from 5% to 40%, no better than placebo. These drugs are effective in patients with PNE.

Age-related Treatments and Recommendations

As a condition that has no single etiology and various causal factors in any one patient, it is not surprising that a single method of treating nocturnal enuresis is often of limited success. Age-related strategies that combine more than one treatment may improve response rates.

Younger than Age 8 Years

For young children and their parents, reassurance and education about enuresis are of utmost importance. They must understand that nocturnal wetting is not the child's fault. There is no place for ridicule or a punitive approach to the problem by parents, siblings, or peers. Previously described motivational and behavioral methods that assist the child in waking to void and that praise successful dryness suit this age group best.

Ages 8 Through 11 Years

For children who still have nocturnal enuresis at this age and for whom the child and family request an intervention, the enuresis alarm gives the best results in terms of response rate and low relapse rate. This also is the age at which intermittent use of medication such as DDAVP can be useful for special events such as an overnight at a friend's home or a camping trip.

Ages 12 Years and Older

Because of the emotional impact of persistent bed-wetting in adolescence, aggressive intervention is indicated. If use of

an enuresis alarm does not stop or greatly reduce the wetting episodes, continuous use of medication is justified as additional treatment. When 2 months of dryness using the combination of alarm and medication are achieved, the medication should be tapered gradually while continuing to use the enuresis alarm.

SUMMARY

Nocturnal enuresis is a common problem seen by the primary care physician. It remains a source of considerable anxiety for the child, parents, and sometimes the pediatrician. In spite of several decades of research, no single explanation or classification of enuresis is sufficient. The nocturnal wetting episode occurs when the child does not awaken during sleep at a time when urine volume exceeds functional bladder capacity, due either to excess urine production, small bladder capacity, or both. This perspective requires the practitioner to take a careful history for polyuria, sleep dysfunction, and daytime bladder symptoms to devise the best treatment for each child. Although a spontaneous cure rate of 15% per year can be expected, intervention may benefit some children through earlier attained dryness and improved self-esteem. Behavior therapies, including alarm systems, have the best long-term results, but they require strong family commitment and do not offer immediate results. Medication has a better short-term cure rate than motivational/behavioral therapy, but relapse rates are high when drugs are discontinued. A combination of behavioral therapy and pharmacotherapy is reasonable if monotherapy fails. The ultimate goal is for the child to maintain nighttime dryness or to self-awaken to void at night.

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