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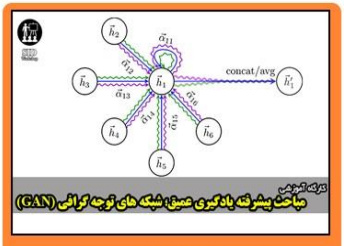

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Primary Nocturnal Enuresis: A Review

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Abstract

Context: Nocturnal enuresis or bedwetting is the most common type of urinary incontinence in children. It has significant psychological effects on both the child and the family. Enuresis nocturna is defined as the inability to hold urine during the night in children who have completed toilet training. It is termed as being "primary" if no continence has ever been achieved or "secondary if it follows at least 6 months of dry nights. The aim of this review was to assemble the pathophysiological background and general information about nocturnal enuresis.
Evidence Acquisition: This review was performed by evaluating the literature on nocturnal enuresis published between 1970 and 2015, available via PubMed and using the keywords "nocturnal enuresis," "incontinence," "pediatric," "review," and "treatment."
Results: Children with nocturnal enuresis produce urine at higher rates during the night, and may have lower bladder capacities. Some children with nocturnal enuresis may also have daytime urgency, frequency, and urinary incontinence. Treatment includes aggressive treatment of accompanying constipation or urinary tract infections, behavioral changes, and medical therapy. Alarm therapy remains the first-line treatment modality for primary nocturnal enuresis. High rates of patient compliance and relapse mean that alternative treatments remain on the agenda.
Conclusions: Nocturnal enuresis is a common problem that has multifaceted effects on both the child and the family. Due to multiple etiologic factors, nocturnal enuresis is still not clearly defined.

Keywords: Nocturnal Enuresis, Incontinence, Pediatric, Review, Treatment

1. Context

Enuresis is defined as the voluntary or involuntary wetting of clothes or bedding with urine for a period of at least 3 consecutive months in children older than 5 years of age. The generally accepted definition, suggested by the American Pediatric Academy, is the involuntary wetting of clothes or bedding by urine during the daytime or nighttime (1). Nocturnal enuresis is more commonly observed in children. It may negatively affect the child's psychosocial development as well as interfere with the development of self-confidence and the ability to socialize.

2. Epidemiology

While many theories have been put forward, the exact etiology of enuresis is still not clearly understood. It is thought that many combined and separate factors may lead to the development of enuresis. The etiology of nocturnal enuresis is multifactorial (2) and is seen more frequently in girls. It is observed in more than 15% - 20% of children by the age of 5, which decreases to 1%- 2% by the age of 17. The spontaneous recovery rate is reported to be 14% per year (3). A positive family history is reported in many children. One study reported that the presence of enuresis in children of sufferers is as high as 77%. It has also been reported that children of parents who did not suffer from enuresis have a 15% risk of developing enuresis, with this rate increasing to 44% if one parent previously suffered from enuresis (4). When children with enuresis and those without were compared, family history was found to be positive in 48.5% (227/468) and 19.4% (1,246/6,421), respectively (5).

Von Gontard et al. determined that genes 8q, 12q, and 13q are responsible for the tendency to develop enuresis (6). Aside from a positive family history, the number of siblings, birth sequence, family's education and economic status, male gender, number of individuals in the family, constipation, and previous history of urinary tract infection have been found to be associated with nocturnal enuresis (7).

3. Three Main Factors in the Pathophysiology of Enuresis

3.1. High Nocturnal Urine Production

Due to the discordance between nocturnal urine production and bladder capacity, the bladder may easily fill at night, leading to the awakening of the child for urination or in children with trouble awakening, incontinence (8). Under normal conditions, nocturnal vasopressin secretion is higher than in the daytime. This leads to 50% less urine production during the night (2).

Additionally, inadequate secretion of the antidiuretic hormone (ADH), which also leads to the production of

more urine, has been seen in these children. The frequency of this is thought to be around 2 out of 3 children (9).

3.2. Nocturnal Low Bladder Capacity or Increased Detrusor Activity

Recently, the Koff hypothesis has been used to attempt to explain the mechanisms of dysfunction in enuresis. Taking into account this hypothesis, researchers in one study found that patients with primary nocturnal enuresis (PNE) have a functional bladder capacity corresponding to 70% of the expected capacity. An increase in bladder wall thickness was also found with ultrasonography of the same patients (10). In another study of children with PNE, electroencephalography (EMG) and cystometry records demonstrated that bladder contractions could not be inhibited in 30%- 32% of enuretic children, and that this lead to their enuresis (11).

3.3. Arousal Disorder

Enuresis may be more correctly analyzed as a problem with awakening from sleep. This problem with awakening has been a focus point in enuresis. In normal children, when the bladder reaches maximum capacity, there is a sudden urge for urination that does not occur correctly in enuretic children. The exact cause behind this mechanism is not known, although some researchers suggest that chronic over-stimulation leads to downregulation of the voiding center (12).

4. Classification of Nocturnal Enuresis

The ICCS classifies enuresis as primary or secondary. Most children with nocturnal enuresis fall into the primary group. Children who have at least 6 consecutive months of normal urinary control followed by commencement of enuresis are considered to have secondary enuresis, which is generally associated with underlying pathologies.

Nocturnal enuresis can be separated into two types:

4.1. Primary Nocturnal Enuresis

Children without a period of 6 consecutive months of nighttime urinary control. This is the most common form.

4.2. Secondary Nocturnal Enuresis

Children with a period of 6 consecutive months of nighttime urinary control before incontinence. Enuresis in this group is associated with organic or psychological causes.

Childhood nocturnal enuresis may also be classified as monosymptomatic or non-monosymptomatic (1).

While children with monosymptomatic nocturnal enuresis (MNE) do not have any daytime symptoms, children with non-monosymptomatic nocturnal enuresis present with urge, frequency, or incontinence due to enuresis. Patients with nighttime wetting plus urge, incontinence, and frequency are considered to have polysymptomatic nocturnal enuresis. More than 80% of patients with enuresis are monosymptomatic. Although it is reported that 25% of patients with PNE are monosymptomatic, the rate may be higher due to the low reporting of daytime symptoms by patients or their parents (13).

5. Work Up

5.1. Urinalysis and Urine Culture

Urinalysis is important for the evaluation of children with lower urinary tract dysfunction (14). Proven urinary tract infection, such as the presence of bacteriuria or pyuria on urinalysis, may require a further radiological workup.

Concentration of a daytime first urine sample may give information regarding renal function, as well as help with the diagnosis of diabetes in the presence of glucosuria. The presence of hematuria may also require a further radiological workup.

5.2. Urinary System Ultrasonography

Urinary system ultrasonography should be performed on all patients with daytime incontinence. Ultrasonography (USG) is important for the detection of renal or bladder abnormalities such as hydronephrosis, ureteral dilatation, ureterocele, and increased bladder wall thickness. It has recently been suggested that measurement of bladder wall thickness is important in the identification of bladder dysfunction. Increased bladder wall thickness is reported in women with detrusor overactivity and children with non-neuropathic bladder sphincter abnormalities (15,16). However, when considering bladder wall pathologies in children with PNE, there is a continuing debate (17). Charalampous et al. demonstrated the value of measuring bladder wall thickness in children with PNE. They also reported that USG may be beneficial for determining the presence of underlying bladder dysfunction (18).

In children with recurrent or febrile urinary tract infections, or where USG has demonstrated increased bladder wall thickness, voiding cystourethrography should be performed (5).

5.3. Urodynamic Studies

Urodynamic studies generally reveal storage problems such as low bladder capacity and decreased bladder compliance or detrusor overactivity in patients with primary enuresis (19-21). Urodynamic study is especially useful for demonstrating neurogenic bladder or outlet obstruction in children with enuresis. Recently it has been demonstrated by urodynamic studies that 25–73% of adults with PNE have bladder dysfunction (22).

6. Approach to Treatment of a Child with Nocturnal Enuresis

First-line treatment of PMNE involves education and giving information on enuresis. In such cases, the spontaneous resolution rate has been shown to be 15% (23).

6.1. Nonpharmacological Treatment

6.1.1. Urotherapy

First-line treatment involves simple behavioral changes such as carrying the child to the toilet at night or awakening him or her for urination, along with daily motivation and exercises aimed at increasing bladder capacity. In children, non-surgical and non-pharmacological methods that correct voiding habits (24) must be the backbone of any treatment (25).

Standard urotherapy (24) involves educating families regarding enuresis and its treatment, offering suggestions for voiding patterns and frequency, limiting fluid intake, and treating constipation when present. The early diagnosis and treatment of constipation not only improves enuresis, but untreated constipation may also lead to treatment refractory enuresis (26).

6.1.2. Limitation of Fluid Intake

Although limiting fluid intake is routinely advised to all patients with enuresis, its efficiency has not been proven (27). Similarly, avoidance of drinks with a diuretic effect (such as those containing caffeine) is advised, although the effect of this has also not been investigated (28).

6.1.3. Bedwetting Alarms

This treatment modality is based on conditioning. It is especially effective in children with difficulty awakening. This modality works by teaching or conditioning the child to awake for urination before bedwetting occurs (29). Alarm treatment can also be defined as a training program designed to increase night-time bladder capacity (30). Alarm treatment is effective in MNE and should be the first treatment choice in children under 8 years of age with adequate family support and no nocturnal polyuria (31).

Alarm therapy teaches children to hold their urine during sleep and awake for urination. It is also the first-line treatment for PMNE (29). There are many types of alarms. Bed pads, bed bells, and oscillators that vibrate when wet have all been shown to have similar effects. Bed pads are placed on the child's bed and give increasing severity of stimulation (sound, vibration etc.) as they come in contact with urine. Their effect must be evaluated after a period of at least 6 - 8 weeks of use, and alarm therapy must be continued for at least 14 dry nights before being discontinued. Treatment success rates are reported to be between 65 - 75%, although 10 - 30% of families are also reported to discontinue treatment on their own (32).

When compared to desmopressin and other behavioral treatments, alarm therapy has been shown to be more effective at decreasing bedwetting episodes (29). Although the treatment success of desmopressin appears to be higher, the recurrence rate after discontinuation is also higher. In children who have benefitted from alarm therapy, increasing nighttime fluid intake has been shown to decrease recurrence rates through overlearning. Alarm therapy may not be appropriate for use in children without toilet training or those with developmental disabilities (29). Despite the lack of clinical data, it appears that the effectiveness of alarm therapy is higher when compared to other methods such as awakening, reward systems, urine-holding exercises, dry bed, or start-stop exercises (25).

6.2. Pharmacological Treatment

6.2.1. Desmopressin

An arginine vasopressin analogue, desmopressin is frequently used for MNE treatment. In a large portion of children with MNE, nocturnal polyuria is seen due to an abnormal circadian release of vasopressin (33). In children with MNE, desmopressin is the second-line treatment option after alarm therapy (25). One study demonstrated the importance of the balance between bladder capacity and nocturnal urine output in children with MNE. In this study, nocturnal urine production was distinctly lower during dry nights under desmopressin treatment compared to untreated wet nights (34). The sudden and inappropriate discontinuation of desmopressin results in high recurrence of enuresis (35) although planned discontinuations have been demonstrated to have low relapse rates (36). Response to treatment is 60 - 70% although some studies have shown a relapse rate as high as 50 - 90% (35, 37). Bradbury et al. reported that the addition of oxybutynin to desmopressin not only increased the success rate, but also decreased the relapse rate (38). Desmopressin is available in tablet or nasal spray form, and its effects last for up to 12 hours after a dose is taken. Its important side effects

include headache, nasal congestion, nosebleeds, abdominal cramps, water intoxication, allergic reactions, hyponatremia, anorexia, nausea, bad taste in mouth, and problems with vision (39).

6.2.2. Imipramine and Other Tricyclic Antidepressants

Tricyclic medications affect the central nervous system by inhibiting the reuptake of serotonin and noradrenaline from synaptic alpha receptors. They show an effect on the sleep center in the brain and also have anticholinergic, antispasmodic, and local anesthetic effects (40). The most frequently used tricyclic antidepressant for enuresis treatment is imipramine. Imipramine is moderately effective (50%) and has a high relapse rate. Clinical response has been shown to be in correlation with plasma levels, although it has been reported that measurement of serum levels are not of any clinical significance (41). Imipramine is cardiotoxic at high dosages, and cases of death resulting from cardiotoxicity have been reported. Therefore, it appears not to be suitable for first-line treatment of enuresis (40).

Its dosage is 25 mg for children under 6 years of age (20 - 25 kg [44 lb, 1 oz to 55 lb, 2 oz] weight) and 50 - 75 mg for those over 11. It is taken orally 1 hour before sleep.

6.2.3. Oxybutynin and Other Anticholinergic Drugs

Anticholinergic treatment is intended to prevent involuntary detrusor contractions. Anticholinergic treatment has been demonstrated to significantly decrease or cure urge incontinence in children, and can be discontinued 6 months after a complete response has been observed. Oxybutynin is a commonly used anticholinergic agent for the treatment of small capacity bladder and detrusor overactivity in children (25). Literature reports the effect of oxybutynin to be between 47 - 71%, with an even higher response rate when it is combined with desmopressin. A recent study found the response and relapse rates of oxybutynin, desmopressin, and imipramine after 6 weeks of use to be 71% vs 63.3% vs 61.3% and 31.8% vs 57.9% vs 63.2%, respectively (42).

The side effects of oxybutynin include dry mouth, headache, nausea, vomiting, tachycardia, and blurred vision. In children who cannot tolerate oxybutynin, Tolterodine may be used, as it has a better side effect profile and is more bladder-selective when compared to oxybutynin (43).

6.2.4. Other Drugs Used in the Treatment of Nocturnal Enuresis

Although many drugs and their combinations have been investigated for use in nocturnal enuresis, only a few have been found to be effective. Despite having demonstrated better effects when compared to a placebo, indomethacin, diclofenac, diazepam, and atomoxetine are rarely used due to their side effects and lack of high-quality data (44).

6.2.5. Combined Therapy

Combined therapy should be considered in patients who are refractory to a single medication. This approach is reported to be more effective and with higher success rates in children with enuresis who have behavioral problems and frequent nighttime bed wetting (45). In a study combining the use of desmopressin and an alarm, it was reported that desmopressin helped the children adapt more easily to alarm therapy (46).

6.3. Transcutaneous Parasacral Electrical Nerve Stimulation

Electrotherapy has recently been reported as an alternative therapy in patients with overactive bladder (OAB). Transdermal parasacral electrical nerve stimulation (TCPSE) has been shown to decrease symptoms by up to 63% (47). In a study of PMNE patients undergoing TCPSE, complete response was reported in 43% and partial response in 21% (48). In a study of patients who were refractory to initial medical treatment or biofeedback, the response rate of TENS was found to be 70.4% after 3 months of treatment (49).

6.4. Functional Magnetic Stimulation (FMS)

Recently, functional magnetic stimulation (FMS) has been developed as an alternative to electrical stimulation therapy for OAB (50, 51). FMS has been reported as an alternative treatment modality in children due to its noninvasive nature and having no side effects (50).

An initial report suggested FMS to be a promising modality for the treatment of nocturnal enuresis in girls (52). Preliminary data from another study showed a positive correlation between cortical arousal and bladder dysfunction in enuretic children. This finding demonstrates the relationship between brain stem dysfunction and bladder dysfunction. In lieu of these findings, animal models have been developed to evaluate the relationship between differing bladder functions and the corresponding brain stem response. During bladder filling, the ventrolateral periaqueductal area is deactivated in response to bladder dysfunction, and it is thought that this process is important in the reversal of dysfunction (53).

Another study reported the most important pathophysiological cause of treatment refraction in children with MNE to be low bladder capacity. It has been reported that ExMI may increase functional bladder capacity in children with treatment refraction through its acute

inhibitory effect. However, in treatment refractory MNE, long-term follow-up and studies with control groups are required to determine if the response is persistent (54).

Complementary and alternative medicine (hypnotherapy, acupuncture, etc.) is commonly used in certain areas of the world. However, there is a lack of data regarding these methods, and their safety and efficacy have yet to be proven with well-designed studies.

7. Conclusions

Although spontaneous remission is seen to a certain extent, each individual case of MNE must be evaluated and separated from non-monosymptomatic forms due to the negative psychosocial effects it has on children. Treatment must involve both the child and family and take into consideration the possible pathophysiological mechanisms.

Alarm therapy remains the first-line treatment modality for PNE. Due to high rates of patient compliance and relapse, alternative treatments remain on the agenda. Desmopressin is the most commonly used medical treatment. It is the choice of treatment where alarm therapy is not available, or in addition to alarm therapy if that has failed when used alone.

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Footnote

Authors' Contribution: All authors have contributed equally in the collection of journals and papers, writing, editing, and submission.

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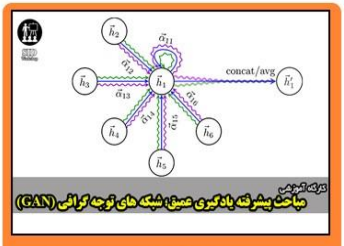

مباحث پیشرفته یادگیری عمیق؛
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