Review Paper

Comprehensive Review of Nocturnal Enuresis in Children

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ABSTRACT

Background: Enuresis is a common problem that affects up to 15% of 5-year-old children and may have significant psychological, emotional, and social consequences for both the child and their family. Enuresis is the inability of toilet-trained children to hold urine during the night. It can be classified as primary and secondary. Secondary enuresis occurs in children who have had a dry duration of more than six months; otherwise, it is called primary enuresis.

Objectives: This narrative review aims to summarize the available data on the epidemiology, etiology, pathophysiology, evaluation, and treatment of children with enuresis.

Methods: This study was conducted through a literature search with the keywords based on Medical Subject Headings (MESH) and were combined with other keywords, including enuresis, pediatric, incontinence, and treatment using PubMed, Embase, Web of Sciences, Scopus, and Cochrane databases.

Results: The initial evaluation of enuresis needs a detailed medical history and a careful physical examination with no need for radiology and invasive procedures. The treatment's mainstay is non-pharmacological treatments, such as behavioral intervention followed by pharmacotherapy. The appropriate treatment chosen depends on the children's age, midnight voiding patterns, and family and child preferences.

Conclusions: Enuresis is a common disorder that affects both the child and the family in many ways. Enuresis's etiology is complex, and it is still not well understood. The child and family must be included in the treatment process, and potential pathophysiological causes must be taken into account.

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1. Introduction

Enuresis is one of the most common childhood problems that are usually benign and gradually disappear with age (1, 2). In general, 5-year-old children should be able to control their urination as the bladder's capacity is increased, and the brain's nerve centers can control bladder contractions (3, 4). Urinary incontinence during sleep at least twice a week for 3 consecutive months in children over 5 years, without congenital or acquired defects, is called enuresis (5-7). Enuresis can significantly impact children and their families, causing shyness, low self-esteem, social isolation, sleep disturbance, decreased school performance, and anxiety (8-10). In addition to causing problems for the patient, such conditions can be stressful for the whole family and lead to parent's intolerance of the child's enuresis (11). As a result, timely diagnosis and appropriate treatment of enuresis are essential.

Given the high prevalence of enuresis in children and its psychological and social impacts, in addition to its effects on the quality of life of children and their families, the current study aims to review the available evidence on the epidemiology, etiology, diagnosis, and treatment of enuresis to give a better perspective on taking care of these patients.

Classification

The International Children's Continence Society has classified enuresis into 2 aspects and each into 2 types to help understand the causes and the proper treatment of this disorder: monosymptomatic vs non-monosymptomatic and primary vs secondary (12). Primary enuresis, which occurs in about 80% of cases, happens when a child does not have a period of overnight dryness that lasts for more than 6 months. Secondary enuresis, which accounts for the remaining 20% of cases, happens when urinary incontinence returns after at least 6 months of nighttime dryness (12, 13). The only symptom present in monosymptomatic enuresis is urinary incontinence. In contrast, in non-monosymptomatic enuresis, the patient has at least 1 sign of lower urinary tract involvement, such as dysuria, frequency, or urgency in addition to urinary incontinence (12, 14). While 25% of patients with primary enuresis are confirmed to be monosymptomatic, this number may be higher because of the low incidence of daytime symptoms reported by children or their families (12).

Etiology and epidemiology

Enuresis is considered a multifactorial disease with a strong genetic component because of comorbidities and immaturity of bladder control mechanisms in the central nervous system (15). Although the disease-specific genes remain unknown, studies show that the disease's inheritance has an autosomal dominant pattern with 90% penetration (5, 15).

The 8q, 12q, and 13q genes were identified to be involved in the development of enuresis in a study by Von Gontard et al. (16). A positive family history has been reported in most of the children. The risk of developing enuresis in children whose parents do not have a history of enuresis is about 15%. This increases to 44% if one parent has had enuresis, and then to 77% if both parents had a history of enuresis (17). In Safari Nejad's study on 7, 562 children, family history was positive in 48.5% of children with enuresis, while this was positive in 19.4% of children without enuresis (18). Another study on 140 children demonstrated that family history was positive in 57.2% of children with enuresis, while this was positive in 28.6% of children without enuresis (19). In addition to positive family history, parents' educational level, birth order, family economic status, the number of siblings and family members, a history of previous urinary tract infections, and constipation are associated with enuresis (19, 20).

The prevalence of enuresis is almost similar in different cultures. However, its prevalence varies at different ages: 15% of 7-year-old children (21), 10% of 10-year-old children (5), 2% of adolescents (15), and 0.5% to 1% of adults are affected by this disease (4, 14). Enuresis is more common in boys compared to girls with a 3 to 1 ratio, but the difference decreases after the age of 10 years (5, 14). Spontaneous recovery of enuresis is reported to be 14% per year (22). Further, 20% to 30% of patients with enuresis suffer from at least one psychological, behavioral, or social disorder, which is twice as high as the general population (23). The most common of these disorders is poor concentration and hyperactivity. Meanwhile, it is hypothesized that sleep disorders may link enuresis to such disorders (4, 23).

Pathophysiology

Researchers believe that various factors are involved in the pathophysiology of enuresis, and each patient shows a combination of them. Therefore, they explain why some people respond to specific treatments that

are unsuccessful in others (4). The most common pathophysiological mechanisms include nocturnal polyuria, high arousal threshold, and bladder dysfunction.

Nocturnal polyuria

Nocturnal polyuria plays an essential role in enuresis; however, it does not explain why children do not wake up for urination (24, 25). Clinical findings in nocturnal polyuria include consuming more fluids in the late afternoon and evening, soaking absorbent underwear, and a large volume of urine in the early morning despite enuresis (26). The mechanisms of nocturnal polyuria include increased fluid intake at bedtime, low response to antidiuretic hormone (ADH, vasopressin), and decreased ADH secretion (27, 28). The relationship between ADH secretion and nocturnal urination is challenging. In healthy children, overnight urine output decreases because of the increased secretion of ADH and other regulatory hormones that follow a circadian pattern (29).

The bladder can fill quickly at night based on the difference between the bladder capacity and the nocturnal urine production, resulting in the child's waking up to urinate or incontinence in children who have difficulty waking up (30). In healthy children, vasopressin is secreted more at night than during the day, which leads to a 50% reduction in overnight urine production (31). Nocturnal polyuria may be associated with vasopressin deficiency or changes in its circadian rhythm (13).

Bladder dysfunction

The bladder dysfunction mechanism in enuresis has been explained using the Koff hypothesis; accordingly, researchers have noted that the bladder's functional capacity in patients with primary enuresis corresponds to 70% of the predicted capacity. An ultrasound of the same patients revealed an increase in bladder wall thickness (32).

Electromyography and cystometry revealed that bladder contractions were not inhibited in 30% to 32% of children with primary enuresis, resulting in enuresis (33). Bladder dysfunction is more common in patients who have also daytime incontinence. It can manifest as decreased bladder functional capacity or abnormal urodynamics, such as nocturnal detrusor muscle hyperactivity associated with constipation (4).

High arousal threshold

When the bladder reaches its maximum capacity in healthy children, the child suddenly tends to urinate; however, this mechanism does not occur properly in children with enuresis. This mechanism's exact cause is unclear, although some researchers believe that chronic overstimulation reduces the response to stimuli in the discharge center (34).

Evaluation

Medical history

To evaluate patients with enuresis, a complete history should be taken and a careful physical examination must be performed to identify signs or symptoms of other underlying diseases. Physicians should ask about the frequency, time, and volume of bedwetting when evaluating children with enuresis. Moreover, lower urinary tract symptoms during the day should be examined, as these symptoms may not be mentioned voluntarily by the child or parents. It is necessary to assess the child's and parent's concerns regarding enuresis, as well as their motivation and willingness for intervention. Table 1 provides an overview of the most essential questions in taking a patient's history with clinical answers (25, 26, 35-40).

Voiding diary

A urine diary helps to identify children with non-monosymptomatic enuresis or other conditions that may require evaluation or referral to a subspecialist. The diary should include the following items (26, 36):

1) The times of urination during the day in total;

2) To predict bladder capacity, the volume of each urination should also be recorded;

3) Symptoms of the child's lower urinary tract, such as dysuria, dribbling, and difficulty starting or stopping urination should be recorded.

Physical examination

Physical examination should focus more on identifying secondary enuresis causes as findings in monosymptomatic enuresis are usually normal. The physical examination should be complete, and a thorough evaluation of the abdomen, genitals, perineum, lumbar, and nervous system should be performed. Table 2

summarizes the physical examination findings in children with enuresis (25, 26, 35-40).

Laboratory and imaging evaluations

Urinalysis is adequate for the initial laboratory evaluation of monosymptomatic enuresis. If urinalysis shows glucosuria or proteinuria, it indicates diabetes or chronic kidney disease, which requires further evaluation, including blood sugar, serum creatinine, and blood urea nitrogen. Urine culture should also be performed when bacteriuria or white blood cells are found in the urinalysis (41, 42). Kidney ultrasound can be used to diagnose kidney diseases and abnormalities in addition to anatomical malformations. Bladder ultrasound should evaluate the lower urinary system's malformations, bladder capacity, urinary retention, and increased bladder wall thickness. Moreover, the rectal diameter can be examined on bladder ultrasound to diagnose constipation (40, 43).

Charalampous et al. investigated the importance of measuring bladder wall thickness in children with primary enuresis and found that ultrasound would reliably detect bladder dysfunction (44). Voiding cystourethrography should be performed in children with febrile or recurrent urinary tract infections, and patients whose ultrasound indicates an increase in bladder wall thickness (18).

In patients with primary enuresis, urodynamic evaluation can reveal storage issues, including detrusor overactivity, decreased bladder compliance, and low bladder capacity (32, 45). Moreover, a urodynamic study may help to detect bladder outlet obstruction or neurogenic bladder (40). Magnetic resonance imaging should be performed in children with lumbosacral abnormalities or abnormal perineal, and lower extremity neurological examinations (46).

Treatment

Before starting the treatment, the doctor should understand the parent's and child's expectations about enuresis treatment. Some parents may need reassurance that enuresis is not because of a physical disorder. Also, parents may not be interested in starting a long-term treatment (39). Another critical point is that the doctor should emphasize to the parents that enuresis is not the child's fault, and the child should not be punished for it (39). The importance of this issue becomes clear when polls show that 25% to 33% of parents punish their children for enuresis, which is sometimes a physical punishment (47, 48).

Parents should also be advised at the beginning that the treatment may be long, often recurrent, and may fail in the short-term. Parents should be willing to participate in the treatment, the family environment should be supportive, and follow-up sessions should be ongoing (6, 13).

Non-pharmacological treatments

The first-line treatment for monosymptomatic enuresis is to educate the child and parents and provide accurate information about enuresis as in such cases a spontaneous recovery rate of 15% has been reported (49). This training should include some behavioral improvement, such as taking the child to the toilet before sleep or waking him up to urinate overnight, as well as exercises to increase the bladder capacity (37). Moreover, teaching families about enuresis and its management, providing recommendations for urination habits and duration, reducing fluid intake, and treating constipation are important factors (50, 51).

In addition to education and increasing the effectiveness, motivational therapy can be used. Motivational therapy is the first-line treatment for enuresis in children from the age of 5 to 7 who do not wet themselves every night (39, 52). Once the child has taken on some of the treatment plan's responsibilities, they can get motivated by recording a history of progress. The rewards that help in motivating the child should focus more on behaviors, such as going to the toilet before bed instead of focusing on the child's dryness at night (39, 53). Increasing the rewards when the child adapts to the agreed-upon behaviors helps in achieving a drier night period. For example, a sticker on the calendar can indicate a dry night, and after 7 consecutive stickers, a bigger reward (a book) can be considered for the child (53, 54). Moreover, the punishment should not be the withdrawal of the reward (gift) that has already been offered to the child (55). Motivational therapy is successful in approximately 25% of children and is estimated to lead to significant progress in treating more than 70% of children (49). In a systematic review study, Caldwell et al. reported that reward methods were associated with fewer wet nights, higher recovery rates, and lower recurrence rates than non-rewarding methods (56).

The other non-pharmacological method of treatment is alarm therapy. Enuresis alarms are activated

Table 1. Main questions in taking the history of children with enuresis

Questions		Importance of the Question and Clinical Answer
General history	1) What is the child's age?	Younger children may recover spontaneously without treatment. Non-pharmacological treatment may be provided if children between the age of 5 and 7 years have sufficient motivation.
	2) Does enuresis bother the child?	If it does not bother the child, propose delaying therapy till the child is motivated or until he or she is 7 years old.
	3) Has the child had a history of a 6-month dry period?	This introduces secondary enuresis, which should be considered for psychosocial stress and other comorbidities in the child.
	4) Has any treatment been done before?	Failure of bedwetting alarm is often because of insufficient compliance and may improve with proper counseling or desmopressin.
Characteristics of enuresis	1) How frequent is enuresis (night episodes and days of the week)?	Enuresis that occurs each night or has several episodes per night does not have a good prognosis.
	2) When does enuresis occur at night?	Primary mono-symptomatic enuresis is characterized by excessive urination during the first hours of sleep.
	3) Do absorbent underpants get wet at night?	This introduces nocturnal polyuria. Desmopressin therapy would be beneficial for the child.
	4) Does the child experience a large volume of urine in the early morning despite having enuresis?	This introduces nocturnal polyuria. Desmopressin therapy would be beneficial for the child.
	5) What are the drinking habits of the child during the day, especially in the evening and afternoon?	Behavioral modifications can improve the child's habits. Polydipsia is one of the symptoms of diabetes mellitus that needs to be ruled out. Taking desmopressin is contraindicated when the child has psychogenic polydipsia.
Comorbidities	1) What are the child's symptoms during the day? (Dribbling, frequency, urgency, incontinency, poor flow, straining during voiding, incomplete emptying, urination < 4 or > 7 times a day, holding maneuvers, urine leakage)	Suggests non-monosymptomatic, overactive bladder, neurogenic bladder, or anatomical abnormalities. The patient should first be evaluated and treated for symptoms during the day. Consider referring to a subspecialist in severe cases.
	2) Is the child suffering from dysuria?	There is a possibility of UTI. Request a urine culture.
	3) Is there a history of UTIs in the child?	Consider dysfunction or malformation of the lower urinary tract or neurogenic bladder. Suggest referring to a subspecialist.
	4) Is the child suffering from constipation? (Hard stools, < 4 stools per week, stool incontinence)	Reduce the bladder's functional capacity. Firstly, treat constipation as it can also treat enuresis.
	5) Is the child suffering from behavioral problems?	They may be more treatment-resistant. A psychiatric evaluation should be carried out. If there is a behavioral disorder, treat it at the same time as enuresis. Consider referring to a subspecialist.
	6) Does the child have any symptoms, such as polyuria, polydipsia, or weight loss?	Consider kidney disease or diabetes mellitus.
	7) Is the child suffering from snoring or does he have daytime drowsiness?	Consider OSA. Request polysomnography.
	8) Is there any history of defects in movement, learning, or developmental delays?	There is no contraindication to bedwetting alarm or desmopressin. If there is an undiagnosed central nervous system disorder, consider a referral to a subspecialist.
	9) Are there any psychosocial concerns?	Examine possible stressors. Assess family dynamics and whether the family supports treatment. Avoid using a bedwetting alarm if there are concerns about possible punishment by parents.

UTI: urinary tract infection; OSA: obstructive sleep apnea.

Table 2. Physical examination findings in children with enuresis

Physical Examination Findings		Significance and Clinical Response
Head and neck	Enlarged adenoids and tonsils of the child	If the child has snoring or drowsiness during the day, obstructive sleep apnea may be the cause; therefore, it should be treated first.
Abdomen	Hard stool in abdominal examination	Consider constipation for the child and treat it first.
	Bladder or kidneys Enlargement	There may be anatomical malformations of the urinary system; refer the patient to a subspecialist.
Rectum	Fecal contamination is evident in the child's underwear	Stool incontinence or constipation should be considered.
	Hair follicles, lipomas, or dimples on top of the gluteal crease	A neurogenic bladder can be the child's problem that needs further examination and referral to a subspecialist.
	Anal sphincter tone is reduced	A neurogenic bladder can be the child's problem that needs further examination and referral to a subspecialist.
Genital	Evidence of child sexual abuse	Anal and perineum excursions, as well as vulvovaginitis, suggest sexual abuse that requires further evaluation.
	Meatal stenosis, hypospadias, labial adhesions, phimosis	Indications of urinary system malformations that need to be referred to a subspecialist.
Nervous system	Sensory impairment, abnormal reflexes, gait abnormalities	A neurogenic bladder can be the child's problem that needs further examination and referral to a subspecialist.
Height and weight	Delayed growth or malnutrition	The child may have an underlying condition, such as diabetes mellitus or chronic kidney disease that need further evaluation.

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when a sensor on the underwear or the bed detects moisture, then an alarm or a vibrating belt is activated (57). It performs by teaching or training the child to wake up to urinate before bedwetting, which is particularly useful in children who have problems waking up (57, 58). For children under the age of 8 who have adequate family support and no nighttime polyuria, alarm therapy may be the first treatment choice. After a period of at least 6 to 8 weeks, the effect should be evaluated, and the alarm therapy should be continued until the child has at least 14 consecutive dry nights (39). Although 10% to 30% of families discontinue the treatment, treatment success rates are reported to range from 65% to 75% (59). Alarm therapy is the most effective treatment to control enuresis and avoid recurrence compared to desmopressin and other behavioral therapies (60, 61).

In a meta-analysis of 5983 children, the ones who had alarm therapy had fewer wet nights per week than the control group. Moreover, compared to the control group, more children with alarm therapy had a complete response (14 consecutive dry nights). The side effects and problems of alarm therapy include alarm failure, false alarms, the child not waking up, disturbing other family members, and discontinuation because of the difficulty of using the alarm (57).

Another non-pharmacological method is acupuncture, proposed as a treatment for enuresis and relapse (62, 63). While the evidence for this treatment is weak, meta-analysis results show that acupuncture is an effective treatment for enuresis. However, other large clinical trials are needed to prove its effectiveness (64).

Pharmacological treatments

Desmopressin

Desmopressin is a synthetic form of vasopressin used to treat enuresis in children whose enuresis has not responded well to recommendations for fluid intake, toilet training, or reward system, or the children who cannot properly follow the treatment. Desmopressin is better for children with normal bladder function capacity and nocturnal polyuria (36, 65). Approximately 30% of children with enuresis achieve complete dryness with desmopressin, and 40% of patients have a significant reduction in nocturnal wetting (35).

Desmopressin is available as oral tablets, nasal drops, and nasal spray, and its effects can last up to 12 h (66). Desmopressin is given late at night to reduce the production of urine during sleep. The initial dose is 0.2 mg, however, the dose is increased by 0.2 mg up to the maximum dosage of 0.4 mg if necessary after 10 to 14 days (1, 37). Headache, nausea, anorexia, hyponatre-

mia, allergic reactions, abdominal cramps, nosebleeds, nasal congestion, and vision problems are the possible side effects (67). The most common reason for not responding to desmopressin is decreased bladder capacity at night. Other causes include persistent nocturnal polyuria (increased fluid intake at night, increased nocturnal salt excretion, or decreased pharmacodynamic effect of desmopressin) (26).

In a systematic review study that compared the effectiveness of desmopressin with other drugs and alarm therapy in 1649 children, desmopressin was as effective as the alarm therapy. In addition, alarm monotherapy had a much lower relapse rate than desmopressin monotherapy (68).

Tricyclic antidepressants

Tricyclic antidepressants prevent noradrenaline and serotonin reabsorption from α-synaptic receptors in the central nervous system. They also affect the brain's sleep center and have antispasmodic, anticholinergic, and local anesthetic effects (69).

Imipramine is the most commonly prescribed tricyclic antidepressant for the treatment of enuresis, which is about 50% effective. It also has a high recurrence rate after stopping the drug. Studies have shown that the clinical response correlates with plasma levels, although serum levels measurement is not clinically relevant. Imipramine has high cardiac toxicity, and deaths have been reported. As a result, it is not a suitable first-line treatment for enuresis (69).

Anticholinergic drugs

Oxybutynin is a common anticholinergic for treating small-capacity bladder and overactive detrusor muscle in children (70). Studies report a positive effect of oxybutynin from 47% to 71%, and when combined with desmopressin, the effectiveness increases. In the study by Seyfhashemi et al., the response rate after 6 weeks of use was 71% with oxybutynin, 63.3% with desmopressin, and 61.3% with imipramine. They also evaluated the recurrence rate in these patients who had a recurrence rate of 31.8% with oxybutynin, 57.9% with desmopressin, and 63.2% with imipramine (71). Headache, tachycardia, vomiting, nausea, blurred vision, and dry mouth are mostly the side effects of oxybutynin. Tolterodine can be used in children who do not tolerate oxytocin, as it has fewer side effects and is the anticholinergic choice for the bladder compared to oxytocin (72).

Other drugs

Other drugs have been studied to a limited extent. Given the side effects and a lack of high-quality evidence, atomoxetine, diazepam, diclofenac, and indomethacin are rarely used (73). A review article from the Cochrane database states that there is currently insufficient evidence to recommend any of these treatments for enuresis (74).

Combination therapy

Combination therapy should be considered in patients who are treatment-resistant to a drug. This method is more effective and successful in children with enuresis who have behavioral problems and frequent wetting during sleep (75). A systematic review showed evidence of improved treatment in combination therapy with alarm therapy in addition to drug therapy (57). However, various guidelines indicate that if enuresis does not respond or only partially responds to alarm therapy, desmopressin can be combined with alarm therapy (39).

In a study, Rvanshad et al. examined the effects of desmopressin with or without oxybutynin and found that combination therapy with desmopressin and oxybutynin was more effective in children with primary enuresis (76). Another study reported that desmopressin's combination therapy with tolterodine performed better than desmopressin plus oxybutynin (77). Besides, desmopressin is well tolerated with low-dose imipramine and may be an excellent short-term treatment option in patients where desmopressin is not effective enough (78).

In another clinical trial that examined the effect of fluvoxamine in the treatment of resistant primary enuresis and compared it with the combination of desmopressin and oxybutynin, the complete recovery in the fluvoxamine group and the desmopressin-oxybutynin group was 66.7% and 46.7%, respectively. This difference was not statistically significant (79).

2. Conclusion

Primary enuresis is a relatively benign and common problem in children. A thorough history taking and physical examination with laboratory tests and imaging evaluations can help differentiate primary enuresis from other pathological causes of incontinence. Although spontaneous recovery occurs in most patients with primary enuresis, each case should be thoroughly evalu-

ated and differentiated from non-monosymptomatic enuresis because of the adverse psychosocial effects on children. The first-line treatment is behavioral interventions and educating the child and parents about enuresis. Therefore, alternative therapies, such as desmopressin, which is the most common drug treatment, should be considered. The physician should inform the child and parents about the various treatment options to select the best treatment method and refer the child to a subspecialist if he resists the treatment.

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 equally contributed to preparing this article.

Conflicts of interest

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