Review Article ISSN 2835-6276

American Journal of Medical and Clinical Research & Reviews

Nocturnal enuresis in children

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Received: 05 Nov 2024; Accepted: 07 Nov 2024; Published: 10 Nov 2024

Citation: Fatma mohamed mahmoud. Nocturnal enuresis in children. AJMCRR 2024; 3(11): 1-9.

Abstract

Nocturnal enuresis, defined as urinary incontinence during sleep at least twice weekly for three consecutive months in children over 5 years old, is a common childhood condition that significantly impacts both children and their families. This review examines the classification, etiology, pathophysiology, evaluation, and treatment options for nocturnal enuresis. The condition is classified as either monosymptomatic or non-monosymptomatic, and primary or secondary, with primary enuresis accounting for 80% of cases. The pathophysiology involves three main mechanisms: nocturnal polyuria, high arousal threshold, and bladder dysfunction. Genetic factors play a significant role, with a strong familial component following an autosomal dominant pattern. Evaluation includes detailed medical history, voiding diary, physical examination, and basic laboratory tests. Treatment approaches are divided into non-pharmacological (including behavioral modifications, motivational therapy, and alarm therapy) and pharmacological interventions (primarily desmopressin, tricyclic antidepressants, and anticholinergic drugs). While alarm therapy shows the highest long-term success rates (65-75%), combination therapy may be necessary for treatment-resistant cases. This review emphasizes the importance of individualized treatment approaches and family support in managing childhood nocturnal enuresis effectively.

Introduction

Enuresis is one of the most common childhood problems that are usually benign and gradually disappear with age. 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. 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 (**Wannapaschaiyong and Bunman, 2022).**

Enuresis can significantly impact children and their families, causing shyness, low self-esteem, social isolation, sleep disturbance, decreased school performance, and anxiety. 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 (**Collis et al., 2019**).

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 prop-

er treatment of this disorder: monosymptomatic vs non-monosymptomatic and primary vs secondary. 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 (**Gomez Rincon et al., 2022**).

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. 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 (**Dossche et al., 2016).**

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. Although the disease-specific genes remain unknown, studies show that the disease's inheritance has an autosomal dominant pattern with 90% penetration (**Fagundes et al., 2017).**

The 8q, 12q, and 13q genes were identified to be involved in the development of enuresis in a study by **Von Gontard et al. (2001**). 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.

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 (**Safarinejad, 2007**). 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. 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 (**Azarfar et al., 2021).**

The prevalence of enuresis is almost similar in different cultures. However, its prevalence varies at different ages: 15% of 7-year-old children, 10% of 10-year-old children, 2% of adolescents, and 0.5% to 1% of adults are affected by this disease. 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 (**Haid and Tekgül, 2017).**

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. The most common of these disorders is poor concentration and hyperactivity. Meanwhile, it is hypothesized that sleep disorders may link enuresis to such disorders (**Van Herzeele et al., 2015**).

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. The most common pathophysiological mechanisms include nocturnal polyuria, high arousal threshold, and bladder dysfunction (**Nevéus, 2017).**

Nocturnal polyuria

Nocturnal polyuria plays an essential role in enuresis; however, it does not explain why children do not wake up for urination. 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. The mechanisms of nocturnal polyuria include increased fluid intake at bedtime, low response to antidiuretic hormone (ADH, vasopressin), and decreased ADH secretion. 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 (**Naiwen et al., 2021).**

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. In healthy children, vasopressin is secreted more at night than during the day, which leads to a 50% reduction in overnight urine production. Nocturnal polyuria may be associated with vasopressin deficiency or changes in its circadian rhythm (**Tas et al., 2014).**

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 (**Yeung et al., 2004).**

Electromyography and cystometry revealed that bladder contractions were not inhibited in 30% to 32% of children with primary enuresis, resulting in enuresis. 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 (**Nevéus, 2017).**

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 (**Yeung et al., 2008).**

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 (**Nevéus et al., 2020).**

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 (**Naiwen et al., 2021):**

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 (**Bauer et al., 2015).**

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 (**Abrams et al., 2018).**

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 (**Kovacevic et al., 2014).**

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. 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. 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 (**Sá et al., 2021).**

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 (**Walker, 2019).**

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. 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. Moreover, teaching families about enuresis and its management, providing recommen-

dations for urination habits and duration, reducing fluid intake, and treating constipation are important factors (**Rodríguez-Ruiz et al., 2021).**

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. 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 (**Ferrara et al., 2018).**

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. Moreover, the punishment should not be the withdrawal of the reward (gift) that has already been offered to the child (**Ghodsi et al., 2020).**

Motivational therapy is successful in approximately 25% of children and is estimated to lead to significant progress in treating more than 70% of children. 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 (**Caldwell et al., 2013).**

The other non-pharmacological method of treatment is alarm therapy. Enuresis alarms are activated when a sensor on the underwear or the bed detects moisture, then an alarm or a vibrating belt is activated. 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 (**Baird and Atchison, 2021).**

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. Although 10% to 30% of families discontinue the treatment, treatment success rates are reported to range from 65% to 75%. Alarm therapy is the most effective treatment to control enuresis and avoid recurrence compared to desmopressin and other behavioral therapies (**Peng et al., 2018).**

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. Approximately 30% of children with enuresis achieve complete dryness with desmopressin, and 40% of patients have a significant reduction in nocturnal wetting (**Kamperis et al., 2017).**

Desmopressin is available as oral tablets, nasal drops, and nasal spray, and its effects can last up to 12 h. 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. Headache, nausea,

anorexia, hyponatremia, allergic reactions, abdominal cramps, nosebleeds, nasal congestion, and vision problems are the possible side effects (**Gasthuys et al., 2020).**

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) (**Robson, 2009).**

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 (**Caldwell et al., 2016**).

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 (**Caldwell et al., 2016**).

Anticholinergic drugs

Oxybutynin is a common anticholinergic for treating small-capacity bladder and overactive detrusor muscle in children. 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 (**Gunes and Ekinci, 2019**).

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 (**Bolduc et al., 2003).**

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. A review article from the Cochrane database states that there is currently insufficient evidence to recommend any of these treatments for enuresis **(Deshpande et al., 2012).**

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. A systematic review showed evidence of improved treatment in combination therapy with alarm therapy in addition to drug therapy. However, various guidelines indicate that if enuresis does not respond or only partially responds to alarm therapy, desmopressin can be combined with alarm therapy (**Caldwell et al., 2020).**

Conclusion

Primary enuresis is a common, generally benign condition in children. A detailed history, physical

examination, and appropriate laboratory and imaging tests can help distinguish primary enuresis from other potential causes of incontinence. While spontaneous recovery is common, each case should be carefully evaluated, particularly to differentiate primary enuresis from non-monosymptomatic enuresis due to its potential psychosocial impact on children. Behavioral interventions are the first-line treatment, along with educating the child and parents about enuresis. Alternative therapies, such as desmopressin—the most commonly used medication—can be considered if necessary. The physician should discuss all treatment options with the child and parents to determine the best approach and refer to a subspecialist if the child shows resistance to treatment.

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