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Review Article

Enuresis: Etiology, Pathophysiology and Treatment

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ABSTRACT:
Urinary incontinence is a common problem in childhood. In the structure of disorders of voluntary urination in childhood, the leading place is occupied by isolated (monosymptomatic) nocturnal enuresis. The article presents a modern classification of monosymptomatic nocturnal enuresis; the characteristic of possible pathogenetic mechanisms of its development is given. Diagnostic algorithms and issues of non-drug and drug therapy are considered in detail.
Key words: Pediatric urology, neurology, urinary incontinence, enuresis.

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INTRODUCTION

Nocturnal urinary incontinence (enuresis) is a fairly common disease in children; doctors of many specialties are involved in its treatment - pediatric urologists, nephrologists, pediatricians, and neurologists. Nocturnal urinary incontinence (more than 3 episodes per week) occurs in 10% of children under the age of 7 and is the cause of mental and emotional problems in children and their families. The prevalence of urinary incontinence decreases with age. So, in children aged 4.5 years, bedwetting (less than 2 "wet" nights per week) occurs in 21% of cases, and at the age of 9 years - only in 8% of children. More frequent bedwetting is observed in 8% of children at the age of 4.5 years and in 1.5% of children at the age of 9.5 years [1].

According to other authors, spontaneous recovery by adolescence is observed in 15–17% of children [2]. At the same time, persistent enuresis persists in 50% of older patients, which indicates a tendency for the disease to recur [3, 4, 5]. In boys, enuresis occurs 1.5–2 times more often than in girls [5, 6]. The lower age limit for the diagnosis of bedwetting has not been determined, but it is generally accepted that this problem acquires clinical significance from about 5 years of age [7]. The reasons why it is necessary to actively engage in the treatment of this disease are that enuresis violates the child's self-esteem, his social adaptation, which leads to severe depression both in himself and in his parents. If untreated, enuresis can persist; in adults, the incidence of this disease is 2–3% [8, 9].

Therefore, complex therapy is needed to avoid serious consequences for the physical and psychological well-being of the child.

Currently, according to the definition of the International Children's Continence Society (ICCS), enuresis is involuntary intermittent urination during sleep in a child over 5 years old [6]. The following is the ICCS definition of other equally important terms related to urinary incontinence [10]:

- Monosymptomatic enuresis (MSE) is enuresis in the absence of any symptoms of lower urinary tract dysfunction. Patients with MSE are differentiated according to the following criteria: - with or without nocturnal polyuria; - with or without a response to desmopressin therapy; - with the presence or absence of awakening disorders; - with the presence or absence of bladder dysfunction.
- Non-monosymptomatic enuresis (NMSE) - enuresis in combination with other symptoms of lower urinary tract dysfunction, which are mainly manifested during the daytime [11, 12].
- Nocturnal polyuria - hyperproduction of urine at night, defined as an excess of nocturnal urine output by more than 130% of the effective bladder capacity in accordance with age.
- Overactive bladder - Urgent and frequent urination with or without urinary incontinence.

ETIOLOGY AND PATHOGENESIS

The causes of bedwetting are not fully understood. Enuresis results from a combination of the following predisposing factors: polyuria, bladder dysfunction, and difficulty waking up. Some children with bedwetting develop a disproportionate amount of urine at night. This is due to the lack of nocturnal production of the pituitary antidiuretic hormone - vasopressin [13, 14, 15]. It is also known that bedwetting can occur in dry children due to excessive fluid intake before bedtime [16].

The use of vasopressin (an analogue of desmopressin) allows children with urinary incontinence (especially those with polyuria) to stay dry at night [17]. However, the peculiarities of the pathogenesis of bedwetting cannot be explained only by a decrease in the level of vasopressin, because not all children with enuresis have polyuria.

Some "dry" children have nocturia rather than enuresis and in the presence of polyuria it is not clear why children do not wake up to urinate. In many children, bedwetting is caused not by an overflow of the bladder, but by nocturnal overactivity of the detrusor. Indirect evidence of this is the high incidence of enuresis and urge incontinence in the same child, as well as a decrease in the volume of urination in children with enuresis compared with children without enuresis. Overactive bladder is confirmed by urodynamic studies in children with refractory enuresis [18].

As a rule, children with enuresis have sleep disturbance (awakening phase), which prevents them from waking up at night to go to the toilet. Nocturnal urinary incontinence in a child may also be due to "deep sleep", which is confirmed by the observations of parents and research data on the assessment of objective thresholds of awakening. The disturbance in the awakening phase can be caused by the stimuli themselves (in this case, a full or overactive bladder), which act as a constant stimulus, and the body eventually stops responding to them.

Arousal disorder can result from sleep coordination disorders at the level of the brain stem. Currently, there is evidence that three structures are responsible for the basic dysfunction of the brain stem: the macula, which plays a major role in awakening from sleep, the noradrenergic group of neurons in the upper pons and the urinary center which coordinates the urinary reflex and functionally and anatomically overlaps with LC. Blue spot also has axonal connections with hypothalamic cells that produce vasopressin [19].

Recently, work has been actively carried out to study changes in this area of the brain in children with urinary incontinence. Currently, there are two main types of enuresis:

• Enuresis, in which nocturnal polyuria is associated with low vasopressin levels during the night and a high likelihood of response to desmopressin therapy.

• Enuresis, in which the capacity of the bladder is less than the age norm, which is associated with an overactive bladder. This type of enuresis is similar to the subtype NMSE with manifestations of lower urinary tract symptoms, a reduced response to desmopressin, and a higher likelihood of response to forced awakening therapy.

Enuresis can also be caused by a number of diseases: in rare cases, it can be diseases accompanied by polyuria (diabetes mellitus or insipidus, neoliguric renal failure, etc.), urinary tract infection (UTI), constipation, neurogenic urinary bladder, malformations of the urinary tract (urethral valves), snoring or sleep apnea.

Recently, more and more attention is paid to the study of psychological factors and stress in the development and persistence of bedwetting in children. However, a number of studies in recent years have shown that it is not psychological factors that lead to enuresis, but, on the contrary, that enuresis leads to behavioral abnormalities and social maladjustment, and behavioral disorders in children 5 years of age and older are noted regardless of the frequency of enuresis. It has been established that after recovery from enuresis in children, positive psychological changes are usually observed [20].

TREATMENT

Treatment methods for enuresis are based on correcting the pathogenetic mechanisms of the disease. Desmopressin is the first-line treatment for bedwetting. It is an analogue of the hormone vasopressin, which has an antidiuretic effect [21]. As a rule, this drug can completely cure the disease in 1/3 of children with enuresis, in 1/3 of patients there is a partial response, and in 1/3 of patients this drug does not help. The mechanism of action of desmopressin is a decrease in urine production; therefore, nocturnal polyuria is a predictor of the effectiveness of treatment [22]. There is evidence of an effect of desmopressin on the central nervous system. The drug has practically no side effects, even if used for several months and years. However, hyponatremia may occur when the drug is taken in combination with excessive fluid intake [23].

Anticholinergics are the second-line therapy in the treatment of enuresis. The first results of this group of drugs were not encouraging enough, but now there is evidence that tolterodine is effective as an adjunctive therapy in the treatment of bedwetting in children who did not respond to desmopressin therapy [24]. Other commonly used drugs in this group are oxybutynin and propiverine, but their use can be complicated by the development of constipation and UTIs due to increased residual urine volume. The antidepressant imipramine has also been used successfully in the treatment of bedwetting.

Anticholinergics are well-studied drugs and are highly effective in the treatment of hyperreflex bladder

dysfunction. Along with this, they are characterized by a high frequency of systemic side effects, which limits their use. Anticholinergics are not used as monotherapy and are not first-line drugs. The question of the use of anticholinergics is considered if it was not possible to obtain a response to treatment with desmopressin. Enuresis is a serious problem for a small patient, since the long course of the disease adversely affects his psychological state, adaptation in children's groups and ultimately has a detrimental effect on the developing personality. Timely correct diagnosis, a differentiated approach and the appointment of adequate therapy will avoid many difficulties, and in most cases, eliminate the entire problem.

According to placebo-controlled studies, the response rate to treatment is about 50% [25]. The reason for the effectiveness of this drug is also not completely clear, but, most likely, it is based on the noradrenergic effect of the drug at the level of the brain. Currently, imipramine is strictly used in the treatment of persistent bedwetting, since side effects (mainly mood changes) are quite pronounced, and overdose can be fatal. A prerequisite for successful treatment of bedwetting is behavioral therapy, i.e. normalization of fluid intake and the development of correct urination skills. However, to date, there is insufficient evidence for the effectiveness of this approach. However, behavioral therapy does not harm the child and can help reduce bedwetting [26].

CONCLUSION

Thus, the diagnosis and treatment of bedwetting is a rather complex problem that requires a lot of time and attention, both from the patient's side and from the doctor's side. At the heart of the pathogenesis of enuresis, three main mechanisms are distinguished: hyperproduction of urine at night, dysfunction of the bladder and a violation of the awakening process when the urge to urinate occurs. Treatment of enuresis is based on identifying the causes of the disease and their correction. However, in some cases, for the successful treatment of enuresis, only one method or drug is not enough; complex therapy with the use of several groups of drugs is required, which gives the best effect.

In the presence of concomitant neuropsychiatric disorders in children with enuresis, it is justified to prescribe complex therapy using Pantocalcin.

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CONSENT

Written informed consent was obtained from all participants of the research for publication of this paper and any accompanying information related to this study.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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