Nocturnal enuresis secondary to hyperthyroidism – case report and literature review

Abstract
Nocturnal enuresis is a problem which affects a significant number of children in the developmental period. The diagnostic work-up should be completed if the condition does not resolve after five years of age or in older children who experience a recurrence of nocturnal enuresis. This case report presents a 12-year-old boy with nocturnal enuresis secondary to hyperthyroidism. In many cases, nocturnal enuresis is linked to emotional disorders (like school or family problems), but increasingly the condition is rather a consequence than the reason. Currently, nocturnal polyuria, inadequate capacity of the urinary bladder and functional urinary tract disorders are considered to be the most common causes of nocturnal enuresis. It happens, however, that the background of bedwetting is more complex and the diagnosis is not so obvious.

Keywords: hyperthyroidism, nocturnal enuresis, children

Słowa kluczowe: nadczynność tarczycy, moczenie nocne, dzieci
INTRODUCTION

Nocturnal enuresis (NE) is a problem affecting a significant percentage of children in the developmental period. Epidemiological reports are not able to define the exact prevalence of the condition due to dissimulating this embarrassing affliction, but it is estimated that approximately 1.4–28% of children aged 6–12 years old are affected by this problem globally\(^{(1)}\). It is believed that NE is the second most common complaint among children and adolescents at the ages of 6–14 years, right after allergic disorders\(^{(1)}\). NE is more common in boys than in girls\(^{(2)}\).

This condition can be defined as the involuntary passing of the urine that happens at night during sleep. It presents in children who have already learned to control their bladders and have reached the age of five. Bedwetting is a heterogeneous disorder and its occurrence is influenced by many aetiologic factors\(^{(2)}\).

We distinguish primary or secondary and monosymptomatic (MNE) or non-monosymptomatic (NMNE) forms of NE. Primary NE occurs when the child has not yet attained the period of six months of dry nights or has never controlled his bladder since birth. Secondary NE is diagnosed when the child has already achieved dry nights and then experienced an onset of NE. MNE is identified when children do not present with any symptoms of lower urinary tract dysfunction, while children with NMNE exhibit different symptoms involving the lower urinary tract, such as urgency, tenesmus hesitancy, day urinary incontinence and frequent urination of small volumes of urine, increasing and decreasing frequency of urination\(^{(2,3)}\). Approximately 30% of patients are diagnosed with NMNE\(^{(2)}\).

For many years, attempts have been made to find the cause of NE to treat the condition effectively. In the past, it was believed that NE originates from psychological factors. Nowadays, it is claimed that the causative factors include the deficiency of vasopressin, increased nocturnal detrusor overactivity, and lack of ability to wake up to the signals of a full bladder\(^{(4,5)}\).

Micturition and/or storage of urine in the bladder is regulated voluntarily; furthermore, the spinal and supraspinal reflexes are involved in this mechanism. Pontine micturition centre (PMC), which lies in the brainstem, plays a crucial role in the coordination and initiation of voiding\(^{(4)}\). The centre is stimulated by pelvic nerves when the bladder is filled with an appropriate void volume\(^{(6)}\). PMC stimulates the spinal parasympathetic nerves to excrete acetylcholine from the pelvic nerves, which activates the detrusor muscle’s muscarinic receptors, inducing the contractions and micturition. Another structure involved in the voiding process is located in the midbrain, and it is called periaqueductal grey (PAG). It receives essential signals from the higher centres of the central nervous system (prefrontal cortex and hypothalamus)\(^{(6)}\). In addition, PAG is an important centre of the sympathetic nervous system. It has axonal connections with the supraoptic nucleus located in the hypothalamus, which is responsible for producing vasopressin (antidiuretic hormone)\(^{(4)}\). Finally, normal functionality of the lower urinary tract is associated with correct, coordinated and contradictory operation of both parts of the autonomic system. There have been hypotheses about the predominance of the parasympathetic system activity during the child’s sleep or the low activity of sympathetic system, potentially resulting in the episodes of bedwetting\(^{(4)}\).

One can distinguish two basic mechanisms of pathogenesis of MNE. Increased production of urine during the night is defined as nocturnal polyuria, and it is a result of observed lower levels of vasopressin. The child usually urinates once every three to four hours after falling asleep. However, in some enuretic children, nocturnal detrusor overactivity leads to relentless bladder contractions occurring at night. The child usually gets wet several times\(^{(2)}\).

It is known that urinary incontinence can be a cause of emotional problems, but not a result of it. In many cases, NE has an impact on the quality of family or social life and can be a source of stress for children and their parents. Young patients often suffer from low self-esteem, social isolation, and low school performance\(^{(2)}\).

Genetic factors play an important role in the pathogenesis of NE. Children with a negative family history of NE have a 15% risk of developing NE, however the rate increases to 44% when one of the parents suffered from NE in childhood\(^{(2)}\). When both parents had NE, the probability increases to 77%\(^{(2)}\). Several genes are known to be associated with NE, but none of them provide useful information in the pathogenesis of NE\(^{(5)}\).

In a healthy child, the level of diuresis decreases during the night due to the secretion of vasopressin (AVP). In contrast, increased urine production and decreased secretion of AVP have been observed in some children with bedwetting\(^{(5)}\). However, not every case can be explained by the deficiency of vasopressin, and the condition is probably a result of interactions between many factors, for example the excretion of excess calcium, which impairs the renal concentrating mechanisms\(^{(4,5)}\). Polysomnography studies have shown no significant difference between enuretic children and the control group. Only a slight tendency to wetting in the non-rapid eye movement (NREM) phase of sleep was observed\(^{(14)}\).

Urodynamics studies show that a proportion of children with NE present uncontrolled contractions of the bladder detrusor muscle during sleep, which suggest its night-time overactivity\(^{(5)}\).

The overactivity or reduced bladder capacity result in episodes of bedwetting in children who produce normal amounts of urine during the night\(^{(5)}\). Moreover, there is no meaningful difference in the anatomy of enuretic children compared to the control group, which shows that
uninhibited detrusor muscle contractions occur when the bladder is not yet completely full\(^9\).

The literature more often reports that NE can be a result of separate defined disease entities and syndromes which are not strictly connected with the urinary system, as we show in our manuscript. The background of NE may include congenital or acquired abnormalities of the nervous system background. It can also be related to metabolic or endocrine disorders\(^9\).

The study describes the case of a 12-year-old boy diagnosed with NE coexisting with hyperthyroidism.

**CASE REPORT**

A 12-year-old boy was admitted to the children's nephrology unit due to primary NE, in order to undergo a thorough diagnostic work-up and establish the treatment. The patient previously stayed in another paediatric centre. Based on the patient's history, he had a previous urologic consultation and was treated with desmopressin and oxybutynin. Oxybutynin (5 mg once daily for six months) did not bring any improvement. After the introduction of desmopressin (120 µg once daily for six weeks), the nights were dry and, as a result, after nine months of therapy, the dose was reduced (120 µg every two days). This resulted in the relapse of NE.

On admission, the child was in a good general condition. Physical examination revealed an asthenic body structure, poorly developed subcutaneous tissue, moist skin, restlessness of the hands and feet, a faulty posture, red palatal arches, enlarged palatine tonsils, and mucopurulent secretion on the back of the pharynx. The heart rate was regular, 120 bpm. The patient's blood pressure was 115/80 mm Hg.

Laboratory tests, 24-hour urine collection, fluid balance, and ultrasound of the abdominal cavity were ordered. The results revealed: anaemia (haematocrit: 33.9%, haemoglobin: 10.8 g/dL), vitamin D\(_3\) deficiency (vitamin D: 12.56 ng/ml; N: 30–80 ng/mL), decreased iron and ferritin levels (iron 4.5 µmol/L; N: 5.83–34.5 µmol/L; ferritin 6.3 µg/L; N: 20–200 µg/L) and elevated free thyroxine (fT4) levels (3.08 ng/dL; N: 0.30–1.58 IU/L). On ultrasound examination, the thyroid was enlarged, with abnormal parenchyma, showing a heterogeneous, hypoechoic structure with no obvious focal changes. Based on the above-mentioned results, hyperthyroidism secondary to Graves' disease was diagnosed. Thiamazole and propranolol treatment was initiated, resulting in a gradual improvement in the general condition. After three days, in the follow-up tests, fT4 levels were still elevated, but with a clear decreasing trend (1.93 ng/dL). The boy, in a good general condition, was discharged home for further outpatient treatment with recommendations for the use of thiamazole (5 mg three times a day), propranolol (10 mg three times a day), iron supplementation (100 mg once a day), folic acid (5 g once a day), vitamin D\(_3\) (2,000 units once a day), and vitamin B. Bladder training was also recommended, involving gradual extension of the intervals between micturitions during the day and keeping a night-wetting calendar.

Follow-up visits in the nephrology clinic during the next year showed a gradual reduction in the number of wet nights, up to one-off cases. On the other hand, in the endocrinology clinic, a decrease of the thyroid gland was found. The thyroid achieved the first degree of gland size according to the World Health Organization scale.

**DISCUSSION**

The diagnosis of NE (especially important in secondary NE) should begin with an appropriately collected patient history and physical examination. It should be complemented by urine analysis, and laboratory and imaging tests to assess the function of the kidneys, lower urinary tract, and residual urine volume, as well as examination of the body's functions during sleep (polysomnography)\(^10\).

Behavioural therapy, the so-called urotherapy, serves as an introductory treatment of NE and trains children to urinate regularly every three hours and when the child feels the need to pass urine. The therapy also determines an adequate intake and composition of oral fluids during the day as well as the posture adopted during urination and defecation. Urotherapy must be continued for at least two months, also during pharmacological treatment. Currently, there are mobile applications that facilitate urotherapy\(^10\).

In our case, though, it was not effective from the beginning of treatment. Furthermore, in patients with MNE, satisfactory results are achieved using so-called bed alarm therapy. It consists in placing a special sensor in the child's nightwear or bed to detect the moisture that appears as a result of starting micturition and then wakes the child through sound effects or vibrations. After awakening, the child should be encouraged to finish micturition in the toilet. The key point of such treatment is to replace uncontrolled NE with controlled nocturnal urination\(^2,9\). Transcutaneous electrical nerve stimulation (TENS) is another potential treatment.
Complete relief of symptoms or maximum one episode of NE per month
Reduction in the number of wet nights by 90%
Reduction in the number of wet nights from 89% to 50%
Reduction in the number of wet nights by less than 50%

Tab. 1. Evaluation of the effectiveness of NE treatment – modified according to(7)

NE – nocturnal enuresis.

option, particularly in children with NE due to lower urinary tract dysfunction(8).
Therefore, the choice of treatment modality for NE depends on the coexisting disorders, the NE subtype (MNE/NMNE), the severity of the disease, the parents’ motivation and ability, and the child’s motivation. Treatment efficacy is assessed according to the criteria presented in Tab. 1.
Desmopressin and oxybutynin are the most commonly used drugs in the treatment of NE. Desmopressin is a synthetic analogue of vasopressin. The medication increases the reabsorption of fluid from the renal tubules, thereby decreasing urine production. According to the literature, 80% of patients treated with desmopressin have a good response rate; however, there is a high incidence of recurrence. The studies show that a gradual decrease of the dose every three months can greatly reduce the relapse rate(9).
On the other hand, oxybutynin, an anticholinergic and antispasmodic agent that decreases detrusor muscle contractions by blocking the muscarinic receptors, is not typically effective in monotherapy in patients with monosymptomatic NE. Therefore, it is recommended that oxybutynin is combined with desmopressin to obtain a synergistic effect(9).
Moreover, tricyclic antidepressants – such as imipramine – can be used to treat NE in patients who have failed to respond to other therapies. Imipramine works by decreasing rapid eye movement (REM) time, stimulating antidiuretic hormone secretion, and relaxing the detrusor muscle. However, it produces significant side effects (anxiety, dizziness, drowsiness, lethargy, dry mouth, anorexia, vomiting) and serious adverse effects (hepatotoxicity and cardiotoxicity). Consequently, imipramine should not be used on a regular basis(9).
Hyperthyroidism, which occurs in 1–2% of the world’s child population, is most often caused by Graves’ disease(11). It is an autoimmune disorder resulting from the excessive stimulation of thyroid receptors by antibodies, which leads to the production of excess thyroid hormones(11). Graves’ disease was also diagnosed in the case reported in this paper. The basic manifestations of the condition include neurological, eye, skin, bone, endocrine, cardiovascular and digestive system symptoms. However, there are reports of concomitant thyroid dysfunction and lower urinary tract symptoms (LUTS)(12). The dominant symptom of LUTS is pollakiuria, followed by night-time urination and a sudden urge to urinate that cannot be stopped(12). Population-based cohort studies show a higher risk of developing urinary incontinence in women diagnosed with hyperthyroidism compared to the control group(13).
Goswami et al., studying a group of 30 patients with decompensated hyperthyroidism, confirmed that 12 out of 30 patients had bladder symptoms, including four patients presenting with episodes of bedwetting during the night or during the night and day. The authors documented that thyrotoxicosis secondary to hyperthyroidism causes hyperactivity of the sympathetic nervous system and uncoordinated functioning of the entire autonomic nervous system. After euthyroidism was achieved as a result of therapy, the symptoms resolved in all the patients with enuresis. The effectiveness of the used drugs blocking the beta-adrenergic receptors may therefore indicate the involvement of the hyperactive sympathetic system in the development of NE in the course of hyperthyroidism(14).
In this particular case, the treatment of the underlying disease resulted in the regression of the LUTS. The same treatment model was used in the case of our 12-year-old patient and proved to be equally effective. The clinical picture, and the resolution of NE after the casual treatment of hyperthyroidism, confirm that in the above-described case bedwetting could appear as a symptom of hyperthyroidism. Moreover, the literature reports that a deficiency of thyroid hormones results in a reduction of the glomerular filtration rate and an increase in vasopressin concentration(15). Therefore, it can be considered whether in patients with hyperthyroidism the opposite phenomenon will occur. This is indicated by the fact that in the presented case the administration of desmopressin improved the child’s condition.
What is more, thyroid hormones influence the stroke volume of the heart. They increase myocardial contractility and the susceptibility of large and small arterial vessels, leading to a decrease in peripheral vascular resistance and diastolic pressure. Reduced renal blood flow results in the secondary stimulation of the renin–angiotensin–aldosterone system, and an increase in blood volume and preload(16). This can contribute to reducing the afterload and increasing the release of atrial natriuretic peptide (ANP), which intensifies diuresis.
The literature also suggests that the pathomechanism of NE secondary to hyperthyroidism may result from the so-called prepulse inhibition (PPI). It is a neurological phenomenon in which a weaker prestimulus (prepulse) inhibits the body’s response to a subsequent strong reflex-eliciting stimulus (pulse) (Fig. 1). Children suffering from NE are known to have a lower level of PPI. Reduced PPI is a recognised parameter for a loss of the central control mechanism at the brainstem level(17,18).
The catabolism of catecholamines is decreased in hyperthyroidism, and increased levels of dopamine attenuate the PPI in humans. The problem of enuresis in hyperthyroidism might have to be regarded as a cause of temporarily elevated cerebral levels of catecholamines, leading to impaired central control mechanisms. When the thyroid hormone levels are decreased (which, in our patient’s case, was achieved with thiamazole), the levels of adrenaline and dopamine decrease, the PPI level normalises, and enuresis ceases (17).

**SUMMARY**

Both NE and hyperthyroidism are separate disease entities and they occur relatively frequently. However, their concomitance and dependence on each other are also occasionally found. Although the pathomechanism of NE is not yet fully understood, there are multiple mechanisms that link overproduction of thyroid hormones with incontinence disorders in children. Therefore, it is essential to evaluate the patient holistically. The above case perfectly illustrates that nephrological problems might result from endocrine disorders.

**Conflict of interest**

Neither of the authors has any financial or personal affiliation with other persons or organisations that could adversely affect the content of the publication and claim the rights to this work.

**References**