

## Treatment of Children with Overactive Bladder and Nocturnal Polyuria

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### Abstract

**Background:** The proposed method of overactive bladder (OAB) correction in children includes standard drug bladder enlargement using muscarinic anticholinergics. The method is characterized by extra study of the concentration level of diuretic hormone (ADH).

**Objective:** The examination of 150 children aged from 5 to 17 years with OAB included voiding diary, calendar of urinary incontinence, urinalysis for Zimnitsky, uroflowmetry with residual urine determination, and kidney and bladder ultrasound. The observation was conducted over 3 months. In 60 children, we revealed the prevalence of nocturnal urine. We initially divided the patients into groups according to the severity of nocturia based on daily urine output. Group I consisted of twenty children with night diuresis at the level of 40-49% of the daily rate; Group II - fifteen children with 50-59%; and Group III - five children with over 60%. Furthermore, we determined the relative importance of nocturnal urine osmolality in children. When comparing these groups and the level of urine osmolality, we obtained a direct, though weak, correlation ( $r = 0.45$ ;  $p > 0.05$ ).

**Methods:** To reveal ADH deficiency, the method for determining daily and nocturnal urine osmolality was used. When ADH concentration decreases to the level of night osmolality of at least 200 mosm/l and above 458 mosm/l, the therapy is supplemented with desmopressin (Minirin MELT).

**Results:** The effectiveness of this treatment method was higher in 40 children with oxybutynin and Minirin than in those with oxybutynin alone. It is proved by the increase of life periods without episodes of daily and nocturnal incontinence and bladder increase after 4-6 weeks of treatment compared to the group without Minirin reaching the same effect only after 10-12 weeks of treatment.

**Conclusion:** Due to the proposed treatment, the level of nocturnal polyuria decreased, and nocturnal urine osmolality increased in all children.

**Keywords:** Overactive bladder, Nocturnal polyuria, Children, Diuretic hormone, Osmolarity

### Introduction

Overactive bladder (OAB) is a clinical symptom, which includes urgent and frequent voiding combined with daytime incontinence (International Standard Terminology (ICS), 2002). This pathology is observed in 17% of children aged from 5 to 12 years [1]. The major pathogenic factor of incontinence during OAB has always been high intravesical pressure and reduced functional bladder capacity [2]. The treatment of patients with this nosology is aimed at correcting the pathogenetic link with the use

### Article Information

**Article Type:** Research

**Article Number:** JPII02

**Received Date:** 29 December, 2017

**Accepted Date:** 12 January, 2018

**Published Date:** 19 January, 2018

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**Citation:** Morozov SL, Guseva NB, Dlin VV, Korsunsky A (2018) Treatment of Children with Overactive Bladder and Nocturnal Polyuria. J Pediat Infants Vol: 1, Issu: 1 (09-11).

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of drugs that help increase the bladder, such as oxybutynin, tolterodine, trospium chloride and others [3]. However, the treatment results of children with OAB cannot be considered satisfactory due to remaining uncontrolled bladder emptying at night, though with complete relief of the urgent syndrome during wakefulness.

The examination results of patients with OAB at the Speransky Children's Hospital in Moscow during 2007-2011 (16578 persons) showed frequent urination in the night hours and urinary incontinence of two or more times per night in 40% (6458 persons) of the patients [4]. Given the immaturity of the autonomic regulation of the function of the lower urinary tract in children due to uneven development of organs and structures in the growth process, we hypothesized that repeated emptying goes unchecked due to increased nocturnal urine production in children. The combination of nocturnal polyuria and low volume bladder create a sustainable "conflict situation" [5]. Its essence lies in the imbalance between the rate of urine production and the ability of the bladder to its accumulation in the night hours. In these cases, night diuresis exceeds the functional bladder capacity due to the shortage of adiuretic hormone (ADH), which fundamentally changes the usual course of urine elimination process at the level of the lower urinary tract, provoking frequent voiding at night. The previously applied treatment for OAB at night proved to be ineffective.

Here urine osmolality remains below 200 milliosmoles per liter (mosm/l), and its output at the level of over 0.5 ml/hr. The full nephrogenic diabetes insipidus has no natural response to vasopressin. When fluid intake is stopped by these patients, the secretion of vasopressin is enhanced. By the time this sample is completed, the rate of excretion and osmolality (a measure of urine concentration, in which large values indicate concentrated urine and small values indicate diluted urine) [4]. Consumption of water (including water contained in food) affects the osmolality of urine. concentration of active substances in 1 liter of solution) of urine will reflect the physiological level of vasopressin, which influences the intact renal tubules that permeate interstitial medulla. The concentration of urea and sodium chloride was low because of their chronic washout. In other words, the washing process determines the upper limit of osmolality of the urine. Therefore, in patients with primary polydipsia, the concentrating ability of the kidneys will be submaximal, despite the normal secretion of vasopressin. Exogenous vasopressin can increase the osmotic concentration of urine, though only slightly, by less than 9%. The main reason for the restriction of osmosis is the process of washing out the dissolved substances from the brain substance of the kidney, and not in the absence of sufficient secretion of the vasopressin or insensitivity of the renal tubules. Usually, by the end of the test with deprivation of fluid intake, the osmolality of the excreted urine exceeds 400 mosm/kg [6].

In this context, the problem to be solved by the proposed method of diagnosis, allows for a differential diagnosis of diabetes insipidus and increase the effectiveness of the OAB treatment. This problem was solved through identifying the new OAB pathogenetic factor such as nocturia and

developing the appropriate drug treatment. Not only does the bladder capacity increase, but also the correction of nocturnal urine overproduction proves to be a significant result for the introduction of diagnostics of urine osmolality in the diagnostic complex of children with OAB.

## Materials and Methods

We examined 150 children aged from five to seventeen years with OAB. The protocol of examination included voiding diary, calendar of episodes of urinary incontinence, urine test for Zimnitsky, uroflowmetry with residual urine determination, and ultrasound of kidneys and bladder. The observation was conducted over 3 months. In 60 children, we revealed the prevalence of nocturnal urine. We initially divided the patients into groups according to the severity of nocturia as a percentage of the daily urine output. Group I consisted of twenty children with night diuresis at the level of 40-49% of the daily rate; Group II - fifteen children with 50-59% of the daily rate; and Group III - five children with more than 60% of the daily rate. Furthermore, we determined the relative importance of nocturnal urine osmolality in children. When comparing these groups of children and the level of urine osmolality, we obtained a direct, though weak, correlation ( $r = 0.45$ ;  $p > 0.05$ ).

To reveal ADH deficiency, the method for determining the daily and nocturnal urine osmolality was used. During the day, the patient collected two portions of urine: the first from 6 a.m. to 6 p.m. and the second from 6 p.m. to 6 a.m. The urine osmolality was measured by the advanced micro osmometer, Model 3300. The main indicators in a patient with polyuria are the relative density and osmolality of urine. Osmolality characterizes the osmoregulatory function of kidneys. The value of 300 mosm/kg, corresponding to approximately 0.3 osm/l and indicating isotonic urine plasma concentration means no concentration of glomerular filtrate and corresponds to a relative density of urine of 1010 - 1012.

Relative density of urine, exceeding 1012 (urine osmolality above 300 mosm/kg), in patients with polyuria testifies to the excretion of large amounts of salts caused by infusion of saline solutions, osmotic diuresis, use of diuretics, cystic renal medullary lesions or necrosis after recovery or bilateral renal tubule obstruction. Relative density of urine of less than 1005 (urine osmolality below 150 mosm/kg), in a patient with polyuria means virtual absence of ADH secretion.

## Results

The study included 60 children with OAB to determine daily and nocturnal urine osmolality and assess its relationship the level of nocturnal polyuria. The group included 37 boys (81%) and 23 girls (29%) with the average age of  $9,78 \pm 3,1$ . All the children observed had nocturnal polyuria, which amounted to  $57, 7 \pm 8,4\%$  of the daily urine output, with nocturnal diuresis being significantly higher than the daily one ( $P = 0.01$ ;  $P < 0.05$ ) and averaging  $433 \pm 225$  ml versus the daytime rate of  $359 \pm 188$  ml. When assessing the urine density in the Zimnitsky test, the nocturnal urine density was significantly lower than that of daytime - 1008

+ 0.5 ( $P = 0.0004$ ,  $P < 0.05$ ), indicating the lack of osmotic concentration of urine (number = 1010). Furthermore, daily and nocturnal urine osmolality was determined in children. The daily osmolality was equal to  $359 \pm 31.2$  mosm/l, while the night one was  $202 \pm 44.9$  mosm/l, which was significantly below the daily urine osmolality (less than 300 mosm/l) ( $P = 0.0004$ ,  $P < 0.05$ ). Reduction in nocturnal urine osmolality suggests ADH deficiency.

## Discussion

Thus, the indication for Minirin is the ADH concentration with osmolality of 200 mosm/l. Treatment starts with a minimum dose of 60 mcg due to the lack of treatment experience using this medication in patients with OAB. However, the drug was prescribed for 3 months in accordance with the official prescription recommendation for children. Forty patients were treated with 5 mg of oxybutynin 2 times a day, and Minirin in a monthly ascending dose of 60-120-180 mcg before 7 p.m. (this was done for two reasons: the growth trend in urine concentration during the day and avoiding combination of two medications in a single dose). The voiding volume increased by 40% in children under 14 years old from  $45.5 + 15$  ml to  $75.5 + 15$  ml. In children aged from 14 to 17 years, the voiding volume was initially higher at the level of  $58.8 + 18$  ml, and the increase reached 30%, up to  $90 + 20$  ml.

Twenty patients received only 5 mg of oxybutynin 2 times a day. Side effects in the form of dry mucous membranes when taking oxybutynin were observed in only one patient. There were no side effects when taking Minirin and desmopressin of 60 children, 20 were treated with oxybutynin alone for 3 months. The therapy episodes of daytime urinary incontinence stopped, nocturnal episodes of urinary incontinence remained unchanged. We expected the increase in bladder capacity from  $40.3 + 16.2$  ml to  $97.3 + 14.7$  ml. The nocturnal urine volume was 45-51% with no changes, day and night osmolality remained the same, indicating a continuing shortage of ADH. The initial dose of Minirin was raised after one month from 60 mcg up to 120 mcg for all 40 people in connection with the continuing predominance of nocturnal urine of up to 51% of the daily rate. The dose increased from 120 to 180 mcg in 25 patients aged from 14 to 17 years old after one month of reception, as the night diuresis was 42-47% of the daily rate. In 15 patients, the dose remained at the same level of 120 mcg due to the reduction of nocturnal urine down to 36-40%. After

three months of treatment, in all 40 patients the number of night incontinence episodes dropped to 0-1 times a week.

## Conclusion

The proposed method of examination and treatment of children with OAB allows a differential diagnosis of diabetes insipidus, which increases the efficiency of its correction by means of early detection of this disease. When ADH concentration decreases to the level of night osmolality of at least 200 mosm/l and above 458 mosm/l, the therapy is supplemented with desmopressin (Minirin MELT). For identifying the lower level of urine below 200 mosm/l, the patient is sent for treatment to an endocrinologist. The duration of treatment is 3 months. However, the treatment of children with OAB and nocturia is different in that the use of Minirin begins with a minimal dose during the first month which is 60 mcg sublingually before 7 p.m., followed by a dose increase after one and two months for nocturnal polyuria being over 40% of daily diuresis.

The effectiveness of the proposed treatment method was higher in 40 children with oxybutynin and Minirin than in those with oxybutynin alone. It is proven by the increase of life periods without episodes of day and night incontinence and bladder increase after 4-6 weeks of treatment compared to the group without Minirin reaching the same effect only after 10-12 weeks of treatment. Due to the proposed treatment, the level of nocturnal polyuria decreased, and the level of nocturnal urine osmolality increased in all children.

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