MINISTRY OF HEALTH OF REPUBLIC OF UZBEKISTAN

CENTRE FOR MEDICAL EDUCATION

TASHKENT MEDICAL ACADEMY

Overactive bladder - a modern view on the aetiopathogenesis and the possibilities of medical correction

Textbook for urology residents in medical schools

Tashkent-2012

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Overactive bladder – a modern view on aetiopathogenesis and possibilities of its medicamentous correction

Overactive bladder (OAB) is a syndrome characterized by the presence of urgency (compelling urge to urinate), which may be accompanied by frequent urination, urinary incontinence and nocturia (according to the ICS report - International Continence Society terminology on the standardization of lower urinary tract function, 2003).

OAB is quite common in clinical practice and occurs in about 100 million people in the world. Epidemiological studies have shown that OAB is part of the ten most common diseases, staying ahead of well-known diabetes mellitus, stomach ulcer and duodenal ulcer, asthma, osteoporosis. There are about 17% of Europe adult population have symptoms of OAB [11].

OAB occurs with equal frequency in both women and men, its prevalence increases with age.

Many issues concerning the aetiology and pathogenesis of the syndrome, its nature remain valid and continue to attract the attention of most researchers in this field. Urodynamic studies have shown that most patients with urgent and frequent urination have detrusor overactivity, which consists of involuntary detrusor contractions during bladder filling [2].

It is necessary to distinguish between neurogenic and idiopathic detrusor overactivity. It is well established that neurogenic is a consequence of neurogenic disorders (lesion at the supraspinal centers level of the nervous system), and idiopathic detrusor overactivity is a consequence of age-related changes in the detrusor muscle, bladder outlet obstruction, and possibly the anatomical changes of the urethra and bladder [2].

Neurogenic detrusor overactivity pathogenesis theory implies a violation of the bladder innervation. The accumulation of urine in the bladder is the result of its unique ability to maintain low detrusor pressure in the lumen of the bladder, despite the increase of incoming urine volume, called "adaptive capacity" or "compliance". This detrusor ability is provided by the close interaction between the sympathetic, parasympathetic and somatic nervous systems. Any damage at the higher centers level of the nervous system responsible for the bladder accumulation ability, as well as at the level of pathways can lead to a violation of this well-established system. Parkinson's disease, multiple sclerosis, circulatory disorders, tumors, brain injuries can cause neurogenic detrusor overactivity. These diseases are accompanied by failure of the central nervous system control for the bladder storage ability. At the same stimulation threshold of nerve fibers that carry information to the sacral micturition center is reduced, which results in involuntary contraction of the detrusor muscle with a small amount of bladder filling. This is expressed in detrusor hyperactivity, clinically manifested urgent and frequent urination, often with urge incontinence [6].

Block BFM et al. (1997) in the study of positron-emission tomography of the brain in elderly patients with complaints of frequent urination and urge showed that these patients have poor blood circulation in the frontal lobes of the cerebral

cortex. These data support the view that supraspinal lesions often lead to loss of inhibitory control of miction cycle and accompanied by detrusor overactivity [4].

Myogenic theory is based on identifying of morphological changes patterns in the detrusor muscle in patients with idiopathic detrusor overactivity. Histochemical studies show that with age and bladder outlet obstruction, along with an increase in collagen content density of cholinergic nerve fibers in the detrusor wall is reduced. This leads to postsynaptic cholinergic denervation of the detrusor. In the unaltered cholinergic fibers develop increased sensitivity to cholinergic nerve stimulation (acetylcholine), which is manifested by involuntary contractions of the detrusor [12]. This is confirmed by the presence of OAB symptoms in the 40-60% of men with benign prostatic hyperplasia. It is determined with electron microscopy that OAB patients detrusor has disruption of normal intercellular junctions as intercellular junctions and cell membrane protrusions of one myocyte to the next with the convergence of myocyte intercellular boundaries - "tight connection of two parallel planes of adjacent myocytes" [7].

Brading and Turner in 1994. considering the OAB morphological changes proposed a theory of the detrusor overactivity pathogenesis based on increased excitability of myocytes, which are in close contact with each other in areas of denervation [5].

Thus, the modern pattern of idiopathic detrusor overactivity pathogenesis is follows: hypoxia that occurs in the detrusor as a consequence of the age arteriosclerosis or as a result of bladder outlet obstruction leads to detrusor denervation. The consequence of this process is structural changes of the detrusor myocytes (close contact between myocytes with increased nervous excitability and conductivity) as a compensatory response to the lack of neural regulation. In this case any spontaneous or provoked bladder walls stretching (urine storage period) cause to contraction of separate myocytes as "chain reaction" and lead to involuntary detrusor contractions. Present time proposed theory of detrusor overactivity is leading and confirmed by Tse et al. (2000) [13] revealed the characteristic intercellular connections previously described by Elbadawi A. and colleagues in 1993.

In recent years, interesting data on the urothelium role in the regulation of bladder and detrusor overactivity formation produced. It is established that the urothelium is a highly specialized structure capable to perceive mechanical, thermal and chemical stimuli, as well as allocate the neurotransmitters that act on receptors in the afferent fibers. It is also proved that the urothelium has muscarinic receptors, which, with detrusor muscarinic receptors, determine bladder sensory function [8].

There is evidence that release of acetylcholine from nerve endings decreases with age. This leads to an increase in of its production urothelial cells. It is believed that the urothelium tension during bladder filling also cause to release of acetylcholine, which probably plays a role in the bladder contractions regulation and detrusor overactivity development [14].

In addition, the changes detected in the mechanism of the detrusor muscle tone regulation, which depends on the participation of adenosine triphosphate. The latter, as well as acetylcholine, release by urothelium under tension. It is established that increase in adenosine triphosphate release by urothelium of the bladder in neurogenic and idiopathic detrusor overactivity. The increase in the number of purinergic receptors P2X2 in suburothelic layer, detected in patients with detrusor overactivity, may also play a role in the development of OAB symptoms [10]

Subject with OAB syndrome can not control or has reduced control of suddenly appearing, leading to premature urination contractions of the bladder. The OAB clinical picture is characterized by frequent urging for urination, an irresistible urge for urination (so called “urgency”) until incontinence (voiding more than 8 per day) and nighttime urination - nocturia (1-2 urination per night). OAB clinical manifestations bring significant social, physiological, professional, family, physical, and sexual problems [1]. OAB syndrome significantly impairs quality of life, contributes to their social exclusion. Patients are often depressed, self-esteem disturbed due to the inability to hold urine and odors associated. Social and physical activity becomes limited as a result of fear to urine loss or frequent necessity of toilet search. This syndrome is not life-threatening condition, but in severe cases can lead to patients disability of [2].

Despite a significant decline in the quality of life, only 4-6,2% of the patients seek professional help. The main reason for this is that prospective patients often associate their condition with the corresponding age-related changes or find it impossible to cure. [1] In these circumstances, it becomes clear the necessity and importance of OAB differential diagnosis. Diagnosis should be done about diseases that have similar clinic, and, above all, manifested with impaired urination symptoms.

Thus, differential diagnosis should exclude: symptomatic prostatic hyperplasia, pelvic prolapse, atrophic vaginitis, pelvic muscle dysfunction aperture, interstitial cystitis, peripheral neuropathy, diabetes, excessive urination, urinary tract tumors, urinary tract infections, stress urinary incontinence [2].

OAB syndrome is an interdisciplinary problem, since these patients together with urologists may be seen in pediatricians, gynecologists, neurologists, neurosurgeons, gerontologists, as well as general practitioners.

Getting the diagnosis of OAB, professionals need to remember that this is symptomatic diagnosis, the process of setting serves two purposes - the exception of any abnormalities that have similar symptoms and definition of dysfunction type. The most, if not primary, role in the OAB diagnosis is assigned to primary care physicians - general and family practitioners, ambulatory gynecologists and urologists, as professionals who first contact with the patient. Keeping OAB patient should be standardized and familiar to them, since the most part of diagnostics is already possible at the stage of outpatient department without the use of special diagnostic procedures [2].

For the OAB diagnosis the following phases of the survey are required: complaints determination and medical history, voiding diary "frequency/volume,"

the patient's physical examination, including pelvic examination in women, and digital rectal examination of prostate in men, kidneys and bladder ultrasound, residual urine determination, urinalysis, and neurological status assessment.

I. The complaints. There is not necessity of all symptoms for the diagnosis. But the patient's complaint for urgency of urination, which is a key symptom, should be mandatory. Detection of urgency is not complicated diagnostic test; data could be easily obtained from the patient's history.

Questionnaire - surveys of patient's clinical status provide invaluable assistance. They reflect the subjective opinion of a patient about his condition. At the same time, the personal assessment is an objective clinical criteria for the clinician. At the present stage following questionnaires: OAB symptom assessment scale (Homma, 2003), urgency severity scale - IUSS (Bowden 2003), prostate symptoms scale IPSS are popular [2].

II. Medical history. History taking is the primary method of examination. The emphasis should be done on urinary symptoms finding, neurological status, as well as general health and mental status.

It should also determine the duration of the disease and especially the symptoms onset, extent and purpose of the preceding and ongoing drug therapy, the presence of neurological disorders (stroke, dementia, Parkinson's disease, multiple sclerosis, diabetic neuropathy), symptoms from the genital tract in women, sexual function and bowel function, earlier burden urinary tract disease. Gynecological history taking is especially important at women, including information about the labors availability, their nature and duration, data about surgical interventions on the pelvic organs.

Age, diabetes mellitus, long-existing urinary infection, smoking, obesity and anxiety and depression increase the risk of OAB. In elderly patients the symptoms may be associated with constipation, motion limitations, cognitive impairment and medications taking. Diuretics, antidepressants, beta-blockers, sedatives, analgesics and anticholinergic drugs promote diuresis, detrusor contractility and bladder outlet obstruction [2].

It is important that the patient could correctly describe episodes of urinary incontinence: whether they are related to physical activity, or observed at rest, whether preceded by an episode of urinary urgency or not.

It is usual urinary diaries applying in order to clarify the clinical symptoms. Urinary diary allows to assess the patient's symptoms more objectively. Quantity of liquid consumed, the frequency and volume of urination, presence of urgency and incontinence episodes are registered with urinary diary.

Urinary diary is the most important part of the outpatient examination of patients with impaired voiding, since it can be used to assess the following:

1. Diuresis.
2. Behavioral characteristics of urination.
3. Opportunity to visit the toilet in time.

Urinary diary filling in should always precede the decision to perform invasive urodynamic examination methods and purpose of any, even the conservative therapy [1].

III. Physical examination. Physical examination of the abdominal, pelvic and perineal areas is essential for patients with OAB.

1. The total, abdominal (including palpation of the bladder) and neurological status estimation.

- Bladder palpation helps to identify the bladder speaker of the womb, indicating the presence of chronic urine retention.

- Neurological status. His objective assessment is vital, because reveals neurogenic aetiology of OAB.

Patient's mental state, his intelligence, ability to navigate in space and time, related to their own state, memory and attention are examinated. Skin sensitivity in the perineal region, anus, back, thighs and buttocks is investigated to evaluate the sensory innervation. Reduction or complete loss of skin sensitivity may be indicative for generalized peripheral neuropathy (diabetes mellitus, alcohol intoxication, toxic lesions), spinal cord or nerve roots defeat. Motor function is assessed by the severity of lower extremities tendon reflexes, which can provide information about the segmental and suprasegmental CNS disorders. For example, high Babinski tendon reflexes indicate on descending nerve pathways damage from the brain to the anterior horn (upper motoneuron). Reduced activity of these reflexes is evidence of lower motor neuron damage (from anterior horn of the spinal cord to peripheral organs).

Anal and bulbocavernous (clitoral) reflexes examination helps to assess the spinal reflexes safety at the level of the sacral spinal cord (irritation of the afferent fibers of n.pudendus and/or n.pelvicus enters to the sacral spinal cord and back through the n.pudendus efferent fibers).

2. Vaginal and/or rectal examination at women and rectal examination at men. Anatomical position of the vagina and uterus front and rear walls, the bladder neck position, the degree of anterior and posterior vaginal walls prolapse at rest and during straining are evaluated.

The possible presence of abnormal masses in the pelvis, prostate changes, suggests following states diagnosis: hypoestrogenizm, pelvic prolapse, fistula or ectopic ureter, pelvic or suburethral tumors, cyst, stool retention and enlarged prostate. It is very important to assess muscle function of pelvic diaphragm [2].

3. Urethral hypermobility assessment (Q-tip test) and cough test (Valsalva maneuver).

a) Q-tip test – Urethral hypermobility is defined if urethral angle is determined by more than 30 degrees;

b) Cough provocation is test for the evaluation of detrusor involuntary contractions caused by increased intra-abdominal pressure and test for stress urinary incontinence. The test is positive, if coughing or straining leads to involuntary loss of fluid with bladder preliminary filling up to 150-200 ml. It is likely to expect sphincter deficiency if the loss of fluid occurs in the supine position [2]. Time of urine leakage occurrence after an episode of increasing intra-abdominal pressure is very important. Coughing can cause bladder hyperactivity (intravesical pressure increase) and in this case there is some "lag" between the

cough and urine loss. If urinary leakage is not observed in the supine position, then test is repeated in the standing position [1].

Ultrasonography is performed to exclude concomitant bladder diseases, the identification of bladder structural changes, as well as to determine residual urine volume [1].

Determination of residue urine in the bladder is a routine screening test in all patients with urination functional disorders [1].

Urine general analysis performing is the "gold standard" for diagnosis of inflammatory processes [1].

IV. Treatment. OAB treatment becomes necessary when the actual symptoms are accompanied by patient's quality of life decreased [9].

Despite the relatively high prevalence of the OAB, to date so far, best practices has not yet developed for the treatment of this condition. This is due, on the one hand, a variety of clinical manifestations, and with another - low efficiency and a large number of existing drugs side effects.

Detrusor hyperactivity treatment can be done in three ways:

1. Behavioral therapy.
2. Drug treatment.
3. Surgical treatment.

In accordance with the recommendations of the ICS, drug treatment is a priority in the treatment of patients with OAB. In general, the following groups of drugs are used: anticholinergic, drugs with mixed type of action, alpha - adrenoblockers, beta blockers, antidepressants, prostaglandin synthesis inhibitors, vasopressin analogues [1].

In accordance with the recommendations of the International Advisory Board for urinary incontinence (International Consultation on Incontinence (ICS)) anticholinergic agents (M-cholinoblockers) are actively recommended (Category A, first line drugs) drugs for the treatment of OAB [3.9]. This recommendations level based on the systematic reviews materials, meta-analysis and the results of randomized controlled trials [1].

The treatment success determines the quality of life. The main task is to restore the lost control of the bladder storage capacity. With this purpose in modern practice following anticholinergic drugs are widely used: trospium chloride (Spasmeks), tolterodine (Urotol), Solifenacin (Vesicare) and oxybuthynin (Driptan). Their use effectiveness of is not in doubt. Drugs are amines, derivatives of ammonium, wherein one or more hydrogen atoms substituted by alcyl or aryl groups. Why has this drugs group such activity? The answer is simple. There are muscarinic M2 (80%) and M3 (20%) (subtypes of cholinergic) receptors in the urinary bladder. Detrusor contraction occurs after the stimulation of detrusor muscle M3-cholinergic receptors by acetylcholine. M-choliniblickers block muscarinic receptors, inhibiting the binding of acetylcholine to the receptor, and preventing, thereby, the contraction of the bladder wall muscle fibers.

In order to confirm this position at the Republican Specialized Center of Urology (RSCU) a number of studies on the efficacy of OAB drug therapy among men and women are evaluated. One of them included a clinical trial of trospium

chloride (drug "Spasmeks") in 20 patients (10 men and 10 women) aged 15 to 74 years.

The criteria for inclusion in the study were patients with idiopathic OAB syndrome with or without urinary incontinence. Patients consumed the drug trospium chloride (TCh): 1 tablet 2-3 times daily with a duration of 30 days. The mean daily dose ranged from 15 to 45 mg. Within a month, the test was monitored every 10 days by assessing the drug effectiveness (urinary diary, OAB symptom scale, uroflowmetry and bladder ultrasound). For patients taking the drug, improvement of overall health, mood and sleep were reported.

The TCh drug was well tolerated by patients, with the exception of 5 (25%) cases, when the following side effects were noted: 2 cases with dry mouth, and 1 cases of dyspepsia, visual disturbances and micturition respectively during treatment.

5 (25%) patients had clinical improvement occurred on 3-d day, 6 (30%) - on 5-th day, and 1 (5%) patients – on 6-th day, and 7 (35%) – 7-th day, and 1 (5%) patient had minimal OAB clinical signs improved.

In assessing the effect due solely to the drug action, it was found that 15 (75%) patients treated with TCh found a marked effect (complete or almost complete elimination of symptoms), 4 (20%) - moderate (partial removal of symptoms) and 1 (5%) patients had minimal (slight improvement).

In assessing the impairments severity of patients with OAB on the Clinical Global Impression (CGL Scale) the following was revealed: 1 (5%) patient had extremely severe course, 8 (40%) patients had severe course, 5 (25%) patients had significant severity, 4 (20%) had moderate severity and 2 (10%) patients had soft severity.

After TCh drug therapy 11 (55%) patients marked significant improvement, 8 (40%) patients marked a clear improvement, 1 (5%) patient marked minimal improvement.

11 (55%) patients had an imperative incontinence. As a result of treatment patients general condition and quality of life has improved considerably, and control examinations revealed a significant decrease or absence of urinary incontinence episodes.

Also group of 24 men with neurogenic OAB who underwent ischemic or hemorrhagic stroke, Parkinson's disease, discirculatory encephalopathy or multiple sclerosis was observed and treated in RSCU with or without urinary incontinence. The average age was 51 years (from 34 to 75). The main neurological diagnosis was performed by neurological examination, including brain magnetic resonance and computed tomography, neurophysiological studies. Urological examination evaluated OAB subjective clinical symptoms, as well as the dynamics of the lower urinary tract symptoms (LUTS). LUTS severity was assessed with IPSS scale, OAB symptoms assessment scale (Homma, 2003) and urinary diary.

General and bacteriological analysis of urine, general clinical blood tests, urinary system ultrasound with residual urine determination, uroflowmetry with assessing effective bladder capacity (EBC) were performed in all patients. All men

received TCh in a dose of 15-45 mg/day, 3 times per day during 1 month. Trospium chloride dose was reduced or treatment was discontinued in case of side effects appearing. Men quality of life was assessed by KNQ (King's Health Questionnaire) questionnaires filling up.

Patients noted improvement as the 20%urination frequency reducing, 31% increase of the urgent desires number, 18% EBC increase after 10 days of TCh taking in dose of 15 mg/day.

In consideration of the lack of side effects, TCh dosage was increased up to 45 mg/day. The results were evaluated after 3 weeks. Urination frequency decreased for 35%, the urgent desires number - for 45%, EBC increased for 25%. Side effects such as headache in 1 (4.1%) patient, constipation in 3 (12.5%) patients, dry mouth in 6 (25.0%) patients were noted.

The emotional status of men improved, anxiety and irritability decreased ($t = 2,44$; $p = 0,015$), as well as sleep quality improved ($t = 2,35$; $p = 0,019$) after TCh intake.

TCh in therapeutic dose of 45 mg/day is the most effective for OAB treatment in neurological patients with supraspinal lesions.

Thus, the TCh is a highly effective and good tolerated in neurogenic and idiopathic OAB treatment, both at men and women, with or without urinary incontinence. It is noted not only OAB symptoms reduce, but also significantly improvement of the patients quality of life.

It should be noted that side effects frequency was clinically insignificant after TCh intake. This fact makes it a very promising drug in the OAB treatment, as in mono- and combination therapy, highlighting it among the analogues.

It is very important to determine the number of side effects and tolerability, because anticholinergic drugs (antimuscarinics) are commonly used for a long time. Doctor should help the patient to find the right remedy and to control the processes of its application.

SITUATIONAL TASKS

Case № 1.

54 years old patient, complains for the constant urge to urinate, frequent urination up to the imperative urinary incontinence, nocturia up to 5 times per night.

Anamnesis: suffered an acute ischemic stroke month ago; prostate is normal in the digital rectal examination

- The preliminary diagnosis?
- What research is needed to confirm it?
- Treatment?

Case № 2.

42 years old female patient turned to the doctor with complains for frequent urination with small portions, imperative urinary incontinence, nocturia up to 2 times per night. There is traumatic childbirth in anamnesis. Bladder ultrasound is normal.

- The preliminary diagnosis?
- What research is needed to establish the diagnosis?
- What diseases should be differentiated?

TEST QUESTIONS

1. Which of these symptoms is typical for OAB?
   A. Frequent urge.
   B. Irresistible urge for urination - urgency, even incontinence.
   C. Frequent urination with small portions.
   D. Night urination - nocturia.
   E. All of the above mentioned symptoms *
2. Which of these symptoms is a key symptom of OAB?
   A. Frequent urge for urination. *
   B. Irresistible urge for urination - urgency, even incontinence.
   C. Frequent urination with small portions
   D. Night urination - nocturia.
   E. All of the above mentioned symptoms
3. Which of these factors increases the risk of OAB?
   A. Age and diabetes mellitus
   B. Long-term urinary infection
   C. Obesity and smoking
   D. Anxiety and depression
   E. All of the above mentioned symptoms *
4. The purpose of "frequency/volume urination diary" examination is:
   A. Daily objective assessment of the urine maximum and average flow rate.
   B. Daily objective assessment of urination curve features.
   C. Objective assessment of urination by the duration of each act of urination and volume of urine registration.
   D. Objective assessment of urination by registration of frequency and residual urine volume after each urination.
   E. Objective assessment of urination by urine frequency and volume registration.*
5. What are the patient examination stages the most necessary for the OAB diagnosis?
   A. Complaints elucidation and a history of "frequency/volume urination diary"
   B. Physical examination, including rectal and/or vaginal examination with a cough test.
   C. Urinary tract ultrasound with residual urine definition
   D. Urinalysis and neurological status assessment
   E. All of the above mentioned stages.*
6. Point the indications for OAB treatment.
   A. OAB with urinary incontinence.
   B. Reduced quality of patient's life .*
   C. Neurogenic form of OAB

D. Idiopathic form of the OAB
E. All of the above mentioned situations.

7. Which group of drugs is a first line treatment for OAB?
A. Alpha-blockers.
B. Antideprssants.
C. Anticholinergics.*
D. Beta - blockers.
E. Inhibitors of the prostaglandins biosynthesis

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