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INFLUENCE OF THE AUTONOMIC NERVOUS SYSTEM ON THE CLINICAL COURSE OF OVERACTIVE BLADDER

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Overactive bladder (OB) is a disease which is very easily diagnosed, but presents considerable difficulties in the choice of treatment mode. At present the specialists turn their attention to this syndrome due to a wide spread of the disease, its negative impact on quality of life, social and economic importance.

Pathogenesis of OB is complex. Thus, under conditions of urothelium atrophy which takes place because of estrogen deficiency in postmenopausal women, in violation of its GAG protective layer, barrier function of urothelium are violated, which leads to its damage. The appearence of urination disorder symptoms are associated with the fact that atrophic mucosa of urethra and triangle of bladder are hypersensitive to even minimal portions of urine [1]. Aging process also play a role in OB development including lowering ability of tissues to repair, their elasticity reduction, increased apoptosis and cell atrophy, degeneration of nerve endings, smooth muscle tone change, deterioration of urothelium and its GAG protective layer. It can be a result of manifestation of bladder outlet obstruction that causes OB symptoms in men suffering from benign hyperplasia, prostate cancer and chronic prostatitis [2].

Detection of overstress and exhaustion of regulatory mechanisms plays an important role in preventing damage to the breakdown of adaptation and the emergence of pathological abnormalities and diseases. Anxiety and depression, which causes failure of serotonergic and noradrenalinergic structures of the central nervous system, reduce the amount of serotonin in the segmental centers urination. It is able to reduce sympathetic reflex of filling and retention of urine in the bladder on one

side and cause disinhibition of parasympathetic reflex of emptying bladder. Such dysfunction is proved by heart rate examination [3].

OB is diagnosed by exclusion of the nervous system pathology; diseases of surrounding organs and lower urinary tract can cause pollakiuria (more than 8 times a day), imperative urge for urination, nokturia (2 or more times a night) and urgency incontinence. Therefore, examination of the patient should be aimed primarily at the differential detection of possible reasons for its purposeful causal and pathogenetic correction. It is important to use such methods which are available in everyday medical practice. Opportunities of diagnosing dysfunction of autonomic nervous system (ANS) in violation of the act of urination were revealed by a pilot study [4] using the method of spectral analysis of heart rate variability (SA HRV) during retrograde cystometry. Analysis of heart rate variability (HRV) is a quantitative method for evaluating the mechanisms of neurohumoral regulation of the heart, the ratio between the sympathetic and parasympathetic departments of the ANS.

The purpose of research was to determine the characteristics of autonomic act of urination in OB, to evaluate changes in heart rate variability indices during the natural filling bladder and to study a possibility of adaptation capabilities correction taking into account autonomic regulation background.

Subjects and methods. The study involved 63 patients, all women with symptoms of lower urinary tract that met diagnostic criteria of the International Continence Society of (ICS) for overactive bladder. The clinical features of the patients were identified in the choice of the group: 1 group consisted of 29 women with “sensory” OB symptoms without incontinence, 2 group — 16 women with urgency incontinence, 3 group — 18 patients with OB with algetic syndrome. All the patients during 3 months before the study did not receive drugs that could affect the ANS. These data were compared with data in the control group (11 healthy women of the same age of those in the main group).

A daily monitoring of ECG simultaneously with the registration of the daily rhythm of spontaneous urination followed by spectral analysis of HRV is our original method, which allows to identify patterns of ANS activity under conditions of physiological filling of bladder, formation of urination and under emotional stress

with a specific “urinary” component allowing to make objective adaptive capacity of bladder.

At the first stage of the study all the patients had urological, gynecological, neurological examination to exclude systemic diseases that could cause OB symptoms. Also there was performed evaluation of objective and subjective symptoms of OB using questionnaires of quality of life of patients, the intensity of algetic syndrome, dysuria symptoms. All patients were carried out an objective examination, assessment of complaints, medical history, ultrasound examination of the urinary system with determination of residual urine, uroflowmetry.

At the second stage, patients were prescribed standard pattern of study including two diagnostic procedures: daily monitoring of ECG in a normal activity of the patient, while registrating the daily rhythm of urination by filling out a urinary diary in which patients reported the appearance of the first time urination, time of occurrence of intense vesical tenesmus, imperative feeling of urination, episodes of incontinence and the time and volume of each urination.

A daily monitoring of ECG findings were analyzed using computer programs. HRV parameters were calculated automatically with a 5 minutes frequency of recording. Electrodes were imposed so as to get the allocation of maximum amplitude wave R, thus ensuring correct recognition of QRS complex and analysis of obtained data [5].

At the third, main stage, there was performed CA HRV during multiple, different degrees of filling and emptying of the bladder within a 24 hour period. There were calculated HRV temporal and spectral parameters to evaluate the autonomic balance. According to the recommendations of the Committee of Experts of the European Society of Cardiology and the North American Society of pacing and electrophysiology there were assessed temporary HRV indices: the standard deviation of the average duration of all R-R intervals during the day (SDNN), the standard deviations the duration of average R-R intervals during the 5-minute intervals (SDANN), square root mean squared differences of successive intervals R-R (rMSSD), percentage of successive intervals RR, the difference between them is greater than 50 ms (pNN50), the average of the standard deviations of the average

values of the length of RR intervals in 5-minute intervals (SDNIDX). Increasing values of temporal parameters of HRV were regarded as increased parasympathetic influence, decline — as sympathetic activation [4]. Expectant ratio of total number of R-R intervals to the number of intervals with the most common duration — tension index (TI).

The ANS departments activity was differentiated by spectral analysis — the following HRV frequency values were determined: power spectrum of the low frequency (0.05–0.15 Hz) — LF, reflecting mainly the impact of the ANS sympathetic department, the power spectrum of the high-frequency (0.15–0.40 Hz) — HF, gives an indication of the influence of the parasympathetic division of ANS. Very low frequency oscillations (VLF) — 0.003–0.04 Hz — presumably reflecting humoral effects on the regulation of heart rate. It was calculated sympatho-parasympathetic index — the ratio of low and high frequency components (LF/HF) — a sort of balance of sympathetic and parasympathetic activity.

The results were treated by methods of variation statistics, probability of arithmetic values difference was determined using the Student t-test, differences at $p<0.05$ were considered reliable.

Results and Discussion

According to the study results there were revealed some features of OB — remitting disease course in 39 cases. Exacerbation of the disease is associated with emotional stress in 43 women; 25 patients had lack of frequent urination or urgent impulses in certain social conditions — at home, on vacation, when doing interesting or urgent work. Acute traumatic event in the onset of OB (within 12 months before the first symptoms) was found in 42 women in the study group. Among the causes of emotional stress there observed such as incontinence in a public place (12 women), prolonged retention of urine due to shame (15 women), family illness due to disease of the pelvic organs, incorrect diagnosis of urogenital diseases (18 women), the death of friends or relatives (12 women), divorce, prolonged troubles at work (28 women).

We conducted SA HRV examination in the control group to assess changes in performance in normal and determine their orientation vector. First of all there were evaluated parameters SA HRV at rest and adequacy of adaptation at physiological

filling bladder. At rest in the control group it was observed eutonia with a slight predominance of parasympathetic influences. During the urge to urinate, which formed naturally and was evaluated as an urge of weak intensity, did not require voluntary effort for continence, we noted a statistically significant increase in indicators of parasympathetic activity segmental level ($p < 0.01$), respectively, with a significant decrease in VLF ($p < 0.002$), a decrease in sympathetic-parasympathetic index ($p < 0.001$), increasing the power spectrum Ptot ($p < 0.001$). In this regard, we found that the normal adaptive response to physiological filling bladder is increase in parasympathetic activation. With intensive urge for urination there were not observed more significant redistribution of HRV spectrum indices. These data showed a balance of autonomic tone and adequacy of reservoir function of bladder.

When analyzing the output parameters of HRV in patients with cystalgia (3rd group) it was observed a decrease in ANS general activity (SDNN values), etc. and increasing predominance of sympathetic nervous system (rise in LF/HF values) in comparison with 1st and 2nd group patients (Table 1), indicating a major stress of regulatory systems in patients with the 3rd group.

In 27% of women from 1st group in 61% of women from 2nd group and 78% of women in the third group of rest there was observed a pronounced sympathicotonia caused by the predominance of suprasegmental segmental VLF, LF influences with a corresponding increase in sympathetic-parasympathetic index. In SA HRV at the moment of urination of different intensity (Tables 2, 3) there were no significant changes in the distribution of HRV power spectral indices, although main groups, in contrast to the control group, the urge was more intense at the stage of its natural occurrence that, however, did not cause any changes in the distribution of spectral fluctuations, pointing out the rigidity of adaptation mechanisms: providing bladder reservoir function was carried by prevailing of suprasegmental structures influence. Thus, when OB during physiological filling of bladder due to the disruption of regulatory capacity an adequate redistribution of sympathetic-parasympathetic relations in the form of increased parasympathetic activation do not take place. Due to intensifion of adaptation mechanisms at the background of stress there occurs earlier formation of imperative tenesmus.

In 11 patients with OB (all women of the 1st group) SA HRV obtained data at rest and during urodynamic tests showed a predominance of segmental parasympathetic influences while providing bladder adaptation and autonomic tone balance of this group of patients.

After analysis of final indices including autonomic regulation background, among the examined patients a treatment group was formed. The selected 33 patients (7 — from the 1st group, 12 — from the 2nd and 14 — from 3rd group), in violation of autonomic act of urination due to stress of central neurohumoral sympathetic influences. Drug therapy of OB today is a desire to change the neurotransmitter effect on the lower urinary tract. These results together with data on the role of serotonin and g-aminobutyric acid (GABA) in the regulation of the act of urination allowed to offer selective serotonin reuptake inhibitors (SSRIs) and cyclic structural analogue of GABA as pathogenetic treatment of OB symptoms. This task was solved by a combined therapy with a specific serotonin reuptake inhibitor Sertraline hydrochloride starting treatment with a dose of 25 mg at night, in a week, increasing the dose up to 50 mg and with the drug Gabapentin (from the antiepileptic group that has structural similarity to the GABA neurotransmitter) — at the 1st day — 300 mg once a day, at the 2nd day — 300 mg 2 times a day, in the future — 300 mg 3 times daily with general course 12 weeks.

The effectiveness of therapy was assessed by urinary diaries, the results of testing the quality of life (QoL) in connection with symptoms of lower urinary tract cystalgia intensity on D. H. Barlow scale. Comparing objective data (dynamics of pollakiuria intensity, night pollakiuria, performance urination) and a subjective assessment of the effectiveness of the doctor and patient treatment, there was a statistically significant decrease in frequency of pollakiuria and urgency in 69% of cases. This is confirmed by decrease in intensity of OB “sensory” symptoms in this group of patients: the number of twice decreased pollakiuria episodes, night pollakiuria — 1.5 times, and the intensity cystalgia decreased from an average 3-4 to 0–1 points. In patients with preserved frequent urination, it was noted the increase in the average effective volume of urination. Episodes of urgency urinary incontinence ($p < 0.05$) and its frequency ($p < 0.001$) significantly decreased. Nokturia remained in

42% patients, but its incidence has declined significantly. Decreasing of the general QoL score pointed out improvement of quality of life after the therapy course. Thus, in some OB patients (61%) there is an imbalance of autonomic regulatory mechanisms in the empty and filled bladder, such dysfunction is clearly proved by heart rate study.

Conclusion:

1. Spectral analysis of heart rate variability during natural formation of the first and intense urge to urinate at night reveals features of autonomic installations of urination in patients with overactive bladder.

2. The study revealed that response to physiological filling bladder with the gradual formation of urination is segmental parasympathetic activation in healthy somatic women. The OB group of patients with cystalgia (78% of patients) has a reduction in the activity of segmental mechanisms in the regulation of detrusor tone with compensatory suprasegmental stress. Providing adaptation to intense urge to urinate is achieved by tension of the central sympathetic influences. In 61% of OB patients with urgency incontinence increased sympathetic activation has been observed even with insignificant filling of the bladder. When imperative urination mechanisms of detrusor tone are realized by sympathetic segmental level while preserving suprasegmental increase of sympathetic influences. This suggests that even slight filling of the bladder is perceived as a significant physiological stress, which is accompanied by an increase in sympathetic influences.

3. Pathogenetic effect SSRIs Sertraline hydrochloride therapy in combination with Gabapentin in treatment of functional disorders of the lower urinary tract is positive dynamics of dysuria symptoms intensity, and in improving the performance of urination (removal of residual urine, pronounced increase in the average effective volume of the bladder and urination efficiency factor), indicating to optimization reservoir-evacuation function of the bladder, regulating effect on the detrusor tone and closing apparatus of the bladder neck.

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The purpose of research was to determine the characteristics of autonomic act of urination in OB, to evaluate changes in heart rate variability indices during the natural filling bladder and to study a possibility of adaptation capabilities including correction bladder background autonomic regulation.

Key words: overactive bladder, autonomic nervous system, incontinence.

Table 1. Analysis of baseline 3 HRV in groups of patients

Indicator	The value of the indicator (M ± m) in groups of patients			
	control group (n=11)	1 group (n=29)	2 group (n=16)	3 group (n=18)
SDNN, ms	141 ± 8	166±18	118±11*	98±5*°
SDANN, ms	124 ± 15	103±14	97±11	92±13
SDNN index, ms	54 ± 7	46 ± 10	35 ± 6	31±7*
RMSSD, ms	27 ± 12	28 ± 15	25 ± 12	23 ± 9
TI, %	21±1,7	23,2±1,4	25,4±2,4	27,2±1,4*

Note. Differences of indicators are reliable as compared to the following: * — patients in the control group; ° — in patients with group 1 (P <0.05).

Table 2. Analysis of frequency HRV in patients with 2st group (n=16)

Indicator	The value of the indicator (M ± m)			
	tranquility	first urge to urinate	intense urge to urinate	incontinence
VLF, %	47 ± 2,1	45 ± 2,4	46 ± 1,9	51 ± 2,5
LF, %	32 ± 2,3	33 ± 3,1	30 ± 2,9	32 ± 3,4
HF, %	21 ± 1,8	22 ± 2,6	14 ± 1,9	17 ± 2,9
LF/HF standard units	1,5±0,21	1,5±0,27	2,14±0,23	1,88±0,27

Table 3. Analysis of frequency HRV in patients with 3rd group (n=18)

Indicator	The value of the indicator (M ± m)		
	Tranquility	first urge to urinate	intense urge to urinate
VLF, %	56 ± 2,4	54 ± 2,1	58 ± 2,7
LF, %	27 ± 3,0	25 ± 2,3	31 ± 2,6
HF, %	17 ± 1,9	19 ± 2,9	11 ± 1,7
LF/HF standard units	1,53±0,27	1,31±0,22	2,8 ±0,41