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THE OVERACTIVE BLADDER MODEL ANATOMICAL AND MORPHOLOGICAL CORRELATES

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Abstract

After the overactive bladder modelling one could see the urinary ways in vivo changes registration using MRI with MR-urography before and after the diuretic load. The morphological investigations results proved the overactive bladder properties using MRI-registration. The internal organs and urinary ways showed no changes during the early terms. 30 days after the overactive bladder model induction one could register the morphological changes resulted in the ureterohydronephrosis development. The overactive bladder model stability and its adequate type to clinical condition was proved on the basis of the performed functional and morphological studies together with pathological changes dynamics characteristic for ureterohydronephrosis were studied.

Key words: urinary incontinence, overactive bladder, upper urinary ways, MR-uroghraphy, ureterohydronephrosis.

Actuality of urogenital diseases and urine incontinence problem in women naturally increases with life duration prolongation. This tendency registered not only in the EU countries but also in USA [1, 2].

The results of epidemiological studies indicate that overactive bladder (OAB) incidence in adults equals to 10-20%. OAB frequency significant differences in the general population of men and women were not detected [3, 4]. The prevalence of women aged below 60 is noted, while the OAB incidence in the elderly is higher comparing with the same in males [2]. The OAB frequency in men and women aged from 20 to 29 years was respectively 4.3 and 6.6%, aged from 80 to 89 years - 41.5 and 32.5% [5]. The authors predict that OAB frequency will increase. If in 2000 in 5 European countries there were 20.2 million sick patients over 40 years old, 7 million of the - with the urgent urine incontinence [2, 5]. It might be predicted that in 2020 such patients will be 25,5 millions, 9 millions of which - with urgent urine incontinence. Accordingly, an increase in the number of patients will increase the annual direct costs of their treatment from 4.2 million euros - in 2000 to 5.2 million - in 2020 [5].

The magnitude of the problem is caused by the anatomical and physiological features that accompany the aging population. It is multidisciplinary, since it complicates the course of various diseases, in particular in the field of urology, andrology, obstetrics, gynecology, oncology, neurology, and also congenital malformations of the genitourinary system, traumas of small pelvic organs, spinal cord, etc [6].

For the purpose of studying the anatomical and functional changes of the kidneys and upper secondary urinary ways (UW) that arise after the OAB model creation, the experimental trials were performed using MRI-urography and histological methods.

Materials and methods

The OAB model was reproduced on sexually mature white female rats, body weight 250-280 g. Animals once a day for 14, 30 and 90 days intraperitoneally injected a solution of the drug hombiotensin, which contained reserpine 0.45 mg.

During work with laboratory animals the requirements of "Scientific and practical recommendations for the maintenance of laboratory animals and work with them" were followed (certify by State Pharmacological Center of Ministry of Health Care of Ukraine, protocol N8, from 22.06.2012).

All animals during the experiment were performed an MRI with UW visualization due to our modified programs with MRI-urology in the mode of hydrography before and after diuretic administration. The survey was performed in condition of a drug sleep using the magnetic resonance imaging machine “Philips INTERA 1.5 T”.

In order to monitor the UW life-time changes MRIs with MR-urology were used before and after diuresis. The contrast of the tissue image on the tomograms depended on the

time needed for the relaxation of the protons, more precisely, from the two components: T2 is the time of transverse (spin-spin) relaxation and T1 is the time of the longitudinal (spin-lattice) relaxation.

T1W-TSE, T2W, T2W-SPAIR images with identical orientation and cut-off parameters were obtained to characterize the tissues. Urogramm 3D SENSE before and after diuretic loading was used to determine the UW functional capabilities. The research was conducted in the Coil SENSE-BODY, the sections were oriented coronally at a small angle, approximately parallel to the spine.

T1W-TSE images in the coronal plane were obtained using the Turbo SE (fast spin echo) with the following parameters: TR 490 ms, TE 10 ms, matrix 416x512, FoV 478 mm, thickness of cut 2 mm, through 0.5 mm. T2W-TSE images in the coronal plane were obtained using the Turbo SE (fast spin echo) with the following parameters: TR 3539 ms, TE 80 ms, matrix 407x528, FoV 468 mm, thickness of cut 2 mm, 1 mm.

T2W-SPAIR images in the coronal plane were obtained with the following parameters: TR 4000 ms, TE 80 ms, matrix 407x528, FoV 468 mm, thickness of cut 3 mm, 1 mm. Urogramm 3D SENSE images in the coronal plane were obtained with the following parameters: TR 1216 ms, TE 650 ms, matrix 230x576, FoV 293 mm.

The research was carried out in accordance with the method of thick block (total two-dimensional image from the block of fabrics of a given thickness) or thin sections (thickness of the cut from 0.5 mm); With MIP, Urogramm 3D SENSE-Reconstruction received a three-dimensional image of liquid-containing structures. The images were formed from both a single data collection unit and through the "gluing" of several blocks to analyze broader areas of interest.

On the received images the UW variants of structure and mutual relation were diagnosed. In the analysis of primary thin sections, the Urogramm 3D SENSE image was evaluated in detail by the layers of small fluid structures.

Since *the MR image* is static and is a cumulative scan result in a few minutes, the preparation for the MR study was aimed at creating optimal conditions for obtaining high-quality images, motor artefacts avoiding, urinary bladder (UB) adequate filling and providing adjacent organs with the most advantageous diagnostic position.

White rats were immobilized by sodium thiopental, 5%, 0.2 ml, i.p. and propofol, 1%, 0.4 ml during the trial. Animals were in the lying on the back position fixed for the forelimbs and hindlimbs.

Both UW and UB adequate filling was achieved by physiological water loading. The method of MRI - MR-urography in the mode of hydrography with diuresis load included the receipt of a series of sections and postprocessing processing, the construction of three-dimensional images. The topogram was performed in three orthogonal projections.

To diagnose the UW condition from the cup pelvis complex (CPC) to UB, the first noncontact MR-urography was performed in the frontal projection (T2 FSE image, FOV 36-48 cm, TE from 1100 ms or more, TR from 20 000 ms, scan duration from 20 s to 1 min). The next step was diuretic i.v. injection at a rate of 0.8 mg/kg body weight.

After UW and UB conditions estimation a scan in the coronal plane was performed with T2 FSE, then in T1 mode with identical orientation of the sections, as in Ah T2 - weighted image (WI). The sequence T1-FSE was used.

Next, a second MR-urography, identical to the first with respect to the orientation of sections and scan parameters, was performed 5-10 minutes after the administration of the diuretic. The use of diuretics made it possible to evaluate and compare MRI-urographic images before and after loading.

In this way anatomical and functional changes of the UW were evaluated. Duration of the study do not exceeded 15-20 minutes. The resulting images were analyzed on Philips workstations using Extended MR WorkSpace 2.6.3.3 software.

For histological study animals were taken out from the experiment in 14, 30, 90 days by thiopental-sodium, 5% overdose. Kidneys with ureter and UB were removed, the material was fixed in formaldehyde, 10% solution, dehydrated in alcohols of increasing concentration, clarified in chloroform, sealed in paraffin. Sections with thickness of 5-7 microns were stained with hematoxylin and eosin, picrofuxin for van Gizon. To evaluate the functional activity of the tissues, the Schiff-iodic acid (SIA) method for McManus was used. The preparations were photographed and studied using a light microscope Leica ICC50 HD.

Results and their discussion

In order to objectively evaluate the UW changes we have thoroughly studied the UB and UW normal anatomy. On MR images, normal UB had a droplet shape in all planes. The dimensions, shape, wall thickness and position of UB depended on the degree of filling it. Unmodified UB is symmetric, located on the midline in the cavity of a small pelvis. There was a distinction between the apex, the body, the bottom and the neck - the lower part of the narrow part of the UB that passed into the urethra. UB neck was better visualized on sagittal sections, it was conical. UB is a hollow muscle organ, physiological volume 0.65-0.75 ml (Figure 1).

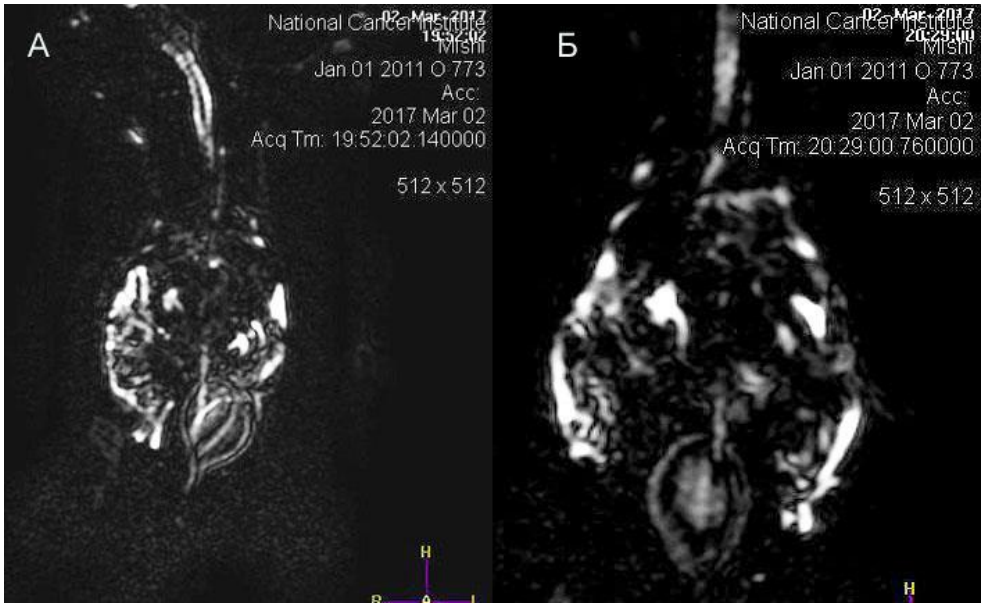

Fig. 1 MR-urography (*UROGRAMM 3D SF NSE*) on the 30th day of the OAB modelling.

In MR tomograms, despite the presence of several anatomical membranes, the UB wall had the form of a linear structure of reduced intensity, similar to the intensity of the signal from the skeletal muscles. At T1-WI, the intermediate intensity of the MR signal between low-intensity urine and high-intensity perivascular tissue was noted. On T2-WI, the UB wall was clearly visualized due to differentiation from high-intensity urine and moderately intense perivascular tissue.

Urinary tract - a dual organ, providing passage of urine from the kidneys in the UB. It is a muscular tube of 8-10 mm in length, an outer diameter of up to 455 μm. In non-expanded mucous membranes, the ureter looked like a hypointensive vertical-oriented strip that was poorly differentiated on the background of the intestine. After filling the urine, the ureter had the appearance of a tubular structure with a clear outer contour, on T2-WI - hyperintensive, on T1-WI - hypointensive signal.

There were three parts of the ureter, between which there were no clear anatomical boundaries. The commonality of the muscle of the UB, the intramural sections of the ureter, urethra allowed to consider these parts of the UW as the only anatomical and functional structure.

The study plan included the examination of all animals using the MR-urography in the mode of hydrography with diuresis load according to their own methodology. Conducted a static MRI-urology before and after the introduction of a diuretic. The urothelial tract was

analyzed, the anatomical changes of the kidneys, the UW the adjacent organs of the abdominal cavity, the pelvis as the only anatomical and physiological site were evaluated. After analyzing and comparing the static and divergent MR-urography, the position, shape, size, condition of upper UW and the UB were evaluated. It should be noted that before and after the pharmacological test, it was possible to diagnose not only anatomical, but also functional changes of the kidneys and the UWl. To compare the results of MRI, animals diagnosed with ureterohydronephrosis (UHN) are distributed according to the degree of UW expansion.

The variability of the received radiation characteristics of the anatomical and functional changes of the upper secondary schools allowed to distinguish 3 degrees of their expansion, followed by a comparative analysis of UW changes.

Expansion of the I degree – disturbance of urodynamics of the upper UW from a stasis of urine in the ureter to a moderate expansion with the formation of pyeloectazy with the preserved or slightly impaired kidney function; II degree - pronounced anatomical and functional upper UW disturbance, significant depression of the renal function due to pronounced expansion of the ureter and CPC; III degree – kidney function failure.

On the 14^{th} day of the trial MRI was conducted to assess anatomical structures and detect changes in UB, upper UW and kidney. Despite the presence of OAB clinical manifestations, anatomical and functional changes were within the normal range. Kidneys are typical, parenchyma is preserved. The outer contour of the kidneys is even clear. Upper UW are not expanded. Organs of the abdominal cavity and pelvis without pathological changes. In images in the mode of MR-urography, the UB was visually molded droplet, small in size, with clear contours. Since the upper UW are not extended, they were not visualized on the MR-urogram. UB is filled to the maximum, the contours are clear and even, the volume of 0.7 ml. The upper UW are not expanded, they are not visualized on the MP-urogram.

On the 30^{th} and the 90^{th} days of the trial, anatomic-functional changes in upper UW of different severity were detected. The characteristic signs of changes in the upper UW and degree were the moderate enlargement of the ureter and kidneys CPC, which was manifested by a stasis of urine. The ureters are not dilated. UB filled till 0.85 ml. After diuretics i.v., urine freely passed through the upper UW, a significant expansion of the right ureter in the pyloureterial segment and expansion of the bowl of the right kidney while retaining its function, the parenchyma of the right kidney was unevenly thinned, preserved. Moderate expansion of the bowl of the left kidney, ureter is not dilated, renal parenchyma is retained. UB filled till the volume of 1.1 ml.

Enlargement of the second stage is characterized by dilation of the ureter, kidney parenchyma, or unevenly thinned, as well as the expansion of the bowl. After the introduction of diuretics in animals with second-degree UHN, two variants of the UB change were revealed: in 3 (37.5%) - no significant changes were observed, there were no contractile properties of the upper UHC, renal function was potentially reduced, ureter enlarged in the pyelourethral segments, dilated bowls of both kidneys, UB is as complete as possible, contours are clear, even; in 5 (62.5%) - strengthening of diuresis, suprastenotic enlargement of the ureter, signs of its contraction, indicating a stable obstruction while maintaining the reserve function of the kidney.

In (9.1%) animals, with the UW expansion of the third grade, marked a steady expansion of the kidneys CPC, the ureters expanded along the entire length, winding. Significantly thinned kidney parenchyma was visualized fragmentarily or as a polycystic form. The introduction of diuretics was ineffective, there are no contractile properties of the upper UW. After the introduction of a diuretic on an MR scan, the atony of the enlarged aphthous ureter was revealed, the renal parenchyma was thinned, the suprasenototically enlarged ureter, the vortex, the expansion of the bowl of the left kidney, postgidronephrotic transformation of the right kidney.

The use of MRI-urography in the mode of hydrography and diverising load according to its own methodology allowed to study the features of anatomical changes and functional capacity of the kidneys and upper UW and to distribute animals depending on the degree of UHN. These changes are confirmed by the results of histological studies. Thus, on the 14th day after the OAB model reproduction there were no marked pathological changes in the kidneys, however, there was a plethora of blood vessels, mainly capillaries, both in the cortical and in the brain substance, where it was mosaic.

In the mucous membrane of the ureter, an elevated hyperthrophy of the epithelial plate was observed higher than normal. In the muscle the blood vessels are moderately dilated, full-blooded, and the reduction of myocytes along the length of the ureter is uneven. In the UB, the epithelial plate of the mucous membrane of uneven thickness, in some areas is thinned, myocytes without pronounced changes. Serum without peculiarities.

After 30 days in the kidneys, the blood vessels of the vessels, stasis in the cortical substance (in the capillaries of the glomeruli and the secondary mesh), less pronounced stasis - in the brain substance, glare was mosaic (Fig. 2).

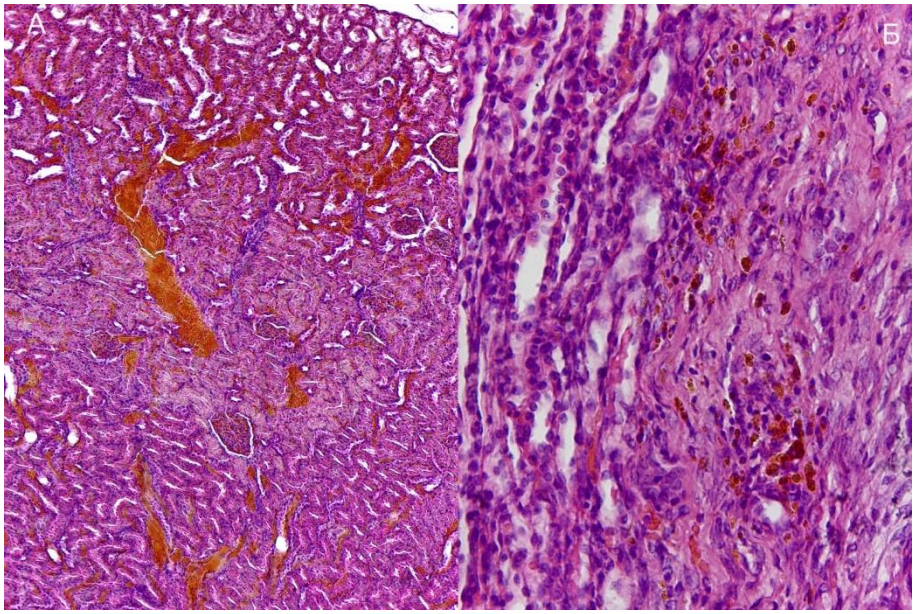

Fig. 2. Flashing cortical substance of the kidney, dystrophic changes in the tubules of the nephrons. 30 days after the reserpine injection. Hematoxilin and eosin colour. Increase x100.

Some animals noted an increase in the diameter of the collecting tubes, they are filled with foam masses; in some cases - atrophic changes in glomeruli and signs of tubulopathy.

In the ureter the epithelium layer of the mucous membrane is uneven in thickness, its own plastic is sealed. The tone of the muscular membrane is moderately reduced, the mucous membrane forms deeper folds than the control, the diameter of the lumen is increased. In the UB epithelial plate of the mucous membrane of uneven thickness, observed increased desquamation of epithelial cells and sealing its own plate of the mucous membrane.

After 90 days in kidney parenchyma, mainly in the cortical substance, dystrophic changes in some animals have progressed up to paranecrosis. In some animals, the seals and growth of the stroma from the cortical substance into the medullar part were observed, in this compacted stroma contained macrophages with fragments of phagocyte red blood cells, indicating not only long stasis and local phagocytosis of dead red blood cells, but also atrophy and replacement of parenchymal cells with connective tissue.

In the ureter, in some areas of the epithelial plate, signs of hypertrophy, on some - increased desquamation, with almost complete exposure of the own plate of the mucous membrane; compared with the previous dates, increased diameter of the lumen.

In UB one could note the atrophic changes in the mucous membrane, an atony of the muscle. The serum is saved.

Conclusions

1. In the early period (14 days) after the reserpine injection the UW functional changes were observed without significant structural disturbances. After 30 days, in addition to functional changes, there were noted morphological, which caused UHN moderate manifestations. These signs progressed over time, resulting in pronounced structural changes in the kidneys and UW.

2. The overactive bladder model stability and its adequate type to clinical condition was proved on the basis of the performed functional and morphological studies together with pathological changes dynamics characteristic for UHN were studied.

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