Chapter 5

MODERN VIEWS ON THE PROBLEM OF VESICOURETERAL REFLUX IN CHILDREN

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INTRODUCTION

Vesico-ureteral reflux (VUR) is a pathological condition in which there is a periodic and/or permanent retrograde flow of urine from the bladder into the ureters due to a malfunction of the anti-reflux mechanism of the vesicoureteral segment[1].

Primary VUR is a fairly common condition, which most researchers associate with congenital anomalies of the VUR associated with defects in its embryological development[2].

VUR is a common condition in childhood, but the exact incidence remains unknown because widespread pediatric screening using micturition cystoureterography, which is the standard reference test for reflux, is not performed as it cannot be implemented a priori.

According to modern data, the specific weight of VUR is from 0.1% to 1.0% of all pathology in the general children's population, accounting for 10% of all diseases of the urinary system in children undergoing inpatient treatment[3].

Every year in Ukraine, 3,600–3,700 children are diagnosed with congenital defects of the urinary tract, with 1/3 of the defects occurring in their upper parts. According to statistics, there are 40–50 cases of congenital and hereditary diseases of the urinary system per 1000 newborns[4]. There are

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reports that the frequency of VUR in the general pediatric population exceeds 2%[5].

However, the frequency of VUR in children against the background of a urinary tract infection increases to 16–77%, and in infants with hydronephrosis of the II – III stage, which is diagnosed during antenatal ultrasound screening, the pathology occurs in 3–19%, while among newborns the prevalence of the pathology is unknown due to the significant invasiveness of early diagnosis methods[6,7,8]. It is reported that 25% of VURs occur at the stage of prenatal screening[9].

1. Causes of vesico-ureteral reflux

Congenital defects of the kidneys and ureters are the most common abnormalities in VUR, which indicates the influence of various syndromes as multifactorial developmental disorders that have many phenotypic effects (manifestations). Some researchers, taking into account the hereditary emphasis in the occurrence of VUR, consider the formation of pathology as a result of a violation of complex signaling pathways and cellular differentiation, the mechanisms of which are genetically programmed, but which can undoubtedly be influenced by environmental factors[10].

The combined existence of VUR with the inflammatory process contributes to scarring of the kidney parenchyma in pyelonephritis, especially at an early age. According to the literature, nephrosclerosis is formed in 30–60% of cases with VUR, which leads to the development of the terminal stage of chronic renal failure in 25–60% of patients, due to a decrease in the

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functional renal reserve, as an indicator of the compensatory capabilities of the kidneys[11,12].

In general, VUR is the initial link in the chain of pathological refluxes in the urinary tract, among which, depending on the level of backflow of urine, the following are distinguished: vesicoureteral reflux, ureteral-pelvic reflux, pelvic-renal reflux, which in turn is divided into fornical (through the cup vault) and tubular (through the renal papilla) refluxes[13].

2. Pathogenesis of vesico-ureteral reflux

VUR, especially against the background of urinary tract infection, can be accompanied by a decrease in glomerular filtration rate, which in turn is complicated by reflux nephropathy, which ultimately leads to hypertension, albuminuria, and chronic renal failure. Reflux nephropathy in the early stages of its development usually does not have obvious clinical manifestations, but is characterized by focal interstitial lesions, atrophy of tubules and nephrons, that is, loss of kidney parenchyma, especially in the development of ureterohydronephrosis[14,15].

With the progression of reflux nephropathy, a uretero-hydronephrotic transformation is formed, which is accompanied by significant anatomical, physiological and functional disorders due to the pronounced loss of the structural elements of the kidney and ureter.

3. Importance of vesico-ureteral segment in VUR pathogenesis

Considering the importance and complexity of the pathogenesis of VUR in such a chain of pathological refluxes, it becomes obvious that an important reason for the possible lack of desired results in the treatment of the pathology

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[13] Булик Р. Є., Попелюк О-М. В., Мельник В. В., Проняєв Д. В. Сучасні уявлення про закладку та ембріогенез сечовидільних органів. *Вісник Вінницького національного медичного університету.* 2022. № 2. С. 328–334.

[14]Nieto V.M.G., Zamorano M.M., Hernández L.A., Yanes M.I.L., Carreño P.T., Mesa T. M. Nefropatía de reflujo y nefropatía cicatricial. Dos entidades tan cercanas pero funcionalmente tan distintas. In *Anales de Pediatría*. July 2022. № 1. С. 40–47. https://doi.org/10.1016/j.anpedi.2021.08.001

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is insufficient knowledge of the details of the anatomical structure of the VUR and subtle physiological mechanisms of antireflux protection.

Studying the functional anatomy of the urinary tract as a whole and especially the physiology and functioning of the vesico-ureteric segment is of primary importance for understanding the mechanism of the occurrence of VUR.

VUR is most often detected during urination against the background of increased intravesical pressure, but it can occur during any of the stages of the urination cycle. Especially in cases of bladder dysfunction.

Despite the fact that many researchers have long held the opinion about the importance of the presence of normal tone of the urinary triangle in the antireflux function of the intravesical part of the ureter, only in 1965 Tanagho EA and Meyers FH, in an experiment on dogs in which the VUR was absent, studied the physiology of the VUR in detail .

During the experiment, the researchers found out the following features: 1. Violation of the integrity (continuity) of the urinary triangle leads to VUR. An incision in the triangle 3 mm below the mouth of the ureter leads to upward and lateral migration of the mouth of the ureter with shortening of the intravesical part of the ureter. After healing of the incision, the VUR disappeared; 2. Unilateral transverse sympathectomy leads to paralysis of the ipsilateral ureter, which in turn causes migration of the mouth of the ureter to the side and up with the occurrence of VUR; 3. Electrical stimulation of the urinary triangle led to displacement of the ureter in the caudal direction, thereby lengthening the intravesical part of the ureter. Such an action is accompanied by the effect of a noticeable resistance to the flow of urine through the vesicoureteral segment, the release of urine through the ureter is suspended. Intravenous administration of epinephrine (adrenaline) caused a similar reaction. At the same time, it was noted that after the triangle was cut, its electrical stimulation or the introduction of epinephrine increased the occlusive pressure of the ureter; 4. When the bladder was gradually filled, the intravesical pressure increased only slightly, while the pressure in the intravesical area of the ureter increased progressively, apparently due to the increase in the stretching of the urinary triangle. It was also noted that a few seconds before the expected sharp increase in intravesical pressure, which is aimed at the implementation of the urination process, the closing pressure of the intravesical part of the ureter increased sharply and remained at a high level for 20 seconds. after cessation of detrusor contraction. Such a sequence of contractions of the structural elements of the vesicoureteral segment and the magnitude of pressures demonstrated that its function does not depend on the action of the detrusor, but is regulated by the tone of the urinary triangle, which vigorously contracts immediately before the act of urination, thus contributing to the opening and straightening of the bladder neck. At the same

time, the intravesical part of the ureter is significantly stretched, "closing" its lumen, precisely during the period of high intravesical pressure. At the same time, which is quite natural, during the urination phase, the release of urine through the urethra into the bladder stops[16].

As a result of an experimental study of the physiology of the vesicoureteral segment, it was concluded that the normal tone of the ureterotrigenal section prevents the occurrence of VUR, since the stimulation of the triangle (electrical or pharmacological) contributes to increasing the occlusive pressure in the intravesical section of the ureter and increasing the resistance to the flow of urine down the ureter, while the cut or paralysis of the urinary triangle causes the development of VUR. Also, the authors, in addition to the presented evidence of the functional contribution of the triangle to the antireflux mechanism, studied its structure, which is described by three layers: the superficial layer, which is a continuation of the longitudinal muscle fibers of the ureter; middle "Waldeyer's sheath", which continues distally; deep – formed by the bladder wall itself.

Thus, the theory according to which the ureteral-bladder antireflux capacity is ensured only due to the intravesical pressure, which presses the intravesical part of the ureter to the detrusor, can be considered untenable.

S. Gil-Vernet in 1973 described the pre-bladder circular sphincter of ureteric origin, which is formed from the most distal circular muscle fibers of the ureter[17].

In accordance with modern views on the pathogenesis of VUR in children, the existing data, although the problem is far from its final solution, testify to the multifactorial processes of the development of the pathological condition, in contrast to the previously existing ideas, which took into account purely mechanical factors of damage to the antireflux mechanism against the background of inflammation in the area vesicoureteral segment. The vesicoureteral segment in boys is represented by a triangle and the neck of the urinary bladder, the internal eye of the urethra, the prostatic part of the urethra, the internal sphincter muscle of the urethra, and in girls by the triangle and the neck of the urinary bladder, the internal sphincter muscle of the ureter. The vesicoureteral segment represents a certain anatomical and functional border between the upper urinary tract, which is characterized by low pressure, and the lower urinary tract, which is characterized by high pressure, thanks to

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[17] Vernet S. G. (1973). Anatomical aspects of vesicoureteral reflux. In *Urodynamics: Upper and Lower Urinary Tract. 1973. C.* 171-178.

which the upper tract is protected from reflux, due to active and passive antireflux mechanisms[18,19].

According to H. Roshan et al., (1996), the functional autonomy of the ureter, its internal organization of fibers and the asymmetry of the orientation of its lumen in the submucosal trajectory of the bladder wall are determining factors of the function of the antireflux valve. An important component of the normal functioning of the vesicoureteral segment is the density and elastic elasticity of the muscle tunnel in the detrusor, which acts as a functional channel that allows the ureter to perform its antireflux function. Hypertrophy of muscle fibers of the ureter, observed in combination with infravesical obstruction, is considered as a compensatory factor in the prevention of VUR, which supports this active mechanism[20].

And the geometric properties, namely the diagonal direction and the length of the submucosal part of the ureter in the vesicoureteral segment are the determining factors of the passive valve mechanism.

The interaction between the components of muscle and connective tissue determines the functioning of most physiological processes. The vesicoureteral segment is a complex structure that is formed as a result of the fusion of the ureter and the detrusor, and which meets certain functional requirements. First, the vesicoureteral segment forms a boundary between the low pressure of the upper urinary tract and the lower urinary tract, which are characterized by large changes in urine pressure. Secondly, the vesicoureteral segment should provide a purely antegrade current direction to the urinary bolus. This becomes possible thanks to the exclusively longitudinal direction of the muscle fibers of the ureter of the intramural section, which does not contribute to its peristaltic activity, but progressively contributes to the reduction of its length according to the principle of a telescopic mechanism, in which the shortened section of the intramural part of the ureter, thickening, partially obstructs its lumen only in the direction of the current urinary bolus, while blocking its retrograde outflow. After the passage of the peristaltic wave, which spreads to the surface triangle, the shortened intramural and submucosal segments of the ureter are pulled by its trigonal expansion of

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muscle fibers to a resting position, thereby temporarily increasing the length of the submucosal part. Such a hydrodynamic principle of the anti-reflux mechanism ensures an anti-grade flow of urine even under conditions of higher pressure in the bladder.

Studies by some scientists indicate that the ureter does not have muscular connections (connections) with the detrusor, but is surrounded by a periurethral connective tissue membrane along the entire intramural part. Such muscular (contractile) "independence" allows the ureter to move relatively freely in its transvesical channel[21].

The direct connection between the lower and upper urinary tracts is confirmed, including experimentally, by the existence of pathology at the level of the vesicoureteral segment when urodynamics in the ureter are disturbed[22]. Normally, the vesicoureteral segment is a kind of valve, structurally represented by an internal sphincter muscle, the front wall of which, almost devoid of muscle fibers of the intramural part of the ureter, closes with an increase in intra-bladder pressure with its back wall, which contains many muscle fibers , and thus, during urination, it prevents the regurgitation of urine into the urethra. Histologically, the closing apparatus of the eye is formed by circularly located muscle fibers in the distal part of the lower part of the ureter, and longitudinal muscles that pass to the bladder wall without reaching its triangle (trigonum vesicae). Normally, elasticity and muscle tone contribute to the adaptation of the ureters to changes in the volume of the bladder, depending on the intra-bladder pressure[23,24,25].

According to the structure of the internal sphincter muscle, several options are distinguished: 1. It is formed of two horseshoe-shaped muscle loops, one of which, more powerful, is located in front and on the sides, and the second, weaker, is directed from the front wall to the back, surrounding opening at the back and on the sides; 2. In the form of a closed muscle ring and a muscle loop on the front wall; 3. Muscle bundles that surround the inner eye of the urethra,

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ring-shaped, are more densely located along the front wall; 4. In the form of a muscle loop that covers the inner eye of the urethra from the front and from the sides, with loosely located transverse muscle bundles along the back wall; 5. Only a muscular loop that goes from the back wall to the front, covering the inner eye of the ureter from the front and from the sides. The first two options are more common in men[26].

In addition, it is believed that the mechanism of closure of the internal sphincter muscle, which has a funnel-shaped shape and lies obliquely, narrowing in the back-to-front direction, involves a venous network of vessels of various calibers, which is placed in three tiers: cavernous veins of the submucosa; veins of the muscular sheath; veins of the adventitia membrane, by swelling of the veins at the level of the inner eye of the ureter, which prolapse in the form of a roller, thereby contributing to even greater closure of the walls of the ureter[27,28].

Many researchers believe that bladder closure is ensured by the prostatic and membranous parts of the ureters, and in women, the entire urethra and elastic fibers in the bladder neck are involved in this process. Separate muscle formations are distinguished, which play an important role in the process of urodynamics. Structurally, such muscle formations include: firstly, the main muscle plate of the urinary bladder, which consists of front and back muscle loops covering the entrance to the urethra; secondly, the surface muscle of the bladder triangle, with which the ureters are connected; the third is the deep muscle of the bladder triangle, which passes into Waldeyer's sleeve (vagina). Despite the fact that some authors believe that the triangle of the urinary bladder provides only the function of emptying the bladder, a certain part of researchers consider the muscular shell of the urinary tract as a single morpho-functional system, which at the ultrastructural level is represented by interweaving in different directions by muscle bundles. In 1983, research by D. Beurton revealed that Waldeyer's cuff is structurally built from two layers: the deep one, the muscle fibers of which surround the juxtavesical, intramural and submucosal parts of the ureter, and which are fixed in the proximal part in the pelvic part of the ureter, and in the distal part, they participate in the formation of the deep vesical triangle and the surface layer of the clutch, which is fixed 2–3 cm proximal to the fibers of the deep layer to the adventitian

[26] Кашперук-Карпюк, І. С. Анатомо-функціональні особливості міхурово-сечівникового переходу. *Клінічна анатомія та оперативна хірургія*. 2012. № 1. С. 95–98.

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membrane of the ureter, and in the distal direction connects the distal part of the ureter and the detrusor[29].

Among the various anatomical prerequisites for the occurrence of reflux in the urinary tract, which, according to various researchers, account for up to 70% of the total amount of pathology, the structure of the distal parts of the ureters, namely their intramural parts, which fix the right and left ureters to the fibro-collagen structure, is of particular interest – bubble triangle Biopsy of the urinary triangle and the wall of the intravesical part of the ureter in patients with primary VUR revealed a pronounced deficiency in the development of its smooth muscles, in contrast to the normal structure, which is represented by a significant number of smooth muscle fibers closely adjacent to each other. Under such conditions, electrical stimulation of the vesicoureteral segment causes only slight contractions of this segment[30].

To date, there are many conflicting interpretations regarding the degree of dominance of the participation of structural elements of the bladder wall in its antireflux provision, such as Waldeyr's membrane, the angle of passage of the ureter through the detrusor muscle, the state of Bel's triangular muscle, etc. Pitel Yu. A. et al., (1990) described the muscle that presses the ureter ("musculus apressor ureters"), noting its importance in preventing the retrograde flow of urine.

Research by Fomina L. V. et al. (2012), it was found that Lieto's triangle has a certain asymmetry, due to the one-sided displacement of the vertices up and laterally. Also, during the research, it was determined that a strand-like branch in the form of a belt that is located along the ureter, and in the thickness of the detrusor muscle forms a circular loop, continuing its belt-like course, ending with the interweaving of muscle bundles of myofibrils directly into the Bela muscle, thus being fixed inside the wall of the urinary bladder to a similar muscle on the opposite side.

According to the researchers, this structure of the muscle structure provides it with the opportunity to take part in the release of urine from the distal parts of the ureters, in which the circular muscle layer is weakly expressed, due to which peristalsis, similar to the one that exists in the upper parts of the ureters, does not exist. That is, the ureter is pushed out of the bladder by the triangular muscle through the belt-like muscle, which during urination is in a state of contraction and squeezes the remains of urine out of the ureter, which prevents the retrograde flow of urine. Considering that the ureters are actually fixed to each other by collagen fibers of the bladder

[29] Tsvigovskiy V., Sokolov V., Rozhkovska G., Dolgushyn O., & Dorofeeva T. Рентгенологічне дослідження сечовидільної системи. Нормальна променева анатомія і фізіологія. Радіологічні ознаки захворювань нирок і сечовивідних шляхів. *European Science*, (sge19-03). 2023. С. 146–172. https://doi.org/10.30890/2709-2313.2023-19-03-017

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triangle, such pushing of the ureter from the wall of the bladder should take place alternately, then from the right, then from the left.

According to the hypothesis put forward by the authors, the retraction of the ureters into the bladder wall occurs due to the contraction of the myofibrils of the detrusor muscle, which are fixed to the tendinous triangle, which is confirmed by the fact of the asymmetry of the Lieto triangle, which can be considered as participation in the creation of antireflux mechanisms when the bladder and triangular are overstretched Bel's muscle.

Thus, according to the proposed hypothesis, the vesical part of the ureter is surrounded by certain components of anatomical formations, which, together with its own structures, ensure one-way excretion of urine. Such anatomical structures include Waldeyra's membrane, the muscles of which are able to push the ureter to a certain distance into the bladder cavity, thereby influencing the angle of passage of the ureter through the detrusor muscle; the submucosal part of the ureter itself, which acts as a passive valve when the intravesical pressure increases; directly the layers of the detrusor muscle, especially in the form of the depressor muscle and the described strap-like muscle[31].

Primary VUR, as a rule, is the result of a developmental conflict between the ureter and the channel of the mesonephric (Wolffian) duct with the formation of insufficient development of the closing apparatus of the eye of the ureter, the main function of which is aimed at blocking the backflow of urine from the bladder to the kidney. Usually, primary VUR occurs as a result of congenital shortening of the intramural part of the ureter, insufficiency (closure) of the edges of the ureter mouth or their dystopia, doubling of the ureters, when the kidney is drained by two ureters, with congenital bladder diverticulum[32].

According to the results of modern neurophysiological and morpho-functional studies of the secondary nature of VUR in children, it was determined that the pathology can occur due to neurogenic changes in the urinary bladder, especially when combined with detrusor-sphincter dyssynergia. Secondary VUR can also appear as a result of surgical manipulations on the bladder, especially after dissection of the bladder triangle, which contributes to the retraction of the ureteral loop.

The most common explanation for the functioning of the antireflux mechanism of the vesicoureteral segment is passive compression, due to high pressure, of the vault of the intravesical part of the ureter, which is located in

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the thickness of the detrusor muscle. The closing apparatus of the eye is provided during an increase in intravesical pressure due to: 1. Oblique direction of the intramural part of the ureter and compression of its lumen during detrusor contraction; 2. Submucous localization of the terminal area, approximately 11.0 mm long, which, when the pressure in the bladder increases, is pressed directly against the muscle layer of the bladder wall[33,34].

According to this theory of the "passive" antireflux mechanism, sufficient intravesical length of the ureter and its diameter are considered the main factors that ensure normal closure of the ureter and exclude the ureter. Given this fact, many researchers consider the lateralization of the intravesical opening (eye) of the ureter, a short section of the transmural and submucosal segments of the ureter relative to its diameter, to be the main cause of VUR. As proof of the correctness of this assumption, the authors put forward the possibility of spontaneous elimination of the primary VUR during the growth of the urinary bladder, due to the lengthening of the submucosal tunnel of the urethra[35].

Fundamental research by J. Oswald et al., (2003–2004) determined that the average length of the intravesical section of the ureters in newborns is 3017.2±388.9 μm on average with an average diameter of 1354±231.3 μm, which corresponds to the ratio is 2.23:1. In fetuses between 11 and 20 weeks of intrauterine development, this ratio tends to decrease, from 0.69:1 to 1.23:1, respectively, which in turn explains the greater frequency and severity of VUR in newborns and premature babies, as well as the possibility spontaneous resolution of pathology[36,37].

The theory of the "active" anti-reflux mechanism of the vesicoureteral segment is based on certain anatomical and functional features of the ureters, the area of the vesicoureteral segment and the bladder. The spiral orientation

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of the smooth myocytes of the muscle membrane corresponds to the idea of the partial nature of urine transport. The entire urinary tract is divided into several cystoids (detrusor-sphincter sections), in which the role of the detrusor is performed by the musculature of the wall of this section of the ureter, which relaxes in the filling phase, and in the emptying phase, it contracts, pushing the urinary bolus in the distal direction, and the role of the sphincter is played by the cavernous vascular formation[38].

It has been proven that the active contraction of the longitudinal muscular and submucous layers of the transmural areas of the ureters contributes to the direction of the urinary bolus in the direction of the bladder. Therefore, any structural and/or functional changes in the distal parts of the ureters contribute to the disruption of the functioning of the active valvular mechanism of the vesicoureteral segment and cause VUR.

Coordinated peristaltic contractions of smooth muscle cells of the walls of the ureter occur as a result of the transformation of the extracellular matrix, through the extracellular production of proteinases and their inhibitors. This mechanism has a profound effect on the progressive maturation of the anatomical and functional capacity of the ureters with the age of the child.

Evaluating the synthesis of the extracellular matrix, and in particular collagen types I and III, proved the important role of matrix metalloproinase produced by connective cells of mesenchymal origin (fibroblasts, myoblasts and CD-68 positive macrophages). Protein S-100 is important as a marker of innervation of the ureteral wall.

It was determined that patients with VUR have an increased expression of metalloproteinase-1 in CD-68+ smooth muscle cells, as well as a significant decrease in the amount of S-100 in neural cells, which is of crucial importance in modifying the activity of the antireflux mechanism. There is a lot of evidence from modern researchers that dysplasia, atrophy, and structural changes in the smooth muscle cells of the ureteral wall are the leading causes of the insufficiency of the active antireflux mechanism of the VUR[39].

Considering the possible existence of these predictors of pathology, back in 1984 Tokunaka S. et al. first introduced the term muscular dysplasia of the intravesical part of the ureter in patients with VUR[40].

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In turn, thinned bundles of smooth muscles of the ureteral wall and their distorted configuration create uncoordinated muscle contractions, along with a reduced number of c-kit positive interstitial cells of Cajal (RY Cajal, 1893), which are considered responsible for pacemaker activity ureter and coordination of its mobility, and which, according to the International Histological Terminology, are recommended to be called interstitial pacemaker cells (IPC) [6].

IPCs generate a slow-wave electrical potential that ensures peristaltic activity of the ureter[41,42].

Accordingly, the decrease in the density of Cajal cells is directly related to motility disorders of the hollow organ, which is well known in patients with slowly transient constipation[43].

The main function of Cajal cells is maintenance of automatic rhythm and coordination of peristalsis, provision of antegrade movement of the urine bolus to the bladder and prevention of retrograde peristalsis. The cause-and-effect fact of the decrease of Cajal cells directly in the area of the MS remains unclear today, although it is known that these cells are derived mesenchyme, the differentiation of which does not depend on the cell lines of the neural crest[44].

Research by S. Arena et al. during 2008–2016, they found a decrease in the concentration of interstitial cells of Cajal in the distal part of the ureter with VUR, while the greater the degree of reflux, the lower the number of interstitial cells of Cajal[45].

There is an assumption that the decrease in the number of IPC may be secondary to the injury of the vesicoureteral segment during episodes of VUR[46]. The fact that the amount of connexin-43 decreases in VUR is

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determined, which is an important hexamer that provides synaptic contact necessary for intracellular signal transmission. Lack of connexin leads to dysfunction and discoordination of the activity of smooth muscle cells, disrupting the peristaltic activity of the ureter.

Manometric studies in the ureters with VUR showed a significant decrease in their lumen of the maximum and basal pressures, especially in the distal parts, which is highly correlated with the degree of pathology.

In secondary VUR, in comparison with the primary violation of the antireflux mechanism, morphologically more pronounced damage to smooth muscle cells with scarring of the walls in the expanded parts of the ureters is observed. In comparison with a normal ureter, with pathology, at the level of the vesicoureteral segment, the decrease in the proportion of muscle relative to collagen is 1:3 versus 1:0.3. Such replacement of muscles by connective tissue leads to scarring of the ureteral wall, which distorts the sufficient contractility of the muscle layer, as a result of which the normal peristaltic capacity of the organ becomes impossible, the tightness of the closure of the ureteral loop is disturbed. Modern studies of structural changes in the intravesical part of the ureter in children with VUR in the sense of the microvascular architecture of the vesicoureteral segment, usually determined the almost complete absence of smooth muscle layers on more than 1/2 of the semicircumference of its wall, which were replaced by an extracellular collagen matrix, and in the remaining muscle endomysial and perimysial fibrosis was observed in bundles. Such fibrotization of the ureteral wall, according to the researchers, contributes to an increase in its rigidity and deterioration of contractility. Such structural and metabolic changes are accompanied by a significant deterioration of tissue angiogenesis, while the expression of vascular endothelial growth factor (VEGF) and the associated density of microvessels are significantly reduced specifically in the distal part of the ureter[47]. In addition, it has been shown that overall microperfusion is potentially impaired, leading to tissue ischemia, and that chronic ischemia induces and maintains smooth muscle dysfunction with subsequent remodeling of the extracellular matrix that causes increased collagen deposition. Thus, the violation of angiogenesis, closing a vicious circle of

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functional and structural changes, thus deepening the violation of the active valve mechanism, thus forming VUR[48,49].

Thus, modern ideas about the pathogenesis of VUR are complex and multi-vector in their links. On the one hand, the change in the configuration of the sarcoglycan (SG) subcomplex, in particular the deficiency of ε-SG and the overexpression of α-SG, explains the apoptosis of smooth muscle cells of the ureteral wall, their atrophy and increased interstitial fibrosis due to the development of structural instability and/or loss of muscle integrity. ulcer plasma membrane. On the other hand, hypoperistaltic or ureteroarrhythmic types of ureteral peristalsis when general microperfusion is impaired contribute to the weakening of the active valvular mechanism in VUR. Types of VUR are very diverse, which led to numerous attempts to create pathology classifications. VUR can occur when filling the bladder – low-pressure reflux (passive), and during urination – high-pressure reflux (active), or both.

If VUR is caused by vesicoureteral segment insufficiency, it is considered primary, and if it develops against the background of obstruction (posterior urethral valve, urethral stenosis, meatostenosis) or neurogenic function of the bladder, it is secondary[50].

4. Classification of VUR according mechanism

According to the degree of expressiveness of the cast of X-ray contrast material, the international classification of VUR has become widespread Heikel-Parkkulainen,(1966) and Campbell, Wein et al., (2007), according to which 5 stages of the pathological process are distinguished[51,52,53,54]:

1. Injection of a radiopaque substance into the distal part of the ureter (pelvic cystoid) without changing its diameter.

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2. Filling with a radiopaque substance of the ureter and cup-pelvic system, which are not expanded.

3. Moderate expansion of the ureter with pyeloectasia and an increase in the size of the kidney cups.

4. Pronounced expansion and knee-like bends of the ureter, deformation of the hollow system of the kidney. Secondary wrinkling of the kidney parenchyma is noted.

5. Hydroureter and pronounced thinning of the kidney parenchyma.

The International Cystographic Classification (1985), on the basis of which five degrees of VUR are distinguished, became widely used:

I st. – only the pelvic part of the ureter is contrasted;

II century – VUR is determined along the entire ureter and collecting system of the kidney;

III century – the injection level of the contrast agent reaches the cup-bowl system with the expansion of the latter;

IV century – the dilatation of the ureter and cup-pelvic system is determined;

V century – a massive VUR with a pronounced dilatation of the ureter and the calyx-bowel system (knee-like bends of the ureter, the kidney parenchyma is sharply thinned).

Taking into account the clinical course of VUR, transient and permanent forms of pathology are distinguished. For the transient form, low cystographic grades and moderate kidney function disorders are more characteristic. As a rule, transient reflux is detected during exacerbation of intercurrent diseases.

In recent years, there is a justified classification of VUR depending on the degree of impaired secretory function of the kidney, according to which three degrees of impaired function are distinguished:

I degree (moderate) corresponds to a decrease in kidney function up to 30%.

II degree (average) – decrease in function up to 60%.

III degree (high) – reduction of kidney function by more than 60%.

Due to this distribution of VUR, the amount of treatment for this disease is largely determined.

It is important to understand intrarenal reflux (IRR), the backflow of urine in the calyces through the tubules into the kidney tissue.

The location of the mouths of the collecting tubules when they flow into the simple papillae in an oblique direction prevents the occurrence of IRR, while the configuration of the mouths that flow into the complex papillae contributes to the formation of reflux. Under the conditions of an increase in pressure in the urinary bladder of >35 ml Hg, which is a critical value, there is a risk of kidney damage. A higher pressure is required for the occurrence of IRR in simple papillae.

Summarizing the material presented, it should be noted that the pathogenesis of primary VUR, the understanding of which is particularly important in pediatric practice, still remains completely unclear, despite the fact that the study of possible mechanisms of its formation can and should be researched at an early embryonic stage body development.

The main information in the descriptions, which are involved in the morphological structure and functional anatomy of the vesicoureteral segment, were obtained with the help of a dissecting microscope and standard staining techniques, which leave a lot of room for the interpretation of the results, due to the impossibility of determining the exact affiliation (ureteral or bladder origin) of the representative structures. And even the cholinesterase staining methods (acetylcholinesterase and butyrylcholinesterase), which were used to identify various components of the ureter and bladder muscles, followed by three-dimensional reconstruction of the vesicoureteral segment based on the activity of the cholinesterase isozyme to study the architecture of the ureter and the antireflux mechanism, do not fully respond to these questions.

Further expansion and deepening of knowledge about the architecture of the microcirculatory channel of the vesicoureteral segment remains important for the further understanding of the pathophysiology of the vesicoureteral segment, due to the fact that the refluxing fragments of the ureters have typical pathological changes that are characteristic of ischemic tissue areas.

CONCLUSIONS

Thus, the analysis of the results of research available today regarding the structure and functional anatomy of the vesicoureteral segment convincingly testify to the complexity and multi-level organization of its antireflux mechanism, in which there is no room for imagination or purely mechanistic manifestations of its work. Therefore, any further research in this direction will undoubtedly contribute to a deeper understanding of the normal functioning of this complex anatomical part of the human urinary system, which will allow the development and implementation of the latest physiological treatment methods in the practice of pediatric surgeons.

SUMMARY

Bladder-ureteral reflux is a pathological condition in which there is a periodic and/or permanent retrograde flow of urine from the bladder into the urinary tract due to a malfunction of the anti-reflux mechanism of the vesicoureteral segment.

According to modern data, vesicoureteral reflux accounts for 0.1% to 1.0% of all pathology in the general pediatric population, accounting for 10% of all diseases of the urinary system in hospitalized children. Bladder-urethral is the

initial link in the chain of pathological reflux in the urinary tract. The leading importance of the mechanism of vesicoureteral reflux is the study of the functional anatomy of the urinary tract as a whole. Bladder-ureteral reflux is most often detected during urination against the background of increased intravesical pressure, but it can occur during any of the stages of the urination cycle. Especially in cases of bladder dysfunction.

Review of literature dataregarding the structure and functional anatomy of the vesicoureteral segment convincingly testifies to the complexity and multi-level organization of its antireflux mechanism. Therefore, any further research in this direction will undoubtedly contribute to a deeper understanding of the normal functioning of this complex anatomical part of the human urinary system, which will allow the development and implementation of the latest physiological treatment methods in the practice of pediatric surgeons.

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