Svekatun V. N., Dmitryakov V. A., Lytvynenko O. S. Clinical laboratory diagnosis of obstructive megaureter in children. Pedagogy and Psychology of Sport. 2020;6(4):11-19. eISSN 2450-6605. DOI http://dx.doi.org/10.12775/PPS.2020.06.04.001
https://apcz.umk.pl/czasopisma/index.php/PPS/article/view/PPS.2020.06.04.001
https://zenodo.org/record/4096161

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 21.09.2020. Revised: 29.09.2020. Accepted: 16.10.2020.

Clinical laboratory diagnosis of obstructive megaureter in children

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Abstract

Introduction. Currently, there are more than 200 methods of surgical treatment of a megaureter, but none of the methods has achieved universal acceptance. Until now, the issues of differential diagnosis of organic and functional causes of ureteral dilatation in children under 3 years of age have not been sufficiently illuminated, there is no generally accepted algorithm for the management of patients with this pathology.

Relevance. The relevance of obstructive uropathies is evidenced by the fact that they occupy the third position in the list of the most common causes of chronic kidney disease in children, and account for 15% of cases. The prognosis of the outcome of obstructive uropathy is determined by the nature of the lesion and the degree of involvement in the pathological process of the kidneys, one of the main homeostatic and endocrine organs in humans. The degree of involvement of various markers in the development and progression of kidney damage in children is still insufficiently understood. All this prompts the search for screening, highly sensitive and specific methods for the diagnosis and prediction of nephrosclerotic changes in children against the background of urinary tract obstruction.

Objective: The study of the clinical and laboratory diagnostic methods, allowing to differentiate functional or organic urodynamic disorders, to determine the tactics of managing patients with obstructive uropathy.

Materials and methods. Since 2016, a study has been conducted of 174 children aged 0 to 18 years. 3 groups of children were identified: 1) with endoscopic treatment (main group); 2) treated with an open surgical method (control group); and 3) a group of children without urinary tract obstruction (reference group).

Results. In the course of the study, it was found that the most optimal values of serum cystatin C, close to the reference group (0.048-0.831 mg/ml) were obtained in children treated with endoscopic correction of the intramural ureter (0.217-0.798 mg/ml).

Conclusions. The tactics of endoscopic treatment of obstructive uropathies in children has advantages in terms of open surgical methods in technical simplicity, minimally invasiveness, maximum physiology, and a decrease in the frequency of postoperative complications. These theses are confirmed by the obtained results of the study of serum cystatin C as a marker of the state of renal filtration. It should be remembered that the effectiveness of endoscopic stenting of the lower ureter depends on the age of the child.

Key words: obstructive megaureter, cystatin C, stenting, ureter, children.

Introduction.

For a long time, a significant part of the leading urologists believed that the only way to restore adequate urodynamics in megaureter is the surgical correction of this malformation. To date, about 200 methods of surgical treatment of megaureter have been developed [1], but none of them has received universal recognition [2]. In addition, most authors point to a significant percentage of early and late postoperative complications and relapses [3]. This, on the one hand, determines the search for new methods of surgical treatment. On the other hand, over the past decade in the literature, the question of the effectiveness of conservative therapy for megaureter has been constantly discussed [1, 2, 3]. In their studies, some authors have shown that organic obstruction of the terminal part of the ureter is found in 12-15% of children in the remaining violations of urodynamics are functional [1, 3]. The issues of differential diagnosis of organic and functional causes of ureteral dilatation in children under 3 years of age are insufficiently covered, there is no tactical algorithm for managing patients with this pathology.

Relevance.

Currently obstructive uropathy occupy the third position in the list of the most common causes of chronic kidney disease in children, and account for 15% of cases [2].

The relevance of obstructive uropathy is also evidenced by the fact that of all patients with chronic renal failure 1/3 are children with urological pathology, 36% of which have obstructive uropathy [4].

Prediction obstructive uropathies outcome determined by the nature and extent of lesion involvement in the pathological process of kidneys, one of the main homeostatic and endocrine organs of human.

In severe cases, obstructive uropathies are accompanied by a decrease or even complete loss of renal function with the formation of renal failure, which leads to the disability of the child.

Thus, this problem is one of the socially significant in pediatric urology.

In addition, it is necessary to recognize the fact that the degree of participation of various markers in the development and progression of kidney damage in children is still insufficiently understood. All this prompts the search for screening, highly sensitive and specific methods for the diagnosis and prediction of nephrosclerotic changes in children against the background of urinary tract obstruction.

Signs of sclerosis of the renal parenchyma, detected in the early stages, will allow a more rational approach to the issue of renoprotective therapy and thereby slow down or prevent further progression of renal scarring, as well as open up new directions and possibilities for the treatment of patients with urinary tract obstruction.

Objective. The study of the clinical and laboratory diagnostic methods, allowing to differentiate functional or organic urodynamic disorders, to determine the tactics of managing patients with obstructive uropathy.

Materials and methods.

Since 2016, a study has been conducted of 174 children aged 0 to 18 years. 3 groups of children were identified:

1) The main group - 18 children with megaureter without active pyelonephritis, in whom the restoration of urodynamics was carried out by using endoscopic bougienage with balloon or frame dilatation of the intramural section of the compromised ureter with orifice calibration and stenting of the ureter with an intraluminal polyvinyl chloride drainage (stent) corresponding;

2) The control group consisted of 64 children with primary obstructive megaureter treated by open surgery (transvesical reimplantation of the ureter into the bladder using the Cohen or Politano-Leadbetter method, or a palliative ureterocutaneostomy was applied);

3) The reference group consisted of 92 children without urinary tract obstruction.

Testing of statistical hypotheses about the difference between the average dependent samples was performed using Student's t-test in the application package «Statistica 6.0 for Windows» (StatSoft Inc., № AXXR712D833214FAN5).

Results.

Since 2016, a study has been conducted of 174 children aged 0 to 18 years. Three groups of children were identified: 1) with endoscopic treatment (main group); 2) treated with an open surgical method (control group); and 3) a group of children without urinary tract obstruction (reference group). The results are shown in table 1.

Table 1. Digital indicators of the level of cystatin C in children of different groups, depending on the type of treatment.

Groups of children	Digital indicators of the level of cystatin C, mg / ml
The main group (n=18)	0,217-0,798
The control group (n=64)	0,289-1,511
The reference group (n=92)	0,048-0,831
Total (n=174)	0,048-1,511

where «n» is the number of children.

On the basis of the identity of the indicators, two groups of children were combined into one: the main group and the reference. group. The hypothesis of the presence of differences in the average dependent samples was tested using the Mann-Whitney test. Authentic significant difference between these two groups, $p < 0.05$.

As seen from the table, the most optimal values, close to the reference group, were obtained in children treated with endoscopic correction of the intramural ureter.

Discussion.

To diagnose malformations of the kidneys and organs of the urinary system and their complications in children, the results of various laboratory and instrumental research methods, assessment of the rate of diuresis, study of the mother's history with the identification of hereditary factors, and especially the clinical state are taken into account. However, there are a number of limiting factors associated with the physiological characteristics of the urinary system of the newborn, difficulties in using special research methods due to age, as well as the scarcity of clinical manifestations [5].

Of the instrumental research methods, the gold standard is ultrasound, since it has sufficient information content, is non-invasive, relatively simple to perform and low in price.

If it is necessary to clarify the diagnosis, the following are used: magnetic resonance imaging or computed tomography of the kidneys with or without contrast, vocal cystography, radioisotope and other studies [6].

Analysis of biochemical parameters of blood serum helps to clarify the nature of kidney damage and the degree of their functional failure. With damage to the renal parenchyma, hyperkalemia, hypo- or hypernatremia, hypocalcemia. Enzyme diagnostics is also important: lactate dehydrogenase, alkaline phosphatase, aminotransferase, glutamate dehydrogenase [7]. Evaluation of the activity of enzymes identified in the urine shows the degree of damage to the structural and functional parts of the nephrons, suggests a prognosis and clarifies the localization of the process.

Most used endogenous markers reduction of glomerular filtration in clinical practice - a serum creatinine or blood urea nitrogen. However, the concentrations of creatinine and blood urea nitrogen are insensitive to the detection of mild to moderate reduction in glomerular filtration rate [8]. In addition, serum creatinine levels are influenced by age, sex, muscle metabolic rate, medication, and diet**.**

In the literature there are data on the assessment of glomerular filtration and tubular dysfunction using the determination of β2-microglobulin in urine and blood by the radionuclide method. The specialty of this marker is that his metabolism almost completely occurs in the kidney. Therefore, an increase in β2-microglobulin in the blood indicates either its increased synthesis or a decrease in filtration by the kidneys, and an increase in its level in urine indicates a predominantly tubular genesis of proteinuria [7]. However, the newborn study β2-microglobulin in the urine has its limitations: a positive result in the urine can only point to the immaturity of tubular apparatus of kidneys.

A potential marker of kidney damage is interleukin-18 (IL-18), which is secreted and degraded almost entirely in the renal proximal tubule. Its appearance in the urine indicates damage to the proximal tubules. IL-18 is a more sensitive indicator of renal damage than serum creatinine and appears 24 hours before the rise in creatinine. IL-18 also has limitations, since the level of proinflammatory cytokines in the urine can increase in sepsis with liver and lung damage, even without kidney damage, in addition, its level in blood plasma increases in inflammatory bowel diseases, rheumatoid arthritis, systemic lupus erythematosus, and for other pathological conditions [9].

Currently, the greatest interest of researchers is attracted to cystatin C as a marker of decreased kidney function. In the literature in recent years, this issue has received increasing attention.

Cystatin C is a non-glycosylated protein, its molecular weight is 13.4 kDa, isoelectric point at pH 9.3, it belongs to the family of inhibitors of cysteine proteinases. It was first detected in patients with renal insufficiency in the cerebrospinal fluid and urine; is synthesized at a constant rate by all nucleated cells, in addition, it is freely filtered through the glomerular membrane of the kidneys and is completely metabolized in the kidneys, and is also not secreted by the proximal renal tubules [10].

Cystatin C is a cysteine proteinase inhibitor, blocks the degeneration of the extracellular matrix, carried out by them. Normal levels of serum cystatin C in a human caused by continuous rate of its synthesis and its elimination rate constant from the body mainly by the kidneys.

The level of cystatin C increases either with pathology caused by an increase in its synthesis, or with a decrease in its excretion. Since cystatin C is excreted primarily by the kidneys, in the absence of cardiac, thyroid, or malignant neoplasms, it can be a reliable marker of renal filtration status. A single determination of the concentration of cystatin C in serum assists with special formulas calculate the glomerular filtration rate (GFR) [11].

Normal values of cystatin C, initially higher at birth, decrease during the first year of life, and remain stable up to 50 years of age, with a further increase after this age. The reference values of cystatin C are presented in table. 2.

Table 2. Reference values of cystatin C depending on age [12]

	Cystatin C, mg / ml	
Age	men	women
0-1 мес	1,49-2,85	1,49-2,85
1-5 мес	1,01-1,92	1,01-1,92
5-12 мес	0,75-1,53	0,75-1,53
1-2 года	0,77-1,85	0,60-1,20
2-19 лет	0,62-1,11	0,62-1,11
19-50 лет	0,5-1,2	0,5-1,2

Cystatin C is considered as a new marker for assessing the filtration function of the kidneys in children who do not have conditions that affect the level of cystatin C (chromosomal diseases, thyroid dysfunction, glucocorticoid therapy, cardiomyopathy, myocardial ischemia, heart failure). In this case, it is a reliable marker of renal filtration

disorders and can become a key indicator in clinical practice in newborns with antenatally detected renal and urinary tract malformations [13].

Until now, the question of the choice of substrate remains controversial: to determine cystatin in blood or in urine [14]. The advantage of studying cystatin in urine, especially in newborns, is that this method is non-invasive and does not have a limit on the number of samples taken. However, in the literature there is evidence that the level of cystatin C in urine is not informative due to its breakdown under the influence of urine enzymes.

Some authors note that the simultaneous determination of cystatin C and creatinine helps to give a more accurate assessment of factors, both related to the glomerular filtration rate and not related to it, as well as to obtain a more accurate prognosis of adverse outcomes [15].

Conclusions

The most severe kidney damage in children, which lead to end-stage renal failure and subsequently require transplantation, develop against the background of congenital malformations of the kidneys and urinary tract. Timely diagnosis and correction of these conditions is necessary to reduce the incidence of adverse outcomes and disability in children.

Despite the advances achieved in the diagnosis of congenital malformations of the kidneys and urinary tract, there are still contradictions in assessing the degree of implementation of antenatally identified signs of impaired urinary tract structure, as well as the clinical significance of markers of renal damage in assessing the state of the urinary system after childbirth.

The difficulty in creating a unified approach to the management of patients with kidney and urinary tract defects is associated with a variety of anomalies. On the one hand, congenital anomalies include a wide range of malformations that can manifest at different levels: kidneys, ureters, bladder or urethra. On the other hand, a significant part of the identified malformations, such as, for example, pyelectasis, are leveled during the first year of a child's life. Thus, the problem of choosing a category of patients for surgery and determining its timing in order to prevent the process of renal tissue remodeling remains unresolved. At the same time, it is advisable to lead some children conservatively. The definition of tactics in such patients also requires clarification. The management of patients with congenital anomalies of the kidneys and urinary tract is a multidisciplinary problem that requires a continuity of doctors of various specialties: obstetricians, ultrasound diagnostics doctors, neonatologists, pediatricians, surgeons, as well as nephrologists and urologists.

The proposed tactics of endoscopic treatment of obstructive uropathies in children has advantages in terms of open surgical methods in technical simplicity, minimally invasiveness, maximum physiology, and a decrease in the frequency of postoperative complications. These theses are confirmed by the obtained results of the study of serum cystatin C as a marker of the state of renal filtration. It should be remembered that the effectiveness of endoscopic stenting of the lower ureter depends on the age of the child.

Prospects for further research. Currently, there is increasing interest in the use of immunological methods for the early (preclinical) detection of obstructive uropathies and clear differentiation of organic and functional causes of urinary tract dilation. The most promising in this direction is the use of accurate markers of renal function in the clinical prediction of the course of pyelonephritis, the condition of the kidneys and urinary tract, the choice of tactics for the management and treatment of children with obstructive uropathy.

Conflict of Interest: None.

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