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The Experience of Physical Therapy of Vesicle-Dependent Forms of Megaureter in Children

The article is devoted to one of the important issues of pediatric urology – mega ureter treatment in children, presence of which is fraught with the development of sclerotic changes in the renal parenchyma and the formation of chronic renal failure. The authors applied the method of physical therapy treatment, including electrophoresis of the bladder and the lower third of the ureter with the anti sclerotic drug. We present results that demonstrate the positive effect of this therapy.

Keywords*: mega ureter, complications, treatment, physical therapy techniques, and children.*

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In pediatric practice the mega ureter is one of the biggest problems leading to kidney complications. First, the violation of the passage of urine along the ureter does not provide an adequate evacuation of the microbial flora, which penetrates into the urinary tract and causes inflammation in the renal parenchyma (pyelonephritis). Second, the internal renal hydrostatic pressure has a negative effect on the renal blood flow. The outcome of chronic inflammatory disorders and renal blood flow is the progression of renal parenchymal damage with the development of sclerotic processes and disturbances of its functions (secondary shrinkage of the kidney, kidney sclerosis), the development of chronic renal failure (CRF), and hypertension [1].

According to the Russian Register of CRF in children in 2000-2004, obstructive urologic pathologies occupy the 1st place and account for 43% of the total diseases forming the CRF [2]. Difficulties in the differential diagnosis of obstructive and non-obstructive forms of mega ureter, severe obstructive pyelonephritis, participation of neurogenic bladder disfunction in the pathogenesis of kidney damage, high rate of comorbidity (myelodysplastic syndrome , anorectic malformations, etc.); and as a consequence, the choice of timing and methods of treatment (conservative or operative) dictate the need for finding fast, accurate and minimally invasive methods for the dynamic evaluation of the functional state of the upper urinary tract [3, 4].

The reduction of peristaltic activity, as well as the violation of the evacuating and closing function of the ureter are directly related to myocyte apoptosis and increased ureteral wall deposition of collagen in the ureter's wall [5]. It is known that the basis of the processes that determine the inflammatory and reparative changes are local and common pathological reactions, which are regulated by an integrated system of intercellular communications through synthesizing biologically active components (cytokines, growth factors, etc.). With long-term damage to the ureter tissue the aggressive biological compounds (hum oral mediators of inflammation) accumulate in the blood, which has a direct impact on the cells of the target organ and the major cellular elements of inflammation, involving them in the center of alteration [6, 7].

In recent years we have intensively investigated the molecular mechanisms of ureter tissue damage in mega ureter. It was found that local and systemic reactions in the urinary system are regulated by cell-cell interactions mediated by transforming the growth factor β1 (TGF β1), as well as changes in activity of several enzymes of tissue such as matrix metalloproteinase (MMR) and their tissue inhibitor (TIMP-1) directly determining the state of the extracellular matrix (ECM)of ureter [5, 7]. Multifaceted role of the superfamily of TGF β1 is reduced to the regulation of the actions of other cytokines that stimulate the synthesis and reduced degradation of ECM, control the development of sclerosis and inflammation in the tissues of the ureter. Increased expression of TGF β1 mediates the development of fibrosis, which in turn contributes to the progression of renal and dysplastic changes in congenital obstructive urologic pathologies [8].

Thus, the increase in the secretion of pro inflammatory cytokines and an imbalance ratio of pro- and anti-inflammatory cytokines may be important in the pathogenesis of mega ureter in children.

Our study involved 15 boys with a vesicle-dependant form of megaureter from 5 to 14 years old. It is known that changes in the ureter of such patients are of a secondary character and depend largely on the severity of the bladder dysfunction. For this reason the treatment strategy is aimed at restoring the reservoir and evacuation function of the bladder.

In order to optimize conservative treatment for children of this group electrophoresis of the bladder and the lower third of the ureter was carried out with the drug Fermenkol, whose action was aimed at the destruction of excess collagen.

The method of electrophoresis

For the procedure of electrophoresis 4 mg of dry active substance, which was a set of 9 collagenolytic proteases with a molecular mass of 23 to 36 kDa, were diluted in 20 ml of a liquid solution for enzyme preparation with pH 5,0 ± 0,5. A gauze, soaked in the solution with the concentration of collagenase at 0.2 mg / ml, was laid on the area of the bladder and ureters. Treatment time was 20-25 min. Duration of the course was 15 procedures.

Within a year the children underwent 3 courses.

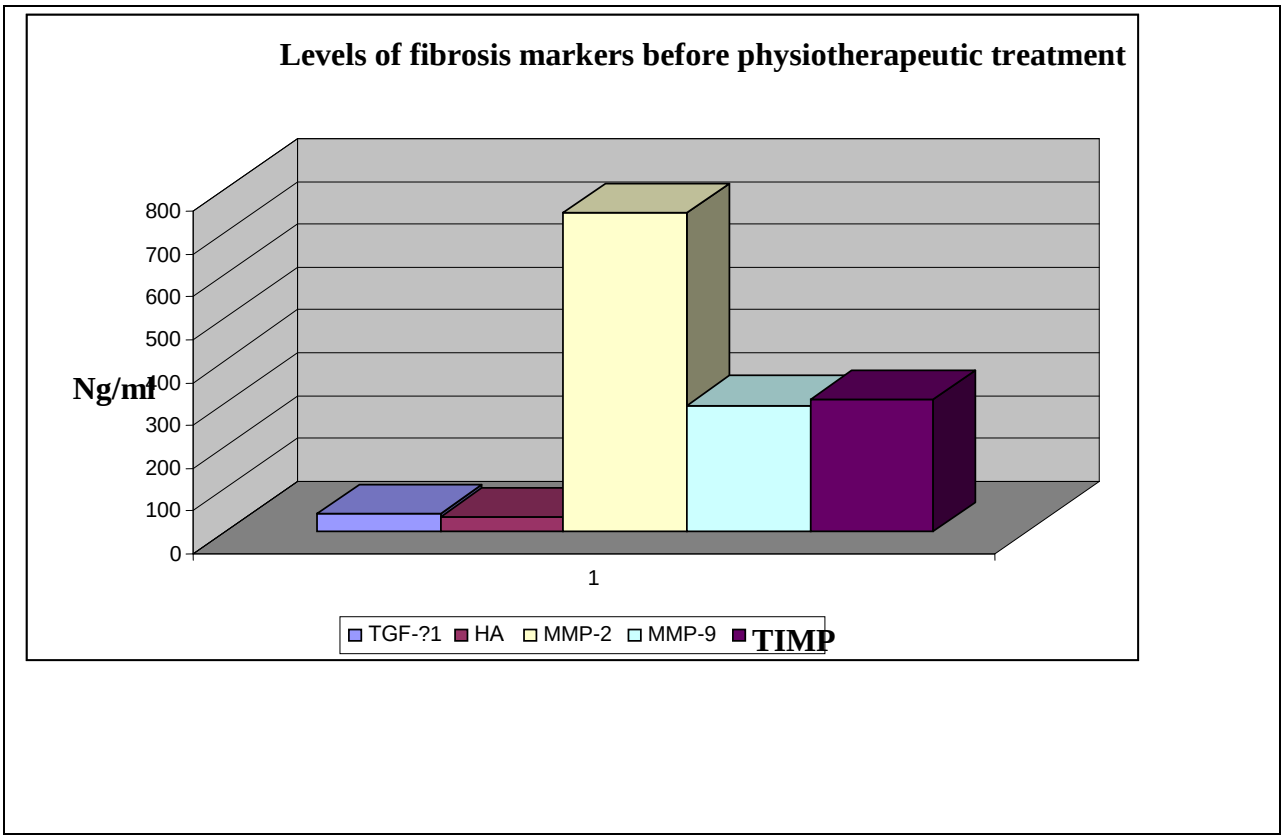
We conducted a study of changes in the content of the pro-and antisclerotic markers of ureter sclerosis in the serum of patients before and after the physiotherapeutic impact using the enzyme-linked immune sorbent method (ELISA).

The changes in TGF βl and HA levels that we have identified indicate the activization of fibrogenesis processes. The activation of fibroblasts, macrophages, epithelial and other cell systems is added to the process of cell infiltration and dystrophy, and they rapidly start synthesizing ECM components, which largely determines the functional failure of the subsequent process of regeneration with the formation of fibrosis, persistent expansion and disfunction of the ureter.

These processes are directly related to contest changes in the matrix metalloproteinases in the serum of patients, evidencing active fibrosis of ureteral tissue and mega ureter in children.

Usually the production of proteases (collagenases in particular) and their inhibitors (tissue metalloproteinase inhibitors) is balanced. A necessary condition of normal physiological processes is the maintainance of a balance between the activity of MMPs and their inhibitors. Violation of this balance can have a profound impact on the composition of the extracellular matrix and can influence different cell functions, including adhesion, migration, and differentiation (Fig. 1).

Fig. 1 **Levels of fibrosis markers before physiotherapeutic treatment**



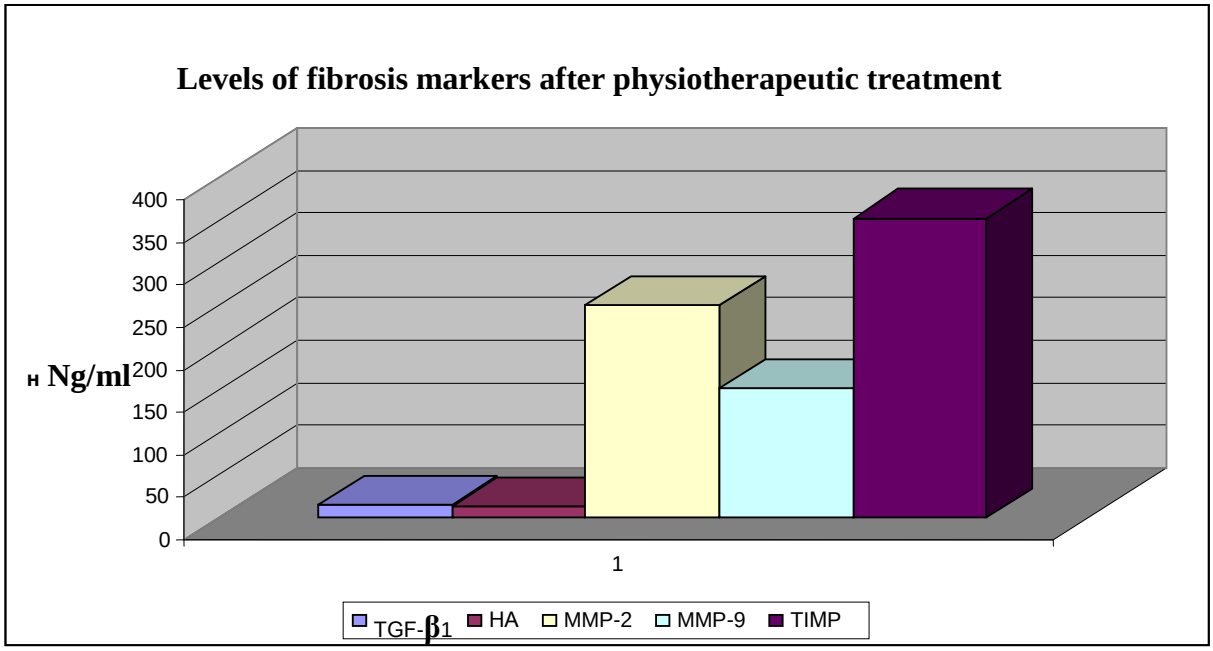
Note: TGF β1 - transforming growth factor β1, MMR-matrix metalloproteinase, TIMP-1 tissue inhibitor of MMR.

After 12 months (3 courses of physical therapy) the concentration of the studied biomarkers was determined in all children again. All the children showed no statistically significant changes in the concentration of HA and TGF β1.

Perhaps after the restoration of the urine passage the activity of sclerotic processes can still remain high for a very short time, which, however, may be due to the slow elimination of cellular infiltration, and can manifest itself in persisting high plasma concentrations of the profibrotic TGF β1.

The data received indicates a slight decrease in the concentrations of MMP-2 (by 1.2 times) in these children; while the amounts of TIMP-1 concentrations equally increased in the studied patients. (Fig.2).

Fig.2: The levels of fibrosis markers after physical therapy



Снизу: **TGF βl HA MMP-2 MMP-9 TIMP**

Note: TGF β1 - transforming growth factor β1, MMR-matrix metalloproteinase, TIMP-1 tissue inhibitor of MMR.

Through the analysis of the results it becomes clear that the processes of collagen formation in the ureter in the process of the children's megaureter disease happens with a significant activation of TGF β1, matrix metalloproteinase and their tissue inhibitors production. Overexpression of MMP under the influence of pro inflammatory cytokines during megaureter

in children is a testament of the crucial role of the balance of MMP, their inhibitors and promoters in the development and progression of the urologic pathology.

Thus, affecting the bladder and ureters with physiotherapy (Fermenkol drug) leads not only to a decrease in collagen formation process, but also to the activation of proteolysis processes.

The descovered laws of changes in the contents of matrix metalloproteinases and the transforming growth factor β1 in the serum during megaureter of different severity levels is recommended to use for monitoring its clinical course in children and assessing the effectiveness of its treatment.

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