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Features of nitrogen oxide and endothelin-1 changes in children with urinary tract infections

Summary

In order to determine the peculiarities of the nitric oxide (NO) and endothelin-1 (ET-1) levels in children with urinary tract infections (UTI), 24 children at the age of 1-16 years were examined. The patients were divided into 3 groups: children with cystitis were included into group I (n = 6); children with cystitis and manifestations of pyelonephritis were included into group II (n = 6), and group III (n = 8) contained children with cystitis associated with glomerulonephritis. The comparison group consisted of 5 healthy children. All children, along with general clinical tests, were assessed for NO and ET-1 levels by IEA. The results of the study demonstrated that in children with UTI there were changes in the content of NO and ET-1, depending on the severity of the disease and associated renal pathology.

Key words: nitric oxide, endothelin-1, urinary tract infections, children

Disfunction of vascular endothelium is one of the most important mechanisms, related wth a number of patolojical conditions. In modern age it has been determined that disfunction of vascular endothelium is connected with changes of endothelin, tissue activator of plasminogen, nitrogen oxide (NO) and other biological mediators. Nitrogen oxide and endothelin especially attract researchers' interest. The role of these substances in regulation of physiological and pathological processes in a body is actively studied at present [1, 2, 3, 9].

In many cases the reason is inflammation,which is the typical respond to local pathological effect in vascularized organs. Most of the researchers have studied nitrogen oxide from the point of its effect to local microcirculation and interactions with other biologically active substances [4, 12].

It is known that nitrogen oxide in a human body is created by L-arginine under the impact of NO-synthase (NOS) and is accompanied by creation of L-citrulline. According to modern theories, two main groups of NOS are differed depending on the activation method: constitutive (neuronal, n-NOS and endothelial, e-NOS) and inducible (i-NOS). Constitutive isoforms facilitate creation of a little amount of NO that participate in regulation of vascular tone in norm of the body. Inducible NOS are localized mainly in macrophages and activated by cytokines during the pathological processes, which is accompanied with creation of NO in a large amount [7, 14].

Short-term ischemic reactions are replaced first by the leading arterio-venous fullness and then by venous stasis, play a leading role both in acute and chronic inflammatory process in microcirculatory system. Increased conductivity of capillaries causes exudate creation that provides transport of protective agents to the imflammatory centre [12]. These processes are regulated with active participation of nitrogen oxide together with histamines, quinenes and leukotrienes. In other words, nitrogen oxide acts as the powerful mediator of the inflammation and has an important effect on the intensity and progress of the process [15].

A key physiologic action of nitric oxide, the endothelium derived relaxing factor, is to activate soluble guanylate cyclase and generated cGMP to cause relaxation. Endothelial nitric oxide synthase is constitutively active, generates NO in response to shear stress and other physiologic stimuli and can limit the constrictor action of endothelin-1 (ET-1). [8] ET-1 is known as the most potent vasoconstrictor in the human cardiovascular system with remarkably long lasting action.

A number of pathophysiological conditions are associated with endothelial cell dysfunction and loss of nitric oxide. The balance between ET and nitric oxide appears critical. In contrast to nitric oxide, shear stress downregulates the transcription of the ET-1 gene and may be related to cell shape and cytoskeletal change [10]. It is well known that inhibitors of NOS increase levels of ET-1. In rats, in vivo treatment with NOS inhibitor to cause hypertension resulted in increased ET-1 synthesis in renal microvessels when NO production is suppressed.

Studying of the role of nitrogen oxide and ET-1 in nephrological pathologies is of great interest. There is information about the permanent synthesis of nitrogen oxide in endothelium of kidney vessels and cells of smooth muscles, glomerular mesangial cells and tubular epithelial cells. Thanks to it, NO interconnected to renin-angiotenzin system and other bio-regulatory systems has a significant effect on renal blood flow, excretory function of kidneys and regulation of tubulo-glucometer balance [7, 13]. ET-1 was found to be a major activator of collagen I formation in renal resistance vessels and in the development of renal fibrosis [11].

But the features of the changes of nitrogen oxide and ET-1 in pathogenesis of inflammatory processes of different types of urinary excretory system have not been studied fully till now, which is undoubtedly of great importance from scientific and practical point of view.

The **aim** of our research was to study the features of nitrogen oxide and ET-1 indices changes in children with different urinary tract infections (UTI).

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Materials and Methods

24 children aged from 1 to 16 with different ethiological diseases of the urinary tract system were examined. The patients were divided into 3 groups. The group I included children with cystitis diagnosis (n=6), the group II – children with pyelonephritis symptoms together with cystitis (n = 6), the group III – children with the diagnosis of glomerulonephritis together with urinary tract infections of severe progression (n = 8). The control group included 5 healthy children.

All children were examined for determination of NO and ET-1 in blood (by the method of immunoferment analysis (IFA) with general clinical examination. The received indicators were worked out with various of statistical methods through calculation of the standard error of average mathematical limit (M) and average numerical price (m). The difference between the groups was assessed according to nonparametric Manna-Whitney, Wilcoxon criteria.

Results and Discussion

The level of NO in the healthy children was 9.9 ± 1.5 mcmol/l. During the analysis of the received indicators 1 healthy child was examined according to Sharl criterion. Analysis of ET-1 level in the same group of children shows that it was 1.25± 0.75 fmol/ml.

The level of nitrogen oxide in patients of the group I was lower about 7.8 % and equal to 9.2 ± 1.8 mcmol/l. (p=0.748) compared to the control group. ET-1 level in this group was 0.65±0.35 fmol/ml (it is lower 48 % in comparison with healthy children).

An obvious difference was noted in NO level compared to the healthy children of the group II. Nitrogen oxide in these patients was 16.4 ± 4.0 mcmol/l, which was higher in 1.6 times than the results received in the healthy children (p=0.394), and in 1.8 times than the results received in the patients of the group I (p=0.173).

ET-1 in children of the group II was 5.2 ±2.17 fmol/ml, which was higher in 4.2 times than the data of the control group (p=0.185), and 8 times higher than the level of ET-1 in the group II of patients (p=0.063).

In our opinion, it is related to the existence of children with pyelonephritis diagnosis in that group. During the mentioned pathology the expressed activity of the inflammatory process of kidneys, leucocitar infiltration of kidney parenchyma and strengthening of hemotaxide effects in granulocytes may cause NO level to be higher compared to cystitis with light progression. In addition, NO performs defense function through damaging effect to bacteria that enter to the organism. [2,5]

Existence of such changes in biosynthesis of nitrogen oxide may be an index of maintenance of inflammatory process in the kidney tissue not with standing to blood and urine indexes being normal and observance of clinical manifestations of pyelonephritis. From the other point, existence of obstruction of the urinary tract may cause violation of renal hemodynamics (as well as microcirculation). In turn it may lead to rise of NO synthesis with vascularizer, natriuretic and diuretic effect which is similar to the effect of prostanoids. [6]

Level of an endothelin is in close interrelation with the NO level, any inflammatory changes in renal tissue which are followed by violations of a vascularization, aggravated with the strengthened synthesis of an endothelin with its vasoconstrictor effect. It is the factor worsening the forecast at renal pathology, accelerating development of nephrosclerosis.

NO level in patients of the group III was 15.7 ± 2.8 mcmol/l, which was higher in comparison to the control group and the group I (57.9 % (p=0.234) and 71.3 % (p=0.137 relatively)). In comparison to the group II this index was lower about 4 % (p=0.948).

Analysis of the ET-1 level in the group III shows, that it was 1.09±0.58 fmol/ml. This data was lower, than in control group and the group II (13 % (p=0.516) and 79.1 % (p=0.049), relatively). But it was higher in comparison to the group I – about 67.3 % (p=0.516).

Probably, it may be explained as follows: infiltration of mucous macrophages happens during glomerulonephrite and activation of mesagial cells. In this case impact of nitrogen oxide may have cytotoxic character. From the other hand, mesangial cells produce eukozanoids, cytokins, free radicals together with macrophages, which are considered facilitators of fibroplazia development. [5] In this case, nitrogen oxide may cause hyperfiltration of mucous with its vascularizing effect and may lead to glomerulosclerosis. About the level of an endotelin, in this group it was much lower, than in the group II , where the patients with pyelonephritis prevailed. The literature data demonstrate that during the long (over several years) course of pyelonephritis exhaustion of production of NO, increase in level of the endotelin possessing vasoconstrictor action, and, as a result, development of nephrosclerosis is observed.

Conclusions

Thus, notation of high level of NO in children with inflammatory diseases of urinary excretion system may be considered as a proof of high activity of the inflammatory process. A certain difference may be noted in the levels of nitrogen oxide and endothelin depending on localization, severity of UTI and existence of another kidney pathology, which may be explained with the leading role of different mechanisms in development of inflammation during pyelonephritis and glomerulonephritis.

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Резюме

Особенности изменений оксида азота и эндотелина -1 у детей с инфекциями мочевыделительного тракта

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С целью определения особенностей уровней оксида азота (NO) и эндотелина -1 (ЭТ-1) у детей с инфекциями мочевыделительного тракта (ИМТ) было обследовано 24 ребенка в возрасте 1–16 лет. Больные были поделены на 3 группы: в I группу (n=6) были включены дети с циститом, во II группу (n=6) – дети, у которых наряду с циститом имелись проявления пиелонефрита, а в III группу (n=8) – дети, у которых цистит ассоциировался с гломерулонефритом. Группу сравнения составили 5 здоровых детей. Всем детям, наряду с общеклиническими исследованиями, проводилось определение уровней NO и ЭТ-1 методом ИФА. Результаты исследования показали, что у детей с ИМТ имелись изменения содержания NO и ЭТ-1, зависящие от степени тяжести заболевания и ассоциированной почечной патологии.

Ключевые слова: оксид азота, эндотелин-1, инфекции мочевыделительного тракта, дети

Резюме

Особливості змін оксиду азоту і ендотеліну-1 у дітей з інфекціями сечовивідного тракту

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З метою визначення особливостей рівнів оксиду азоту (NO) і ендотеліну-1 (ЕТ-1) у дітей з інфекціями сечовивідного тракту (ІСТ) було обстежено 24 дитини у віці 1–16 років. Хворі були поділені на 3 групи: до I групи (n=6) увійшли діти з циститом, до II групи (n=6) – діти, у яких разом із циститом були прояви пієлонефриту, а до III групи (n=8) – діти, у яких цистит поєднувався з гломерулонефритом. Групу порівняння склали 5 здорових дітей. Всім дітям, разом із загальноклінічним обстеженням, проводилось визначення рівнів NO та ЕТ-1 методом ІФА. Результати дослідження показали, що у дітей з ІСТ були виявлені зміни рівнів NO і ЕТ-1, що залежали від ступеня тяжкості захворювання і асоційованої ниркової патології.

Ключові слова: оксид азоту, ендотелін-1, інфекція сечовивідного тракту, діти

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