Renal Doppler Diagnostics in Lead-, Nickel- and Manganese-Exposed Children

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ABSTRACT

Introduction: Under the current unfavorable environmental conditions, chronic diseases of human systems, including the urinary system, having a protective function, are becoming more and more prevalent.

Objective: The aim of the study was to identify ultrasound criteria for early diagnostics of renal pathologies in children, who were exposed to metals of anthropogenic origin (lead, nickel, manganese). In order to achieve this aim, we have assessed renal hemodynamics in children with high blood metal levels. We have also identified a relationship between blood metal levels and an ultrasound examination of renal blood circulation as well as ultrasound criteria for the signs of early renal disorders in patients, exposed to the metals of anthropogenic origin (lead, nickel, manganese).

Materials and Methods: A total of 90 children with minor changes in uranalysis in their anamnesis were examined in this study. The children were divided into a study group (54 patients) and a control group (36 patients). All the patients underwent renal scanning, which was performed using a Toshiba Aplio XG ultrasound scanner (Japan) with a 7-14 MHz linear-array transducer and a 3-6 MHz curved array transducer from multiple views.

Results: We have found out that children with urine and blood samples, containing elevated levels of metals of anthropogenic origin (lead, nickel, manganese), typically demonstrate renal hemodynamic disorders, which can be detected by ultrasound diagnostic methods. The extent of hemodynamic changes was affected by the blood levels of lead, nickel and manganese.

Conclusion: We have determined Doppler ultrasound criteria for early diagnostics of renal pathologies in children with biological samples, containing increased levels of the metals of anthropogenic origin (lead, nickel, manganese). The criteria are poor blood circulation in color Doppler mapping in the subcapsular area (a qualitative assessment); a reduction in relative characteristics of blood circulation (RI < 0.6; PI < 1.1); the difference between the lower and upper bounds of RI value range from the arterial trunk to the peripheral arteries greater than

0.04-0.05. We have shown a true correlation between relative parameters of blood circulation which characterize renal vascular resistance and the blood levels of the metals (lead, nickel, manganese). We have determined high risks of inflammatory and abacterial diseases of the urinary system in children with blood and urine levels of lead, nickel and manganese, exceeding the reference concentrations by 1.5-1.7 fold, in environmentally unfavorable areas.

Keywords: metals, ultrasound diagnostics, renal pathology.

Introduction

In areas with unfavorable environmental conditions, the prevalence of chronic diseases of the human systems, including the urinary system, having a protective function is ever increasing. [1, 7]. According to the official statistical data, during the last five years the incidence of urinary diseases in Russian children has not decreased. On the contrary, in industrialized areas, during

the same period of time it has increased by 50-60 %, that is 2.2 to 2.6-fold higher than the average rates across Russia. In addition, within a one-year period, the rate of incidence increase is 3.0 to 5.5-fold higher, compared with average rates in Russia [3, 7].

Under the current environmental conditions, the understanding of mechanisms of urinary

disease development is changing. It implies that a more important role in the pathogenesis of renal pathology is played by the unfavorable impact of chemical environmental factors of anthropogenic origin [4, 6]. The most apparent impact on the tubulointerstitial renal tissue is that produced by chemical substances, having a direct nephrotoxic effect, when the toxicants (lead, nickel and manganese salts) are in contact with the epithelium of the glomerular and tubular elements of the nephron. The metals (lead, nickel and manganese) increase the oxidation of membrane phospholipids. Therefore, cellular antioxidant enzymes (superoxide dismutase, glutathione transferase, catalase) and some plasma components (transferrin, ceruplasmin, albumin) in combination with these metals, lose their ability to neutralize active radicals. As a result, the metals' pathological effect on cellular membranes and enzymes causes mitochondrial functional disorders, reduced ATP production, decreased ratio of adenosine-5'-triphosphate (ATP) to adenosine diphosphate (ADP) and reduced activity of ATP-dependent enzyme systems. Changes in ATPase activity may lead to electrolytic disorders and, eventually, to changes in the cellular membrane potential. All these processes induce inflammation in renal tubular epithelium which may lead to reduced renal filtration and reabsorption, the retrograde flow of primary urine, increased blood pressure in the Bowman's capsule and therefore an increase in blood pressure in the glomerular capillary network. The activation of the juxtaglomerular apparatus induces rennin hypersecretion. The local effect of the rennin-angiotensin system determines the spasm of preglomerular arterioles, which leads to a dramatic reduction in blood flow in the glomerus and to the deterioration in glomerular filtration, on the one hand, and to the ischemia of the renal tubules, on the other hand. These pathological changes are a morphological basis for the development of chronic inflammatory and abacterial urinary pathology [2, 4, 5].

Therefore, it is necessary to develop non-invasive methods for early diagnostics of renal hemadynamic disorders to detect prenosological entities of renal diseases, caused by exposure to chemical factors, in particular metals of anthropogenic origin.

Ultrasonic methods for the diagnosis of renal diseases are most prevalent, less invasive and rather informative [9, 10]. Although in many renal parenchymal diseases normal grayscale patterns (B-mode) can be observed, it is of importance to enlarge the list of indications to diagnostic Doppler examinations [8]. Compared to angiography and renal isotopic angiography, the renal Doppler examination is a non-invasive and radiation-free technique, having no contraindications.

Objective

The aim of the study was to identify early ultrasound criteria for early diagnostics of renal pathology in children with blood and urine samples, containing elevated levels of metals of anthropogenic origin (lead, nickel, manganese).

Materials and Methods

The diagnostic examination of the children was carried out in accordance with the ethical principles stated by the 2nd revision (1983) of the Declaration of Helsinki.

A total of 90 children with minor changes in uranalysis in the anamnesis (short-term leukocyturia, erythrocyturia, hyposthenuria in acute viral and bacterial infections) were examined. The children were divided into two groups, a study group and a control group. The study group comprised 54 children who lived in areas with unfavorable environmental conditions and whose biological samples contained elevated levels of lead, nickel and manganese compounds. The control group consisted of 36 children, who lived in relatively unpolluted areas and whose blood and urine metal concentrations were lower or equal to the reference concentrations.

The performed comparative analysis showed that metal levels in the blood of the study group children exceeded the lead, nickel and manganese levels in the control group and the reference concentrations by 1.5-1,7 and 1.2-1.6 fold ($p=0.001$), respectively. Similarly, the study group demonstrated urinary metal levels exceeding those in the control group and the reference concentrations (Table 1 and 2).

Renal scanning was carried out using a Toshiba Aplio XG ultrasound scanner (Japan) with a 7-14 MHz linear-array transducer and a 3-6 MHz curved array transducer from multiple views. The scanning frequency was used according to child's age, physical development and the adipose tissue layer thickness. The examination was performed in two stages.

At the first stage, we carried out B-mode gray scale ultrasound scanning of kidneys as well as color Doppler mapping (CDM) of ureteral jets. We assessed the location of kidneys, their

dimensions, shape and contours, the border between renal parenchymal cortex and medulla, the dimensions and structure of the pelvicalyceal system, kidney mobility, the presence of calculi and renal neoplasms, the degree of bladder filling, bladder wall thickness and the presence of urine sediment, the symmetry of ureteral jets and the presence of residual urine after urination.

At the second stage of the examination, we assessed renal hemodynamics. We used color Doppler mapping to visualize the general pattern of renal blood circulation in venous and arterial trees, from the renal artery trunk to the smallest peripheral blood vessels in the renal cortex, and we applied pulse Doppler ultrasound to perform qualitative assessment and quantitative assessment of blood circulation in an examined vessel.

Pulsed Doppler ultrasound was used to subsequently scan the trunk of the renal artery, the segmental artery, the interlobar artery, the arcuate artery, the small interlobar artery, and to perform qualitative and quantitative assessment of blood circulation in the vessels by the curve, which reflects the range of the Doppler frequency shift. The qualitative analysis was visually determined by the shape of the curve, the range of Doppler curves, the systolic and diastolic components and the symmetry of Doppler curves of both kidneys. It was important to perform the quantitative assessment of the Doppler curve. For this purpose we used two groups of parameters, i.e. absolute (maximum blood circulation velocity during systole, end and minimum diastolic blood circulation velocity, average blood circulation rate), and relative parameters (resistance index (RI)), which reflected the microcirculation condition (vascular tone, the condition of arteriolar and capillary walls); pulsatility index – PI, systolic/diastolic ratio – S/D, which are calculated by formulas in the ultrasound scanner software. The criterion of normal hemodynamics is not only normal values of the above-mentioned indices (0.6-0.72; 1.2-1.5; 1.8-3.0, respectively), but also their persistence in the entire arterial tree, from the renal artery trunk to the small interlobular arteries of the cortex. The difference in the lower and upper bounds of RI range should not be more than 0.04-0.05.

Results and Discussion

At the first stage of the ultrasound examination, when kidney B-mode assessment was performed, no apparent morphological structural changes in the children's kidneys and urinary system were observed, which allowed us to exclude undiagnosed latent pathological process in children with abnormal development.

At the second stage of the examination we obtained the following data: 10% of the study group children had poor blood circulation in the subcapsular area in color Doppler mapping, the control group did not demonstrate any changes in the vascularization in color Doppler mapping. In the study group, we obtained the following data on the blood circulation parameters in the entire renal arterial tree: average group linear blood circulation velocity (VBFV) was decreasing from the trunk to the small cortical vessels. VBFV in the renal artery trunk, the segmental artery, the interlobular artery, the arcuate artery and the small interlobular artery was 85.49±5.38 cm/sec, 5.45±3.45 cm/sec, 35.2±2.42 cm/sec, 24.51±1.42 cm/sec and 14.36±1.16 cm/sec, respectively. Angle-independent relative vascular resistance parameters (RI, PI, S/D) were progressively decreasing from the trunk to the peripheral vessels: RI went down from 0.69±0.021 to

0.59±0.022, PI – from 1.32±0.076 to 0.97±0.056, S/D – from 3.303±0.223 to 2.49±0.129, suggesting changes in renal hemodynamics since normal difference in the RI range bounds should not exceed 0.02-0.03. In 50% of the study group children, RI values were less than 0.6 and in 57% of the study group, PI values were less than 1.1.

The data obtained by Pulsed Doppler ultrasound in the control group showed that velocity parameters and indices were normal in the entire renal vascular tree. The range of RI values did not exceed 0.04-0.05.

The correlation analysis showed a true relationship between relative parameters of blood circulation which characterized renal vascular resistance and the levels of lead, nickel, manganese in blood (Table 3), i.e. the right renal arcuate artery RI values and the blood levels of manganese (r=-0.48, p=0.005), lead (r=-0.45, p=0.024) and nickel (r=0.69, p=0.004); the right renal arcuate artery PI values and the blood levels of manganese (r=-0.48, p=0.005) and lead (r=-0.49, p=0.012); the right renal artery trunk PI and blood nickel levels (r=0.76, p=0.001); the right renal arcuate artery S/D ratio and the concentration of manganese (r=-0.5, p=0.003) and lead (r=-0.48, p=0.015) in blood, the right renal artery trunk S/D ratio and blood nickel levels (r=0.75, p=0.001).

Thus, children with urine and blood samples contaminated with the metals of anthropogenic origin (lead, nickel, manganese) typically demonstrated renal hemodynamic disorders, which were detected by ultrasound diagnostic methods. The extent of hemodynamic changes was affected by the levels of lead, nickel and manganese in blood.

A year after the examination, 38% of the children demonstrated persistent urinary changes, i.e. leukocyturia, microhematuria, moderate proteinuria, hyposthenuria and nocturia, which served as an indication to referral to a nephrologist. During a thorough examination of the cohort of patients, 27% of the children were diagnosed with chronic pyelonephritis and 11% - with abacterial tubulointerstitial nephritis. In the control group, only 7% of the children were diagnosed with inflammatory urinary diseases, i.e. non-obstructive pyelonephritis.

Conclusion

In conclusion, Doppler examination of kidneys in children, when exposed to metals, enables us to detect early hemodynamic disorders, which indicate high risks for the development of inflammatory and abacterial diseases of the urinary system. Diagnostic ultrasound criteria are the following changes in hemodynamic parameters: poor blood circulation in color Doppler mapping in the subcapsular area (a qualitative assessment), a reduction in relative characteristics of blood circulation (RI < 0.6; PI < 1.1) and the difference between the lower and upper bounds of RI value range from the arterial trunk to the peripheral arteries greater than 0.04-0.05.

The analysis of renal blood circulation and the identification of Doppler ultrasound criteria, which indicate renal microcirculatory disorders in children, who live in environmentally unfavorable areas and whose blood levels of lead, nickel and manganese exceed the reference concentrations by 1.5-1.7 fold, can be used for early diagnosis of renal pathology. The

implementation of renal Doppler ultrasound for the examination of children in polluted areas will allow reduction in the incidence of renal diseases and higher effectiveness of the prevention and treatment of renal disorders.

Conflict of Interest: None declared.

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Table 1: Blood levels of heavy metals in children with chronic non-obstructive pyelonephritis, μg/dm^3.

Metal	Study group (M ± m)	Control group (M ± m)	Reference concentrations	P-value
Manganese	0.031±0.001	0.019±0.008	0.019±0.002/ 0.011	0.01
Nickel	0.255 ± 0.031*	0.183 ± 0.026	0.229±0.020/ 0.001-0.028	0.001
Lead	0.159 ± 0.014*	0.101 ± 0.009	0.115±0.007/ 0.100	0.05

* - levels which reliably exceed reference concentrations ($p < 0.05$)

Table 2: Urinary levels of heavy metals in children with chronic non-obstructive pyelonephritis, μg/dm^3.

Metal	Study group	Reference concentrations	P-value
Manganese	0.0235±0.0043	0.0163±0.0030	0.0068
Nickel	0.2689±0.0582	0.1604±0.0127	0.0002
Lead	0.1537±0.0319	0.1098±0.0143	0.0119

Table 3: Correlations between ultrasound parameters of blood circulation and blood metal levels.

Metal	Blood circulation parameter	r	p*
Manganese	Right arcuate artery RI	-0.48	0.005
	Right arcuate artery PI	-0.48	0.005
	Right arcuate artery S/D	-0.5	0.003
Nickel	Right renal artery trunk RI	0.69	0.004
	Right renal artery trunk PI	0.76	0.001
	Right renal artery trunk S/D	0.75	0.001
Lead	Right arcuate artery RI	-0.45	0.024
	Right arcuate artery PI	-0.49	0.012
	Right arcuate artery S/D	-0.48	0.015