THE EFFECT OF DIFFERENT TYPES OF HYPOXIA ON THE MORPHO-FUNCTIONAL STATE OF THE KIDNEYS OF FETUSES AND NEWBORNS: THE RESULTS OF OWN LONG-TERM EXPERIMENTAL STUDIES

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ABSTRACT

Introduction. The vast majority of kidney diseases in children and adults have their origins in the antenatal, intranatal or postnatal periods of development. Poor health of women of childbearing potential, complications during pregnancy and delivery often lead to the development of various types of hypoxia (chronic intrauterine hypoxia (CIH), acute intranatal hypoxia, acute postnatal hypoxia (APH), mixed hypoxia (MH)). The latter are a common cause of fetal and neonatal disorders, leading to damage of various organs and systems, including the kidneys.

The purpose is to highlight the main results of own long-term experimental studies aimed at determining the effect of different types of hypoxia (CIH, APH, MH) on the morpho-functional state of the kidneys in fetuses and newborns.

Materials and methods. In this study, the author modelled alpine hypoxia using a sealed pressure chamber from which air was pumped out, creating conditions for a sharp decrease in atmospheric pressure. Histological, histochemical, immunohistochemical, morphometric and statistical research method were used.

Results. Acute postnatal, chronic intrauterine and mixed hypoxia stimulate fibroblastic cells in the kidneys, and chronic intrauterine and mixed hypoxia also induce epithelial-mesenchymal transformation, causing the development of sclerosis, induce apoptosis, proliferation, leading to an imbalance between them due to the prevaling proliferation in acute postnatal and chronic intrauterine hypoxia and apoptosis in mixed hypoxia.

Conclusions. Identified morphological changes in the kidneys of fetuses and newborns developed under the influence of acute postnatal, chronic intrauterine and mixed hypoxia, given the unity of structure and function, will lead to functional changes in these organs in subsequent postnatal ontogenesis in such children and the emergence of different nephrological pathology. This study actualizes the implementation of preventive measures among persons of reproductive age, dictates the need for quality pre-pregnancy training, which should be aimed at timely detection and treatment of genital and extragenital pathology in women.

Keywords: *acute postnatal hypoxia, chronic intrauterine hypoxia, fetus, kidneys, mixed hypoxia, morphology, newborn.*

INTRODUCTION

Nephropathology remains an urgent problem in modern pediatrics due to high prevalence of this pathology in the pediatric population, low efficiency of treatment, high risk of complications, frequent disability [1].

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In recent years, we have seen the atypical clinical picture of kidney disease in children, predominance of both chronic, latent forms, and manifest, aggressive, severe forms [2]. Doctors very often diagnose kidney diseases in children when they already develop irreversible changes and chronicity of the pathological process. The prevalence of pediatric chronic kidney disease in the world ranges from 15 to 74.7 cases per 1 million children. Mortality among children who progress to end-stage kidney disease is 30 to 50 times higher compared to that in general population [3]. In Ukraine congenital malformations and dysplasia of the kidneys, including polycystic kidney disease, glome-

rulonephritis, interstitial nephritis as a consequence of acute kidney damage, hereditary nephritis are common causes of chronic kidney disease in children [4].

The vast majority of kidney diseases in children and adults have their origins in the antenatal, intranatal or postnatal periods of development, as evidenced by numerous epidemiological studies [5, 6].

Poor health of women of childbearing potential [7], complications during pregnancy and delivery often lead to the development of various types of hypoxia (chronic intrauterine hypoxia (CIH), acute intranatal hypoxia, acute postnatal hypoxia (APH), mixed hypoxia (MH)). The latter are a common cause of fetal and neonatal disorders, leading to damage of various organs and systems, including the kidneys.

Purpose, subjects and methods:

1.The purpose of the study is to highlight the main results of own long-term experimental studies aimed at determining the effect of different types of hypoxia (CIH, APH, MH) on the morphofunctional state of the kidneys in fetuses and newborns.

2. Materials & ᴍethods

In this study, the author modelled alpine hypoxia using a sealed pressure chamber from which air was pumped out, creating conditions for a sharp decrease in atmospheric pressure. Every day, we placed mature female rats with an average weight of 220–250 g in conditions corresponding to 7,500 meters hight at 287 mm Hg for 20 minutes at the same time. During the experiment, we ranked the animals into four groups: group 1 – control group – pregnant female rats (n=3) that did not experience alpine hypoxia, some females were removed from the experiment in late gestation to remove fetuses (n=7). The offsprings (n=11) received from the rest of the females, were removed from the experiment on the first day after birth. Group 2 – a study group with simulation of CIH – pregnant female rats (n=4) throughout pregnancy (21 days) were subjected to daily alpine hypoxia, with some females removed from the experiment in late gestation to remove fetuses (n=6). Offsprings (n=10) from the rest of the females were removed from the experiment on the first days of life. Group 3 – a study group with modeling of APH – pregnant female rats (n=2) were not subjected to alpine hypoxia, but their offsprings (n=8) on the first day of life were subjected to alpine hypoxia once for 15 minutes, and then they were removed from the experiment. Group 4 – a study group for modeling MH – pregnant female rats (n=3) throughout pregnancy were subjected to daily alpine hypoxia, then the offsprings obtained from them (n=8) on the first day of life were subjected to alpine hypoxia once for 15 minutes and removed from the experiment.

The study material was the kidneys of fetuses and newborns. The material was fixed in a 10% solution of neutral formalin (pH 7.4) for 24-48 hours according to the generally accepted technique and embedded in paraffin. Serial sections 2 μm thick were made from paraffin blocks and stained with hematoxylin and eosin, according to Mallory, Rego method. The author conducted immunohistochemical studies using monoclonal antibodies (MCA) to CD20 (clone L26), CD4 (clone 4B12), CD68 (clone KP1), CD8 (clone SP16), p53 (clone SP5), Ki-67 (clone SP6), vimentin (clone V9), smooth muscle actin (clone 1A4), desmin (clone D33), cytokeratin 18 (clone CY-90), cytokeratin 19 (clone A53-B/A2.26), CD3. MCA to smooth muscle actin was manufactured by "DAKO" (Denmark), to CD20, CD4, CD68, CD8, p53, Ki-67, vimentin, desmin, cytokeratins 18 and 19 – "Thermo Fisher Scientific" (USA), to CD3 – "Novocastra Laboratories Ltd." (Great Britain). The microspecimens were examined on microscopes "Olympus BX-41" (Japan), "Axioskop 40" (Germany).

Morphometric study was performed on a microscope "Olympus BX-41" (Japan) using the program "Olympus DP-soft version 3.1".

The obtained digital data were statistically processed using the statistical package of the licensed program Statistica 6.0 and Microsoft Excel 2003. The author checked distribution of digital indicators normality in groups. To compare the parameters in the groups, we used parametric and nonparametric methods: Student's t-test, χ^2 test, Mann-Whitney U-test. Differences in groups were significant at $p<0.05$.

Results and discussion

In the renal cortex of newborns exposed to APH, the nephrogenic zone was normal. However, in fetuses and newborns exposed to CIH, and in newborns exposed to MH, the nephrogenic zone was thinned and had a reduced number and density of rudiments of both glomerular and tubular components of the nephron, indicating a delay in nephrogenesis. In newborns, compared with fetuses exposed to CIH, the thickness of the nephrogenic zone decreased. The nephrogenic zone regresses, undergoes sclerosis, and becomes mitotically active [8].

In the cortical substance of the kidneys of newborns in APH renal corpuscles were characterized by a uniform location, while in fetuses and newborns in CIH, in newborns in MH was found uneven location of glomeruli with reduced number and the presence of agglomeral areas.

The number of functioning nephrons in the kidneys plays an important role in the long-term functioning of this organ – their total number is from 300 thousand to 1 million (average 600 thousand) [9].

Deficiency of nephrons is a factor that causes the development of hypertension, kidney disease, increases the susceptibility of the kidneys to their secondary damage in such children in future [5, 10].

The number of nephrons in rats increases not only in intrauterine period, but also in the first days – weeks of postnatal life, and then changes slightly [11]. There are no clear data in the literature on the postnatal formation and development of nephrons in humans. Some publications have noted that nephron formation in humans ends at about 32–34 weeks of gestation, and therefore any nephron deficiency that occurs at birth cannot be compensated by increased nephrogenesis after birth [12, 13]. At the same time, there is scientifically proven data that in premature infants nephrogenesis is observed up to 40 days after birth [12, 14].

Scientists note that given the possibility of the evolutionary reserve of maturation of morphological structures, with timely prediction of pathology (immediately after birth), studying obstetric and gynecological history of the mother, using modern medical technology, may create conditions for maturation of immature structures in nephrogenic tissue and, consequently, prevent the disease [15].

In APH, the shape of mature renal corpuscles was normal, but in CIH and MH, these structures took the wrong shape in places. The size of the renal corpuscles in APH was normal, but in CIH and MH renal corpuscles were small [16].

In fetuses and newborns in CIH, in newborns in MH, renal corpuscles were with reduced or absent of glomerular capillaries. In the renal corpuscles there were signs of circulatory disorders, the severity of which increased from fetus to newborn, and they were minimal in APH, maximum in MH and moderate in CIH. The latter were manifested by plethora and stasis of the glomerular capillaries, thrombus formation, hemorrhage into the renal corpuscle cavity, edema of the basement membranes of the capillaries and the parietal leaf of the Bowman's capsule. In CIH and MH in the basement membranes, edematous changes often combined with sclerosis, as a result of which the basement membrane had an uneven thickness due to the areas of thickening and loosening. Dystrophic, necrotic and desquamative changes of capillary endotheliocytes and epitheliocytes of the outer leaf of the Bowman's capsule developed in the areas where the basement membrane changed. The described changes in the basement membranes with adjacent cellular elements increased from fetus to newborn, were minimal in APH, moderate in CIH and pronounced in MH [16]. The structural changes found in the basement membranes were described in children with some glomerulopathies, characterized by the development of nephrotic syndrome [17].

The author defined the accumulation of fibrin threads in the expanded urinary space of a part of renal corpuscles between the capillaries and the capsule which are known to be the initial manifestations of glomerulosclerosis [18]. Prolonged action of the damaging factor, presented by CIH, led to an increase in the severity of the detected general pathological processes in the glomerular apparatus in newborns compared with fetuses.

When modeling different types of hypoxia in the kidneys of fetuses and newborns, it was found morphological changes not only in the glomerular apparatus of the nephron, but also in the tubular. Although the tubular apparatus of the nephron in comparison with the glomerular apparatus is better protected from the damaging effects of various exogenous and endogenous factors [19], in our study the tubular apparatus was characterized by pronounced changes.

Morphological changes in the tubular component of the nephron were characterized by dystrophic, necrotic and desquamative changes of nephrocytes. In the tubular basement membrane, the basement membrane of the collecting tubules, edematous changes developed in APH, and in CIH and MH edematous and sclerotic changes, in consequence of which the basement membrane looked focally thickened, swollen in places, and thinned in part of the visual field. Desquamated cells and cellular detritus filled the lumens of the tubules and collecting tubules. Structural changes in the tubular system and collecting tubules were minimal in APH, moderate in CIH and maximum in MH, while in CIH they increased from fetus to newborn. Under the action of APH the maximum structural changes were in the proximal tubules compared to other parts of the tubular system and collecting tubules, and in CIH and MH they were

equally pronounced in all tubules and collecting tubules of the cortex and medulla substance of the kidneys.

The involvement sequence of different nephron parts in the pathological process is due to their morpho-functional heterogeneity caused by the complexity and scope of functions, the sequence of functional activities [19]. The maximum changes in the proximal tubules indicated in APH are most likely due to the fact that this part of the tubular system is characterized by greater functional activity, respectively, it is more prone to structural changes.

The immature tubules and ducts in the kidneys of fetuses and newborns of all groups were found. In the control group and in APH they localized mainly in the cortex while in CIH and MH, they were in the cortex and medulla substance of the kidneys. In CIH and MH, the number of immature structures was higher compared to the control and APH, which indicated an inhibition of the maturation of these structures. In CIH immature structures increased in number at newborns in comparison with fetuses.

Glomerular and tubular cysts were found in the cortex and medulla substance of the kidneys in fetuses and newborns in CIH, in newborns in MH. The number of cysts increased in newborns in comparison with fetuses in CIH.

In fetuses and newborns in the renal stroma developed hemodynamic disorders, characterized by stasis of blood cells, predominance of dilated and full-blooded vessels over spasms, thrombosis, hemorrhage and edema. They were minimal in APH, moderate in CIH and severe in MH. In CIH, the severity of these changes increased from fetus to newborn.

A number of scientists noted various hemodynamic disorders in the organs in response to hypoxia. They noticed slowing of blood flow in the vascular bed of organs, sludge of formed blood elements, their sequestration with local increase of blood coagulation potential and development of local microthrombus formation. This, in turn, impairs gas exchange in tissues, increases hypoxia, disrupts vascularization of organs, creates a situation of their microcirculatory blockade with subsequent dysfunction [20].

Signs of circulatory disorders always combine with structural changes in the vascular walls of stroma, manifested by dystrophic, necrotic and desquamative changes of endothelial cells, as well as edema and sclerosis of the layers. Moreover, if damage of endothelial cells and edema of the layers of vascular walls was in all types of hypoxia, in CIH and MH CHV sclerosis was in the wall layers. These vascular endothelial cell lesions were minimal in APH, severe in MH and moderate in CIH, increasing from fetus to newborn. Interestingly, the detected hemodynamic disorders in the renal stroma in all types of experimental hypoxia were more pronounced in the cortex compared to medulla substance. Similar signs of circulatory disorders with structural changes in the vascular walls were also found in the fat capsule of the kidneys of fetuses and newborns, and the degree of their severity was similar to that already described above in the stromal component of the kidneys.

There was a balance between apoptosis and proliferation in the kidneys of fetuses and newborns of the control group, corresponding to the physiological norm [21]. However, in the studied groups, it was determine an imbalance characterized by the predominance of proliferative processes over apoptotic in APH and CIH, and the predominance of apoptosis over proliferation in MH [22].

In the simulation of CIH and MH, it was noticed a decrease of the specific volume of parenchyma and an increase of the specific volume of stroma due to the development of sclerotic changes. Our analysis of immunohistochemical reactions with vimentin, desmin, smooth muscle actin, cytokeratins 18 and 19 revealed several important points explaining the mechanism of sclerosis in the kidneys of fetuses and newborns, developed under different types of hypoxia. First, APH led to an increase in the number and activate the morpho-functional state of fibroblastic cells, including myofibroblasts. Second, CIH and MH led not only to an increase in the number of fibroblastic differon cells, including myofibroblasts, but also to the induction of epithelial-mesenchymal transformation [23]. The author understand the latter as a process of disruption of cell-cell and cell-matrix adhesion of epithelial cells, freeing them from interconnection and their loss of polarity (essential properties of epithelial tissue), reorganization of the cytoskeleton and the acquisition of fibroblast-like cells, enabling movement, remodeling of the extracellular matrix and maintenance of the mesenchymal phenotype [24]. This phenomenon has been demonstrated not only during embryonic development, but also in the postnatal period during tissue repair, as well as in the process of carcinogenesis [25]. At the heart of this process is a change in the transcription program involving many signaling pathways at different

levels of their regulation, ranging from extracellular signals affecting cytoplasmic effects and then nuclear transcriptional regulators [26].

In fetuses and neonates exposed to various types of hypoxia, cellular infiltration was in the capsules and stroma of the kidneys, represented mainly by fibroblastic cells and immune cells. This cellular infiltration increased compared to control and was minimal in APH, moderate in CIH and severe in MH. Among the immune cells it was found CD3-, CD4-, CD8-, CD20- and CD68-positive cells. Interestingly, local immune responses in the kidneys were different, determined by the type of experimental hypoxia. Thus, APH did not affect the number of CD3-, CD4-, CD8-, CD20-cells, i.e. T-cell and B-cell immunity, but led to an increase the number of CD68-cells, i.e. activated the macrophage system. CIH led to a decrease the number of CD3-, CD4-, CD8-, CD20-cells and an increase the number of CD68-cells. MH led to a decrease the number of CD3-, CD4-, CD8-, CD20-cells and an increase the number of CD68-cells. When comparing different types of hypoxia, there was a maximum increase in the number of CD68-cells in MH, a minimum in APH and moderate in CIH. In MH compared with CIH, there were no differences in the number of CD3-, CD4-, CD8-, CD20-cells, but the number of CD68-cells was greater. In CIH, as well as in control, it was found age increase the number of all immune cells [27].

Thus, a comprehensive morphological study of the experimental material allowed to prove the damaging effect of acute postnatal hypoxia, chronic intrauterine hypoxia and mixed hypoxia on the kidneys of fetuses and newborns based on the identified morpho-functional changes.

CONCLUSIONS

1. Acute postnatal, chronic intrauterine and mixed hypoxia lead to the development of respectively minimal, moderate and pronounced morphological changes in the capsules, parenchymal and stromal-vascular components of the kidneys, primarily damaging the vessels of the stroma and parenchyma, where more pronounced changes occur in the tubules, collecting tubules, and in chronic intrauterine hypoxia these changes increase in newborns compared to fetuses. Experimental hypoxia causes the development of hemodynamic disorders, degenerative-desquamative changes of vascular endotheliocytes, epitheliocytes of Bowman's capsules, tubules, collecting tubules, and the latter in acute postnatal hypoxia are observed mainly in the proximal tubules, and in chronic intrauterine and mixed hypoxia in all parts of the tubular system and collecting tubules. Chronic intrauterine and mixed hypoxia promote cyst formation, delay the processes of glomerulogenesis and tubulogenesis. Acute postnatal, chronic intrauterine and mixed hypoxia stimulate fibroblastic cells in the kidneys, and chronic intrauterine and mixed hypoxia also induce epithelial-mesenchymal transformation, causing the development of sclerosis. Acute postnatal, chronic intrauterine and mixed hypoxia induce apoptosis, proliferation, leading to an imbalance between them due to the prevaling proliferation in acute postnatal and chronic intrauterine hypoxia and apoptosis in mixed hypoxia.

2. Identified morphological changes in the kidneys of fetuses and newborns developed under the influence of acute postnatal, chronic intrauterine and mixed hypoxia, given the unity of structure and function, will lead to functional changes in these organs in subsequent postnatal ontogenesis in such children and the emergence of different nephrological pathology.

3. This study actualizes the implementation of preventive measures among persons of reproductive age, dictates the need for quality pre-pregnancy training, which should be aimed at timely detection and treatment of genital and extragenital pathology in women.

DECLARATIONS:

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Consent for publication

All authors give their consent to publication.

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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Data Transparency

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