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The Specifics of the Stromal and Parenchymal Liver Components of 0–6-month-old Dead Children from HIV-monoinfected Mothers

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Abstract

OBJECTIVE: The objective of the study was to determine the specifics of the stromal and parenchymal liver components of 0–6-month-old children from HIV-monoinfected mothers.

METHODS: The morphometric investigation included 84 liver tissue biopsies of 0–6-month-old dead children from HIV-monoinfected mothers. All morphometric parameters of the parenchymal and stromal liver components were calculated using the Avtandilov's microscopic morphometric grid, which was consisted of 100 equidistant points. It was inserted into the microscope's ocular tube with a total ×200 microscope magnification. The number of points that were found on the corresponding types of parenchymal and stromal liver components was calculated. In every case, it was selected 10 random microscopic areas and then all data were obtained, calculated, and presented as percentages.

RESULTS: Morphometric parameters of hepatocytes: Mononuclear hepatocytes – 87.3 ± 6.2% (control – 93.5 ± 7.1), two-nuclear hepatocytes – 12.7 ± 1.3% (control – 6.5 ± 1.2), two-/mononuclear hepatocytes coefficient – 0.14 ± 0.01 (control – 0.06 ± 0.01), and hepatocytes with fat vacuoles – 15.6 ± 1.8% (control – 0.5 ± 0.2). Parenchymal and stromal liver components: Parenchyma – 64.3 ± 2.1% (control – 74.2 ± 1.3), stroma (including blood vessels and bile ducts) – 35.7 ± 1.9% (control – 25.8 ± 1.6), and stroma/parenchyma index – 0.55 ± 0.01 (control – 0.34 ± 0.01). Morphometric parameters of all of the liver components: Hepatocytes – 64.3 ± 3.1% (control – 74.2 ± 4.3), portal tracts – 14.9 ± 1.9% (control – 3.1 ± 0.6), central veins – 9.3 ± 1.3 % (control – 9.3 ± 1.4), sinusoids – 8.8 ± 1.1% (control – 10.5 ± 1.3), and bile ducts – 2.7 ± 0.2% (control – 2.9 ± 0.2). Expression level parameters: Fibronectin – 64.8 ± 4.1% (control – 17.3 ± 2.5), collagen Type I – 13.6 ± 1.7% (control – 9.7 ± 1.9), collagen Type III – 15.3 ± 1.4% (control – 10.1 ± 0.9), and collagen Type IV – 6.8 ± 0.2% (control – 5.9 ± 0.2).

CONCLUSIONS: It was established that in the liver of 0–6-month-old dead children from HIV-monoinfected mothers, the parenchymal component of the liver showed the signs of its reduction, increase of regenerative activity of hepatocytes, and fatty degeneration of hepatocytes with a certain sign of reactive steatohepatitis. Furthermore, it was established that the stromal component of the liver of children from HIV-infected mothers showed the signs of its progressive proliferation and collagenization due to increased production and accumulation of fibronectin, Type I, Type III collagens in the stroma of portal tracts and newly formed septa, and the signs of hepatic sinusoid capillarization due to Type IV collagen accumulation in the space of Disse of the hepatic sinusoids.

Introduction

To date, the issue of HIV is receiving increased attention and a huge amount of resources is being spent in all countries of the world. Any scientific research, any scientific data attracts increased attention from the scientific medical community, the press, and governmental structures. HIV affects all segments of the population, people of any gender and age, including fetuses and newborns from HIV-positive mothers.

According to the Official Bulletin of the United Nations United Nations Program on HIV/AIDS (UNAIDS) for 2018, there are 36.9 million (31.1–43.9 million) people living with HIV worldwide, including 35.1 million (29.6–41.7 million) are adults and 1.8 million (1.3–2.4 million) – children under 15 years of age. The number of HIV-positive women over the age of 15 is 18.2 million (15.6–21.4 million). As of 2018, there are 240,000 (230–260,000) HIV-positive people living in Ukraine, including 5000 (4500–5900) children under the age of 15. The number of HIV-positive women over the age of 15 is 110 thousand (100–120 thousand) [1], [2].

Among HIV-infected patients, adults predominate, which is why there is a clear data gap in the scientific literature regarding children from HIV-infected mothers. Given the specificity of the interaction of HIV with the body, the study is mainly subject to the lymphoreticular system and opportunistic infections in HIV-induced children [3].

The liver is a complex and multifaceted organ that performs many different tasks and which, as studies in adult HIV-infected patients have shown, is an important targeting structure for HIV [4], [5]. There is no information in the scientific literature regarding the subject analysis of which liver structures and how they are involved in the pathological process of HIV infection. Therefore, studying the condition of the stromal and parenchymal components of the liver of children from HIV-infected mothers is an important problem that needs to be addressed.

The aim of this study is to study the features of the stromal-parenchymatous component of the liver of deceased children under 6 months of age from HIV-monoinfected mothers, with the subsequent provision of the data obtained to the scientific community and practitioners to optimize the process of diagnosis of liver disease in children.

Materials and Methods

Eighty-four liver tissue biopsies of deceased children under 6 months of age from HIV-monoinfected mothers (Group N6) and 45 liver tissue biopsies of healthy term infants born from somatically healthy mothers with physiological pregnancy (Group K) were studied. The gestation period for children in Group K was 37–40 weeks. Group K children were died as a result of severe traumatic brain injury (newborns) or premature detachment of a normally located placenta (stillbirth) in childbirth; neonatal life expectancy did not exceed 24 h. Children of Group N6 had an officially confirmed HIV-positive status and died from opportunistic infections (pneumocystis pneumonia, and pulmonary aspergillosis) due to acute pulmonary heart failure. The study of autopsy material was carried out in accordance with the requirements of the "Instructions on the opening of autopsies" (Order of the Ministry of Health of Ukraine No. 6 of January 17, 1995); in accordance with the requirements, norms, and standard provisions on ethics of the Ministry of Health of Ukraine No. 690 of 23.09.2009; "Procedures for the Removal of Biological Objects from the Dead, the Bodies of Which Are Subject to Forensic and Pathological Research, for Scientific Purposes" (2018). The material was collected for the period from 1998 to 2018 at the Odessa and Dnipropetrovsk regional pathological anatomy bureaus.

The age of HIV-monoinfected mothers averaged 26.0 ± 4.1 years (22.0–30.0). These were women of low socioeconomic status who did not plan a pregnancy, had never been examined before, and had not attended a women's consultation during pregnancy. Almost all women found out about their HIV-positive status either shortly before or immediately after delivery and refused to receive antiretroviral therapy. Eight women gave birth at home to their own children and learned of their HIV-positive status only after seeking medical help for the severe and life-threatening opportunistic infections. All women whose children died in the N6 study group had officially confirmed HIV mono-infection without any clinical manifestations of AIDS and without any other co-infections. All women at the time of pregnancy and childbirth were not injecting drug users, did not consume alcohol in large quantities, and had a permanent residence.

For morphological investigation, liver slices were fixed in 10% neutral formalin solution, and then the material was subjected to standard wiring through alcohols of increasing concentration, Nikiforov's liquid (96% alcohol and 1: 1 diethyl ether), and chloroform followed by paraffin. Of the blocks thus prepared, serial sections of 4–5 μm thick were made on a Microm HM – 340 microtome. Serial sections for investigation microscopy were stained with hematoxylin and eosin. Microscopic preparations were studied using a B × 43 optical microscope (Olympus Corporation, Tokyo, Japan).

Regenerative activity of the liver parenchyma was evaluated by the number of mononuclear and two-nuclear hepatocytes. The number of mononuclear and two-nuclear hepatocytes was calculated using the Avtandilov's microscopic morphometric grid, which consisted of 100 equidistant points and was inserted into the eyepiece of the microscope with a magnification of the microscope ×200. The number of points that fell on mononuclear and two-nuclear hepatocytes was calculated. In each drug was performed on 10 randomly selected fields of view, and then the obtained data were calculated and presented as a percentage [6].

Furthermore, the ratio of two/mononuclear hepatocytes (TMHC) was calculated by the formula:

TMHC=Number of two-nuclear hepatocytes (%)/Number of mononuclear hepatocytes (%)

To assess the condition of the stromal component of the liver used Avtandilov's microscopic morphometric grid, which consisted of 100 equidistant points and inserted into the eyepiece of the microscope with a magnification of the microscope ×200. The number of points that fell on the stromal (portal tracts, septa) and parenchymal (hepatocytes) components was calculated. In each drug was performed on 10 randomly selected areas of view, and then the obtained data were calculated and presented as a percentage. Furthermore, the stroma/parenchyma index (SPI) was calculated by the formula:

SPI=Stroma (%)/Parenchyma (%)

To assess the condition of the vascular component of the liver and the state of the bile ducts used Avtandilov's microscopic morphometric grid, which consisted of 100 equidistant points and inserted into the eyepiece of the microscope with a magnification of the microscope ×200. The number of points that fell on the vascular component (central veins and sinusoids) and

bile ducts was calculated. In each drug was performed on 10 randomly selected fields of view, and then the obtained data were calculated and presented as a percentage.

Immunohistochemical features of liver stroma were studied by indirect immunoperoxidase method on paraffin sections 3–5 cm thick. In all cases and in each drug were performed on 10 randomly selected fields of view, and positive signals (positive expression in the form of brown color) were measured using an Avtandilov's microscopic morphometric grid, which consisted of 100 equidistant points and inserted into the microscope eyepiece with magnification ×200. The number of points that fell on the positive signal was calculated, and then the data obtained were calculated and presented as a percentage. Each drug was examined for 10 randomly selected fields of view, and then the data obtained were calculated and presented as a percentage.

To assess the expression level of fibronectin used antibodies against fibronectin (polyclonal mice; 1:100; sc-8422; Santa Cruz Biotechnology, Inc.). The blocks were heated for 60 min at 60°C, deparaffinized with xylene and washed in alcohols with decreasing concentration. Antigens were obtained with citrate buffer (pH 6.0) in a microwave oven for 5 min. After treatment with 1.5% H2O2 at 37°C for 30 min to block endogenous peroxidase activity, the preparations were incubated with primary antibodies overnight at 4°C and then incubated with secondary antibodies (PV-9002; OriGene Technologies, Inc., Beijing, China) for 30 min at room temperature. Finally, the sections were stained using diaminobenzidine followed by hematoxylin contrast.

Antibodies against Type I and III collagen (polyclonal rabbits; 1: 600; Abcam, Cambridge, UK) were used to evaluate the expression level of Type I and III collagen. The blocks were heated for 60 min at 60°C, deparaffinized with xylene and washed in alcohols with decreasing concentration. The drugs were first pre-incubated in 3% H_2O_2 solution for 10 min at room temperature to block endogenous peroxidase activity, and then the antigen was extracted with citrate buffer (pH 6.0) in a microwave oven at 95–98°C for 12 min followed by incubation for 5 min at room temperature to block non-specific background staining. Then, incubation was carried out at room temperature for 30 min with primary rabbit polyclonal antibodies against Type I and III collagen. The obtained preparations were washed 4 times with buffer, treated with streptavidin, peroxidase, and chromogen 3,3′-diaminobenzidine. Finally, sections were stained using diaminobenzidine followed by hematoxylin contrast.

Type IV collagen antibodies were used to assess Type IV collagen expression (polyclonal mice; 1: 100; Leica Biosystems, Newcastle, UK: PHM-12, UK). The blocks were heated for 60 min at 60°C, deparaffinized with xylene and washed in alcohols with decreasing concentration. The antigens were obtained with citrate buffer (pH 6.0) in a microwave oven for 5 min and then cooled at room temperature for 20 min. After treatment with a 3% H_2O_2 solution at 37°C for 30 min to block endogenous peroxidase activity, sections were incubated with primary antibodies overnight at 4°C and then incubated with secondary antibodies (K-ASSAY Collagen Type IV Staining Kit, Kamiya Biomedical Company, USA) for 30 min at room temperature. Finally, sections were stained using diaminobenzidine followed by hematoxylin contrast.

Statistical processing of the results was performed using the standard statistical software package "STATISTICA 10.0" and "MS Excel." The arithmetic mean (M) and standard error of the mean (m) were calculated for the obtained values. The Mann–Whitney U test was used to assess the significance of differences between the groups.

Results

Microscopically in the liver of Group K, a normal beam-radial structure, uneven plethora of sinusoids and central veins, and a few small foci of extramedullary hematopoiesis were observed. Hepatocytes had a slightly granular eosinophilic cytoplasm and a rounded basophilic nucleus.

Microscopically, in the liver of Group N6, a fuzzy beam-radial structure, anemia, and "tortuosity" of sinusoids, central veins, and small-focal lymphoid infiltrates were observed. Hepatocytes often had foamy eosinophilic cytoplasm and hyperchromic nuclei; in places, their binucleate forms appeared. Furthermore, in the hepatocytes of all areas of the liver lobules revealed small droplets of fat vacuoles in the form of optical voids.

In the liver of Group N6, throughout the parenchyma in the cytoplasm of hepatocytes and in Disse spaces along the course of the sinusoids, the matrix protein fibronectin was found in a sharply increased number compared with Group K (Figures 1 and 2).

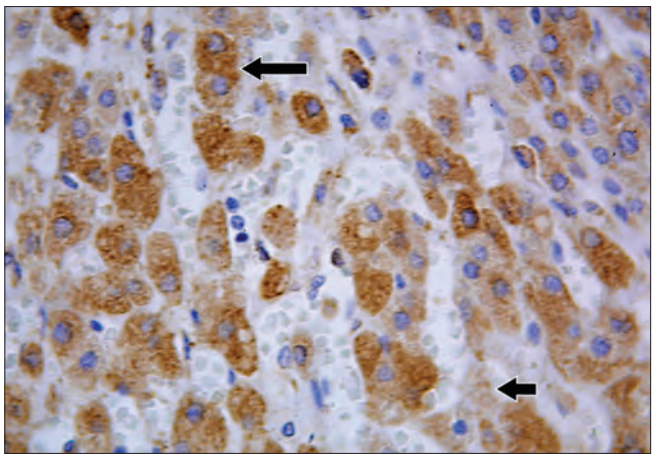

Figure 1: Liver of a child of Group K. Matrix protein fibronectin in the cytoplasm of hepatocytes (long arrow) and in the Disse spaces in the course of sinusoids (short arrow). Indirect immunoperoxidase method ×400

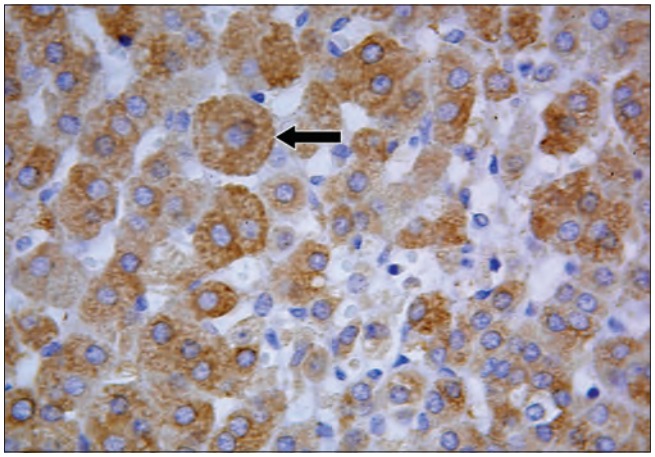

Figure 2: Liver of the child of Group N6. Matrix protein of fibronectin in the cytoplasm of hepatocytes (arrow) and in Disse spaces in the course of sinusoids. Indirect immunoperoxidase method ×400

Collagen I (Figures 3 and 4) and III (Figures 5 and 6) types with high expression level compared to Group K were presented in the stroma of the portal tracts of Group N6, which were represented by loose fibrils with a distinct parallel orientation. Furthermore, in Group N6, collagens I and III types were detected in Disse spaces in the course of sinusoids in increased numbers. Collagen Type III in group N6 formed distinct interparticle septa, which, however, did not yet connect adjacent portal tracts.

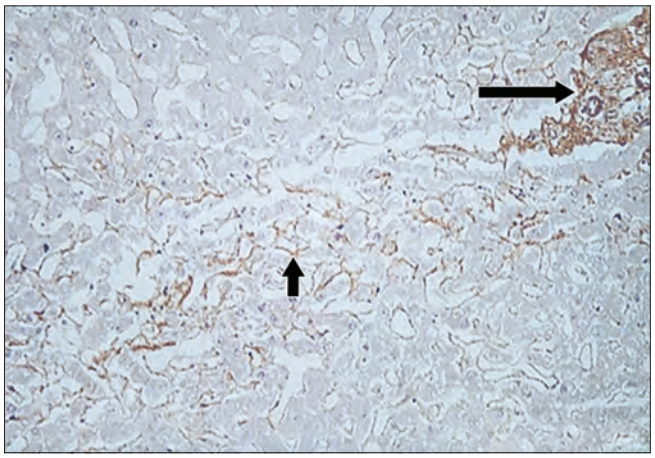

Figure 3: Liver of the child of Group K. Expression of Type I collagen in the stroma of portal tracts (long arrow) and in Disse spaces in the course of sinusoids (short arrow). Indirect immunoperoxidase method ×200

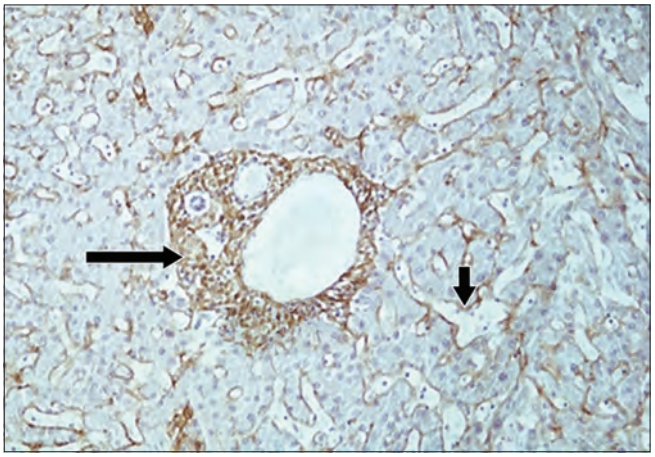

Figure 4: Liver of the child of Group N6. Increased expression of collagen Type I in the stroma of portal tracts with the beginning of the formation of interparticle septa (long arrow) and increased expression of collagen Type I in Disse spaces in the course of sinusoids (short arrow). Indirect immunoperoxidase method ×200

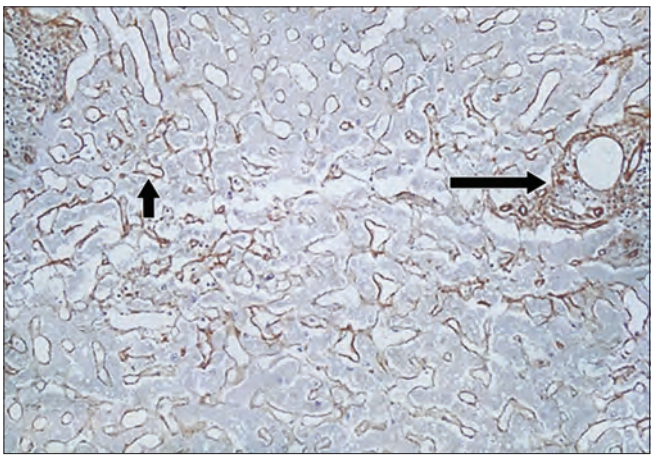

Figure 5: Liver of the child of Group K. Expression of Type III collagen in the stroma of the portal tracts (long arrow) and in the Disse spaces in the course of sinusoids (short arrow). Indirect immunoperoxidase method ×200

Around the central veins, portal vessels, and especially in the Disse spaces in the course of sinusoids, Group N6 showed increased expression of Type IV collagen compared to Group K (Figures 7 and 8), which formed dense, compact, and discontinuous fibrils.

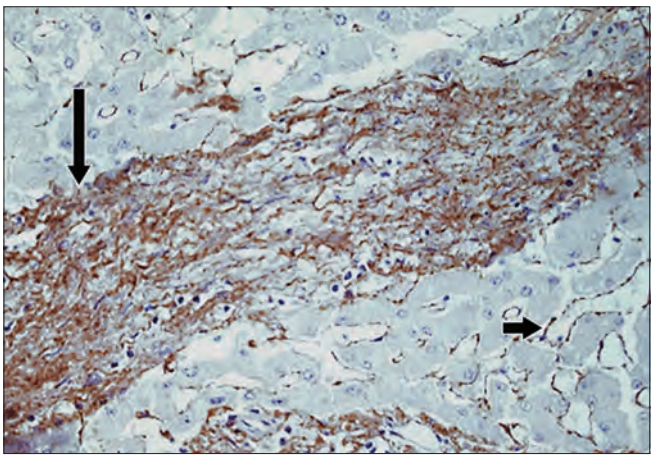

Figure 6: The liver of a child of Group N6. Increased expression of collagen Type III in the stroma of portal tracts for the formation of interparticle septa (long arrow) and increased expression of collagen III type in Disse spaces in the course of sinusoids (short arrow). Indirect immunoperoxidase method ×400

Morphometric parameters of the hepatocytes of children to HIV-infected mothers and children of the control group are presented in Table 1.

Stromal/parenchymal parameters of the liver of children from HIV-infected mothers and children of the control group are presented in Table 2.

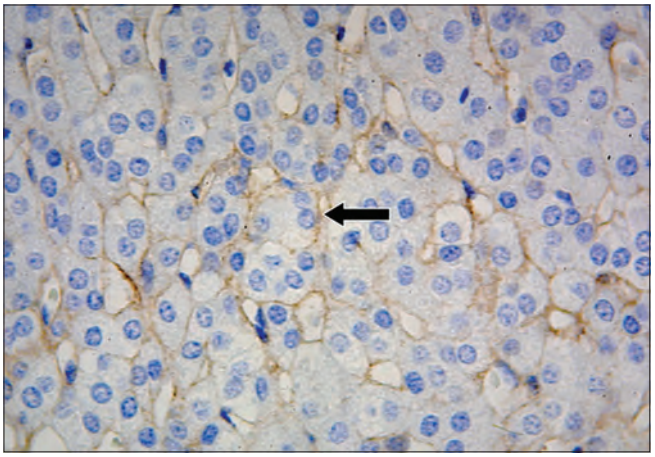

Figure 7: The liver of a child of Group K. Expression of Type IV collagen in Disse spaces in the course of sinusoids (arrow). Indirect immunoperoxidase method ×400

The morphometric parameters of all components of the liver of children from HIV-infected mothers and children of the control group are presented in Table 3.

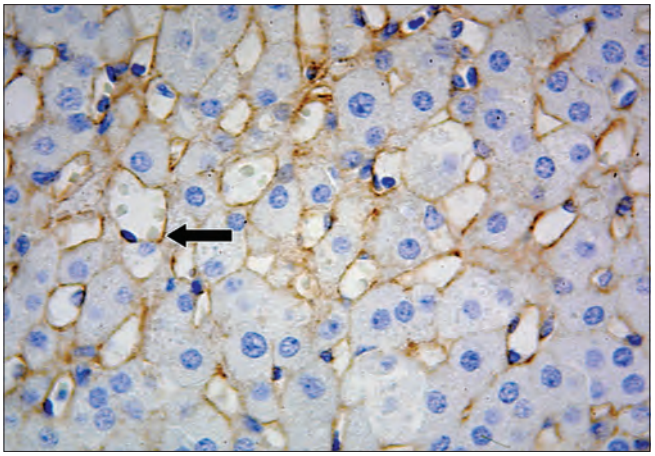

Figure 8: The liver of a child of Group N6. Increased expression of Type IV collagen in Disse spaces along the course of sinusoids (arrow). Indirect immunoperoxidase method ×400

Indicators of the level of expression of fibronectin, collagen I, III, and IV types in the stromal component of the liver of children from HIV-infected mothers and children of the control group are presented in Table 4.

Table 1: Morphometric parameters of the hepatocytes of children to HIV-infected mothers and children of the control group (M±M)

Indicator	Study group	
	K	N6
Mononuclear hepatocytes, %	93.5 ± 7.1	87.3 ± 6.2
Two-nuclear hepatocytes, %	6.5 ± 1.2	12.7 ± 1.3*
TMHC	0.06 ± 0.01	0.14 ± 0.01*
Hepatocytes with fatty vacuoles, %	0.5 ± 0.2	15.6 ± 1.8*

*p<0.05 compared to similar indicators of Group K

Discussion

As can be seen from Table 1, in the liver, normal mononuclear forms of hepatocytes predominate over dual nuclei (93.5% vs. 6.5%, respectively). Children of Group N6 recorded an increase in two-nuclear hepatocytes 1.9 times in comparison with the control group ($p < 0.05$), which was considered as a sign of increased liver regenerative activity in response to its damage.

Table 2: Stromal and parenchymal parameters of the liver of children from HIV-infected mothers and children of the control group (M±m)

Indicator	Study group	
	K	N6
Parenchyma, %	74.2 ± 4.3	64.3 ± 3.1*
Stroma (including vessels and BD)%	25.8 ± 2.6	35.7 ± 2.9*
stroma/parenchyma index	0.34 ± 0.01	0.55 ± 0.02*

*p<0.05 compared to similar indicators of group K

Many authors point out that as patients progress HIV infection, fatty hepatosis develops in patients. Fatty hepatosis is considered a benign condition and may regress upon the termination of a pathogenic stimulus, but the fact of the presence of fatty hepatosis indicates severe metabolic abnormalities in hepatocytes, which leads to increased accumulation of fatty acids in their cytoplasm. In the presence of fatty hepatosis, reactive steatohepatitis can develop, which is chronic inflammation with the gradual development of fibrosis, which is already considered an irreversible process [7], [8]. This study documented the presence of fatty hepatosis in the liver of children from HIV-infected mothers with signs of reactive steatohepatitis. The number of hepatocytes containing fat vacuoles (Group N6) was sharply increased compared to the control by 31.2 times ($p < 0.05$).

Table 3: Morphometric parameters of all components of the liver of children from HIV-infected mothers and children of the control group (M±m)

The liver component	Study group	
	K	N6
Hepatocytes, %	74.2 ± 4.3	64.3 ± 3.1*
Portal tracts, %	3.1 ± 0.6	14.9 ± 1.9*
Central veins, %	9.3 ± 1.4	9.3 ± 1.3
Sinusoids, %	10.5 ± 1.3	8.8 ± 1.1
Bile ducts, %	2.9 ± 0.2	2.7 ± 0.2
Total, %	100	100

*p<0.05 compared to similar indicators of Group K

Table 4: Indicators of the level of expression of fibronectin, Type I, III, and IV collagens in the stromal component of the liver of children from HIV-infected mothers and children of the control group (M±m)

The liver component	Study group	
	K	N6
Fibronectin, %	17.3 ± 2.5	64.8 ± 4.1*
Collagen I type, %	9.7 ± 1.9	13.6 ± 1.7*
Collagen III type, %	10.1 ± 0.9	15.3 ± 1.4*
Collagen IV type, %	5.9 ± 0.2	6.8 ± 0.2*

*p<0.05 compared to similar indicators of Group K

As can be seen from Table 2, in children from HIV-infected mothers (Group N6), there was a significant decrease in parenchymal and a significant increase in stromal components of the liver ($p < 0.05$ in both cases). As can be seen from Table 3, in children from HIV-infected mothers (Group N6), the increase of the stromal component of the liver was due to a significant increase in the volume of portal tracts 4.8 times compared with the control ($p < 0.05$).

The extracellular matrix (ECM) is a key component of the liver. Forming a connective tissue framework, ECM

is a surface for adhesion of different cell types, space for cell proliferation and migration; reservoir for signaling molecules [9]. Continuous ECM remodeling in chronic liver injury involves excessive accumulation of matrix proteins, proteoglycans, and carbohydrates, leading to the development of liver fibrosis with subsequent hepatic failure [10]. As the world literature shows, regardless of the causes of liver damage, activated stellate cells produce and deposit in the ECM large quantities of collagen I, III, IV types, and fibronectin [11]. HIV infection is a powerful both a direct and an indirect factor in liver damage activates stellate cells in the liver [12].

Collagens I and III types predominated in the stroma of the portal tracts and formed thin septa, as well as they were found in the Disse spaces in the course of sinusoids. As can be seen from Table 4, in children from HIV-infected mothers (Group N6), Type I and III collagen had significantly higher expression compared to control ($p < 0.05$ in both cases). In the liver of children from HIV-infected mothers (Group N6), Type IV collagen was found not only in Disse spaces in the course of sinusoids but also in the increased veins in the central veins and portal vessels compared to controls ($p < 0.05$). Fibronectin was the predominant ECM protein compared to Type I, III, and IV collagens in the liver of children from HIV-infected mothers. It was found in large quantities in the stroma of portal tracts, septa, and spaces of the Disse in the course of sinusoids in all cases of study. In Group N6, fibronectin expression level was increased by 47.5% compared to control ($p < 0.05$).

Thus, in the liver of children from HIV-infected mothers was recorded pronounced steatosis, reactive steatohepatitis, progressive proliferation and collagenic stroma, and capsaisina sinusoid, which led not only to significant parenchymal loss but also a sharp violation of metabolic processes between the blood sinusoids and hepatocytes.

Conclusions

It was found that in the liver of deceased children under 6 months of age from HIV-infected mothers, the signs of its reduction were recorded in the parenchymal component of the liver (total number of hepatocytes: K – 74.2 ± 4.3%; N6 – 64.3 ± 3.1), increase in the level of regenerative activity of hepatocytes ECM (number of two – nuclear hepatocytes: K – 6.5 ± 1.2%; N6 – 12.7 ± 1.3), and fatty hepatosis (number of hepatocytes with fatty vacuoles: K – 0.5 ± 0.2%; N6 – 15.6 ± 1.8) with signs of reactive steatohepatitis.

It was established that in the liver of deceased children under 6 months of age from HIV-infected mothers, signs of its progressive proliferation and collagenization were recorded in the stromal component of the liver (volume of the stromal component of the liver: K – 25.8 ± 2.6%; N6 – 35.7 ± 2.9) due to increased production and accumulation of fibronectin (K – 17.3 ± 2.5%; N6 – 64.8 ± 4.1), collagen Type I (K – 9.7 ± 1.9%; N6 – 13.6 ± 1.7), Type III (K – 10.1 ± 0.9%; N6 – 15.3 ± 1.4) in the stroma of portal tracts and formed septa, and capillary sinusoids due to the accumulation of Type IV collagen (K – 5.9 ± 0.2%; N6 – 6.8 ± 0.2) in Disse spaces in the course of sinusoids.

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