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MORPHOLOGICAL CHANGES IN THE LIVER IN PATIENTS WITH OPIOID DEPENDENCE IN THE ABSENCE AND PRESENCE OF COMORBID CHRONIC HEPATITIS C

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Summary

Aim. To determine the clinical significance of morphological features in assessing toxic or viral liver damage in patients with comorbid opioid dependence and chronic hepatitis C.
Materials and methods. The study involved histological preparations of liver tissue from 48 patients with opioid dependence according to ICD-10 criteria (F 11.30). Among them, 18 patients had opioid dependence without chronic hepatitis C, aged 22 to 40 years (16 males and 2 females), and 30 patients had opioid dependence with chronic hepatitis C according to ICD-10 criteria (B18.2), aged 22 to 38 years (27 males and 3 females). Ultrathin liver tissue sections were examined using an EM-100 electron microscope at an accelerating voltage of 75 kV and a magnification of x12000.
Results. In cases of high-progressive opioid dependence without chronic hepatitis C, significant features included the presence of large steatotic granules in the centrilobular and periportal zones, impaired lipid granule degradation processes, a significant increase in Kupffer cell activity, and the transformation of Ito cells into fibrocytes.
Low histological activity of comorbid chronic hepatitis C is characterized by moderate lymphomonocytic infiltration in the portal tracts, increased lipid granule destruction in the centrilobular zone of liver lobules. In cases of moderate activity of comorbid chronic hepatitis C in drug-dependent patients, there is a significant increase in necrotic and apoptotic changes in hepatocytes of the portal and periportal zones, an increase in the number and density of lipid granules, and a significant increase in collagen deposits in the perisinusoidal space, periportal, and centrilobular zones of liver lobules.
Conclusions. 1. In clinical practice, it is advisable to use morphological studies of the liver in patients with opioid dependence and chronic hepatitis C to verify significant profibrogenic factors: the progression of steatotic granule deposits in hepatocytes, impaired degradation processes, Kupffer cell activation, and Ito cell transformation into fibrocytes. 2. Morphological studies of the liver in patients with opioid dependence with and without comorbid chronic hepatitis C allow for an objective assessment of the predominance of toxic or viral liver damage in each patient and determine the priority in treatment.

Keywords: **opioid-related disorders, chronic hepatitis C, fibrosis, liver steatosis**

INTRODUCTION

The global health sector strategy on viral hepatitis aims to reduce new hepatitis C virus (HCV) infections by 80 % by 2030, including a 30 % reduction by 2020. Careful monitoring of comorbid chronic hepatitis C (CHC) in drug-dependent patients is being conducted worldwide. In 2016, the incidence of primary HCV infection in Australia decreased by 53 % among injection drug users following the unrestricted availability of direct-acting antiviral (DAA) therapy against HCV [1].

The projected life expectancy of individuals with opioid use disorders and those with substance use disorders who use injection drugs is reduced by 25 years compared to the general population. A significant reason for this is comorbid chronic liver diseases [2].

Verification of CHC in patients using opioid drugs and starting substitution therapy is important. In a study of 563 drug-dependent patients undergoing opioid agonist substitution therapy, anti-HCV antibodies were found in 68 % (73/107), and 57 % (24/42) had HCV viremia [3].

People who use injection drugs represent a high-risk group for HCV infection, reaching 90 % among drug-dependent patients in Taiwan [4]. Patients who use injection drugs are the main population group for HCV treatment [5]. In the course of antiviral therapy with direct-acting agents, the Integrated-Test-Stage-Treat (ITTREAT) study found an HCV PCR positivity prevalence of 84 % among 765 patients, with 19 % already having liver cirrhosis [6].

Despite effective direct-acting antiviral agents (DAAs), HCV prevalence remains high among people who use injection drugs, and nonadherence to therapy remains a major obstacle to HCV elimination in this subpopulation. Timely verification of CHC has shown that more than 90 % of patients achieved sustained virological response at 12 weeks after treatment (SVR12) (95 % CI: 88.1-93.2 %), significantly reducing the possibility of liver fibrosis progression in this patient group [7].

In addition to CHC itself, other comorbid factors can be significant in the pathogenesis of liver fibrosis progression in drug-dependent patients. A study of 524 drug-dependent patients found significant liver fibrosis in two-thirds of those receiving substitution therapy, associated with alcohol consumption, high body mass index, and exposure to hepatitis B virus [8].

Integrated HCV treatment for people who use injection drugs is cost-effective compared to standard treatment methods [9]. For HCV patients, virus elimination is associated with an improvement in health-related quality of life (HRQOL) [10].

Finding reliable morphological criteria for CHC activity, assessing profibrogenic factors, and objectifying the severity of fibrotic changes in various parts of the liver lobules in patients with opioid dependence is significant. Morphological studies of liver tissue in CHC patients have shown that activated hepatic stellate cells (Ito cells) may be a factor in enhanced liver fibrosis. Various immunohistochemical markers can identify different subpopulations of these cells, which determine different pathogenetic mechanisms of fibrosis progression in CHC patients [11, 12, 13].

Morphological studies have found that hepatic stellate cells participate in both physiological and pathological processes in the liver. During CHC progression, activated stellate cells transform into myofibroblasts, which are important cells in liver fibrosis development. Currently, HCV infection still lacks specific markers for accurately identifying the state and progression of the disease [14].

In liver pathomorphology studies in CHC, analyzing the state of sinusoidal endothelial cells (LSECs), characterized by the presence of pores (fenestrations), is important. The electron microscopy analysis and the assessment of CD32, CD31, and caveolin-1 expression showed that LSECs exhibit significant morphological changes in HCV infection but maintain their phenotypic identity. Capillarization was observed only in early fibrosis stages. Thus, the severity of LSEC modifications may correlate with hepatocyte damage and fibrosis stage, providing new insights into the pathogenesis of chronic hepatitis C [15].

Immunohistochemical studies on changes in lymphatic sprouts and mature lymphatic vascularization in the liver of CHC patients have also been conducted. Intralobular/parenchymal necroinflammatory activity was mostly mild or moderate. The number of portal lymphatic sprouts increased with structural changes, peaking in cirrhosis. This study found no significant relationship between the proportion of portal lymphatic sprouts or mature portal lymphatic vessels and the degree of periportal/periseptal activity [16].

A thorough analysis of morphological and ultrastructural changes in the liver of opioid-dependent patients with comorbid CHC can expand knowledge on the pathomorphogenesis of liver damage progression, understand possible side effects of methadone substitution therapy, determine the predominance of toxic or virus-induced damage to liver lobules, which is important for determining pharmacotherapy priorities.

AIM

To determine the clinical significance of morphological features in assessing the toxic or viral origin of liver damage in patients with comorbid opioid dependence and chronic hepatitis C (CHC).

MATERIALS AND METHODS

A cross-sectional study was conducted using histological preparations of liver tissue from 48 patients with opioid dependence (OD). The overall group included 18 patients with OD aged 22 to 40 years (16 males and 2 females) without comorbid CHC and 30 patients with OD and comorbid CHC aged 22 to 38 years (27 males and 3 females).

Inclusion criteria were as follows: 1) adults aged ≥18 years, 2) diagnosis of OD established according to ICD-10 criteria (F 11.30), 3) diagnosis of «chronic viral hepatitis C» established according to ICD-10 criteria (B18.2) and determined using anti-HCV IgG antibodies

and polymerase chain reaction (PCR) for HCV with genotypes 1, 2, 3, 4, 4) willingness to sign written informed consent to participate in the study.

Exclusion criteria included patients who: 1) were coinfected with human immunodeficiency virus (HIV) or hepatitis B and D viruses (HbsAg, HbeAg, anti-HbeAg, anti-HbcIgM, anti-Hbc IgG, anti-Hbs, anti-HDV IgG, anti-HIV IgG) at the time of inclusion; 2) had severe extrahepatic manifestations (e.g., cryoglobulinemia or membranoproliferative glomerulonephritis); 3) had chronic kidney disease stages 4-5 (glomerular filtration rate < 30 ml/min/1.73 m^2); 4) had decompensated liver disease (Child-Pugh class B or C), including current or past ascites, esophageal or gastric variceal bleeding, portal vein thrombosis, hepatic encephalopathy; 5) had any current or previous malignancies, including hepatocellular carcinoma; 6) had acute hepatitis, had acute hepatitis, including that of alcoholic etiology; 7) had concurrent liver diseases such as autoimmune hepatitis, primary biliary cholangitis, hemochromatosis, alpha-1 antitrypsin deficiency, etc.

The group of patients with OD without comorbid CHC was divided into 2 subgroups: the first subgroup (6 individuals) with a low-progressive variant of opioid dependence with a daily intake of opiates up to 15.0 ml, and the second subgroup with a high-progressive course and daily opium doses of more than 15.0 ml (12 patients).

The group of patients with OD and CHC was divided into 2 subgroups according to the activity of the process. The group with minimal CHC activity (up to 8 points according to Knodell) included 18 patients (60.0 %), and the group with moderate activity (from 9 to 15 points according to Knodell) included 12 patients (40.0 %). Among the 30 patients examined, the fibrosis stages were as follows: F0 in 3 patients (10.0 %), F1 in 9 (30.0 %), F2 in 7 (23.3 %), F3 in 7 (23.3 %), and F4 in 4 (13.3 %).

Liver biopsy was performed under ultrasound guidance with local anesthesia. The size of the biopsy fragment obtained was more than 10 mm and 0.8 mm in diameter. The following staining methods were used for histological samples: hematoxylin and eosin, Van Gieson's picrofuchsin [17], the fibrosis stage was determined according to METAVIR [18], and the histological activity index was determined according to Knodell R. G. et al. [19].

For electron microscopy, a particle of liver tissue with a volume greater than 1 mm^3 was separated, immersed in a 2.5 % solution of glutaraldehyde, and then fixed in osmium tetroxide according to Palade. Ultrathin sections were prepared using an UMPT-4 ultramicrotome from Sumy V. O.L. «Electron,» then contrasted with uranium and lead compounds and examined in an EM-100 electron microscope at an accelerating voltage of 75 kV with magnifications ranging from 12,000 to 22,000 [20].

Methods of investigation included: bibliosemantic, systemic approach and analysis, morphological, morphometric, descriptive and graphic modeling.

RESULTS

For patients with a mild progressive course of chronic liver disease without comorbid hepatitis C virus (HCV), moderate lipid granules were predominantly observed in the centrolobular areas of liver lobules, with preserved granular endoplasmic reticulum and significant development, along with hyperplasia and hypertrophy of mitochondria, reduced glycogen content in hepatocyte cytoplasm, an increased number of phagolysosomes in macrophages, and low activity of Kupffer cells. In patients with a highly progressive course of chronic liver disease without HCV, significant findings included the presence of large steatotic granules in the centrolobular and periportal zones against a background of increased phagolysosome numbers (Fig. 1).

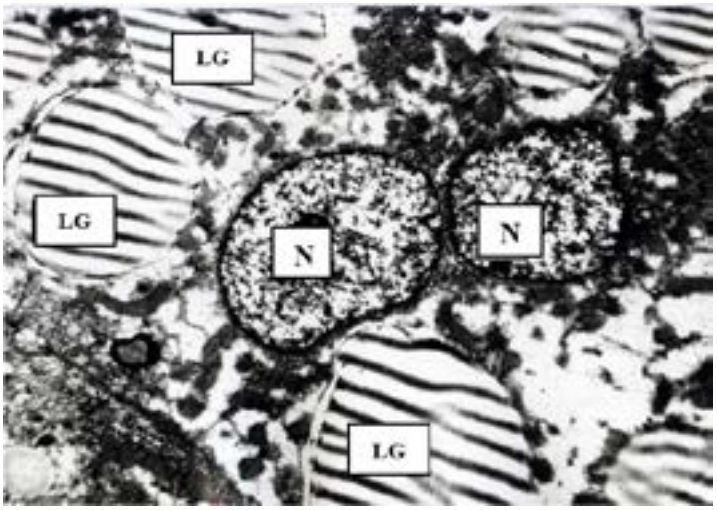

Figure 1. Multiple lipid granules in the centrolobular zone of the liver lobule. Electron micrograph of liver tissue from patient D., ×12,000. (N – nucleus of the hepatocyte; LG – lipid granules).

In this group of patients, there was a depletion of the granular endoplasmic reticulum in the cytoplasm of hepatocytes, an abundance of free ribosomes, a reduction in glycogen content, and disintegration of mitochondria. In the sinusoids of the lobules, the number of Kupffer cells and transformed Ito cells into fibroblasts increased, along with a greater severity of fibrotic changes in the perisinusoidal space (Fig. 2).

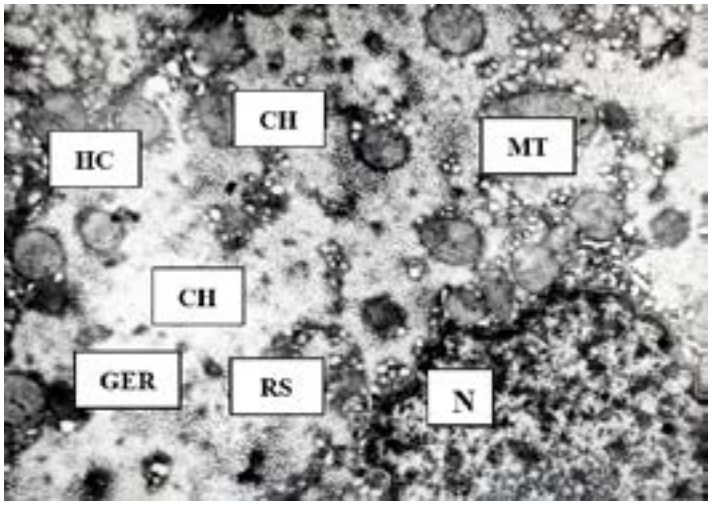

Figure 2. Reduction in the area of granular endoplasmic reticulum in the cytoplasm of hepatocytes; increase in the number of mitochondria with disrupted cristae; and a significant number of free ribosomes. Electron micrograph of liver tissue from patient K., magnification ×12,000. (HC – hepatocyte, RS – ribosomes; MT – mitochondria; N – nucleus; CH – cytoplasm of hepatocyte; GER – granular endoplasmic reticulum).

Analyzing the state of the liver in patients with chronic hepatitis and low activity of comorbid chronic hepatitis C, we identified the following morphological changes in the periportal zone of liver lobules: moderate lymphomonocytic infiltration of portal tracts, increased activity of Kupffer cells, and degranulation of Ito cells (Fig. 3).

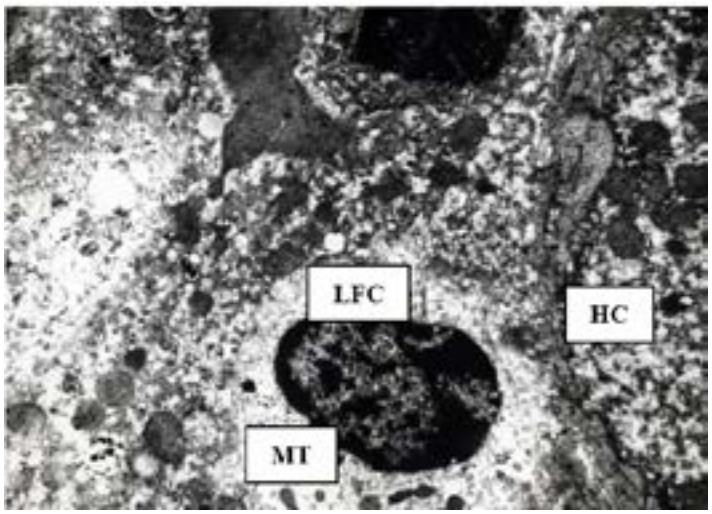

Figure 3. High activity of the portal zone lymphocyte, with numerous mitochondria in the cytoplasm. Electron micrograph of liver tissue from patient N., magnification ×12,000 (LFC – lymphocyte; HC – hepatocyte; MC – mitochondrion).

In the hepatocytes of the centrolobular zone, shifts of lipid granules of the cytoplasmic organelles were observed, along with a reduction in the area of the granular endoplasmic reticulum, a significant increase in the number of free ribosomes, depletion of glycogen content in the cytoplasm of the hepatocytes, and an increase in the contact between mitochondria and lipid granules. Moderate activity of comorbid chronic hepatitis C in patients with OD was accompanied by an increase in necrobiotic changes in the hepatocytes of the portal and periportal zones. Periportal zone hepatocytes contained significant lipid deposits with signs of organelle destruction and the release of contents from phagolysosomes (Fig. 4). Additionally, moderate activity of chronic hepatitis C was associated with a significant increase in the number of phagolysosomes in Kupffer cells, along with increased activity in the portal and periportal zones.

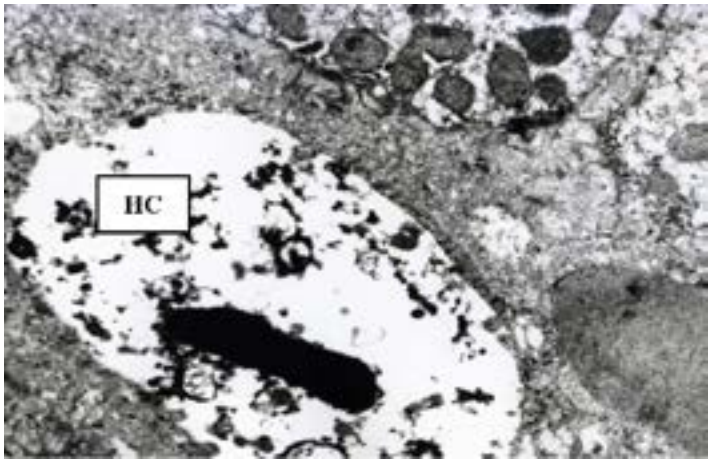

Figure 4. Signs of necrosis in hepatocytes in the periportal zone of the liver lobule. Electronogram of liver tissue from patient H., magnification ×12,000 (HC – hepatocyte).

In the majority of hepatocytes across all three zones, organelles were preserved, with a developed granular endoplasmic reticulum predominantly along the cell cytoplasm's periphery, indicating the maintenance of the protein-synthetic properties of the hepatocytes. The agranular endoplasmic reticulum was significantly developed in the perinuclear zone of the hepatocytes, suggesting an activation of lipid synthesis processes and an increase in their detoxification properties.

In hepatocytes of the periportal zone, there was a notable increase in the quantity and density of lipid granules, an expanded area of the agranular endoplasmic reticulum, destruction of the granular reticulum, and a depletion of glycogen granules in the hepatocytes.

In the periportal zone, a significant increase in activated Kupffer cells was observed, with an increase in nuclear size. In Ito cells, there was a noticeable clearing of cytoplasm from lipid droplets and a transformation of these cells into fibroblasts.

The increase in the activity of hepatic stellate cells against a background of opioid intoxication was accompanied by a significant deposition of collagen fibers in the pericellular and perisinusoidal spaces, predominantly in the periportal zones of the liver lobules, leading to the development of progressive liver fibrosis (Fig. 5).

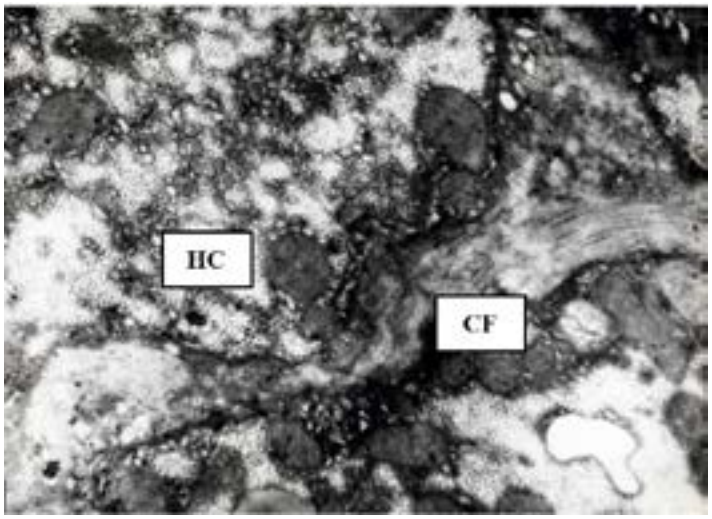

Figure 5. Increase in the number of collagen fibers in the periportal zone upon activation of fibrocytes. Electron micrograph of liver tissue from patient G., magnification ×12,000 (HC – hepatocyte; CF – collagen fibers).

Thus, patients with chronic hepatitis C infection (CHC) display morphological signs of viral and toxic liver damage: the presence of fibrosis in both the centrilobular and periportal zones, which are characteristic of productive inflammation. The glycogen content in hepatocytes was preserved in portal and periportal hepatocyte zones, while mild glycogen depletion was observed in the centrilobular zone. Most liver cells exhibited hypertrophy and hyperplasia of mitochondria, with swelling and transparency of their matrix, indicating strain on energy

processes in hepatocytes and compensatory function of mitochondria during short-term opioid intoxication. In the space of Disse, there were predominantly low-activity Kupffer cells with a moderate number of phagolysosomes, alongside a small number of lipocytes whose cytoplasm was filled with lipid droplets, indicating slight activation of fibrogenesis processes. Only isolated areas of liver lobules showed signs of mild pericellular fibrosis with the formation of single collagen fibers.

DISCUSSION

People who use injection drugs represent a high-risk group for HCV infection, with rates reaching 90 % among drug-dependent patients. The Integrated-Test-stage-Treat (ITTREAT) study found that the prevalence of positive HCV PCR results among drug users was 84 %, with 19 % already showing morphological signs of liver cirrhosis.

In addition to timely diagnosis of hepatitis C virus (HCV), assessing the activity of hepatitis and the severity of liver tissue fibrosis is crucial. Early laboratory and morphological verification of this pathology allows for timely initiation of antiviral treatment, leading to a sustained virological response in more than 90 % of patients.

Significant comorbid factors, such as alcohol use, chronic hepatitis B, high body mass index, and hepatic steatosis, may contribute to the progression of liver fibrosis in most patients with chronic hepatitis C (CHC). It is appropriate to seek reliable morphological criteria for assessing CHC activity, evaluating profibrogenic factors, and objectively measuring the degree of fibrotic changes in various parts of liver lobules in patients with CHC. Currently, HCV infection still lacks specific markers for accurately detecting the condition and progression of the disease.

Morphological studies of liver tissue in patients with CHC have shown that activated hepatic stellate cells (Ito cells) may be a contributing factor to exacerbated liver fibrosis. There are a few studies on the pathomorphology of the liver in CHC that, through electron microscopy, have examined the state of liver sinusoidal endothelial cells (LSECs). Electron microscopy analysis and evaluation of CD32, CD31, and caveolin-1 expression revealed that, during HCV infection, LSECs undergo significant morphological changes but maintain their phenotypic identity. Thus, the severity of LSEC modifications correlates with hepatocyte damage and the stage of fibrosis, providing new insights into the pathogenesis of chronic hepatitis C.

In the course of immunohistochemical studies on changes in lymphatic sprouts and mature lymphatic vascularization in the liver of patients with chronic hepatitis C (CHC), no significant relationship was found between the proportion of portal lymphatic sprouts or mature portal lymphatic vessels and the degree of periportal/periseptal activity. The use of immunohistochemical markers for productive inflammation in the liver is complicated by the high costs of reagents and equipment. Therefore, this proposed study attempts to analyze morphological and ultrastructural changes in the livers of patients with opioid dependency and comorbid CHC.

It has been established that the pathomorphological signs of fatty liver disease with moderate opioid consumption include the accumulation of lipid droplets in the centrolobular zone of liver lobules, a significant increase in their degradation processes, an increase in the number of lipophagosomes, and a moderate increase in the activity of Kupffer cells. Significant daily consumption of opioids (more than 15 ml per day) is associated with pronounced steatosis of hepatocytes not only in the centrolobular but also in the periportal zones, disruption of lipid degradation, destruction of mitochondria, transformation of Ito cells into fibrocytes, and deposition of collagen fibers in the perisinusoidal space.

In patients with opioid dependence who consume significant amounts of opioids daily (more than 15 ml), there was a pronounced accumulation of steatosis granules in hepatocytes in both the centrolobular and periportal zones, disruption of lipid degradation, destruction of mitochondrial crystals, a decrease in glycogen content in the cytoplasm of hepatocytes, a reduction in the area of the granular endoplasmic reticulum, a significant increase in the activity of Kupffer cells, and the transformation of Ito cells into fibrocytes, along with collagen fiber deposition in the perisinusoidal space. Significant profibrogenic factors in patients with fatty liver disease without comorbid CHC include the progression of steatosis granule deposition in hepatocytes, activation of Kupffer cells, and consequently, the transformation of Ito cells into fibrocytes.

The analysis of morphological changes in liver tissue of patients with chronic hepatitis C (CHC) and low histological activity shows evidence of productive inflammation in the liver tissue, moderate lymphomonocytic infiltration of the portal tracts, increased quantity and activity of Kupffer cells, and the presence of large lipid droplets with high density in centrolobular hepatocytes, along with a decrease in the area of the granular endoplasmic reticulum and glycogen deposits.

In patients with comorbid chronic hepatitis C and drug dependence, there are observed necrotic and apoptotic changes in hepatocytes of the portal and periportal zones, an increase in the number and activity of lymphocytes in the portal and periportal zones, significant steatosis in hepatocytes specifically in the periportal zone, and substantial collagen deposits in the perisinusoidal space, as well as in the periportal and centrolobular regions of the liver lobules.

Thus, electron microscopy studies of the liver in patients with opioid dependence and chronic hepatitis C allow for an objective assessment of the severity of necrotic changes in hepatocytes, the predominance of either toxic (such as steatotic granules in centrolobular and periportal

zones, destruction of mitochondrial crystals, etc.) or viral genesis (lymphomonocytic infiltration, activation of Kupffer cells, transformation of Ito cells into fibroblasts, etc.) of liver damage in each examined patient. Assessing the intensity of productive inflammation and the degree of steatosis and fibrotic changes in liver tissue will enable evaluation of the prognosis for the combined course of chronic hepatitis C.

The results obtained will enhance knowledge regarding the pathomorphogenesis of progressive liver injury, understanding the possible causes of side effects from methadone maintenance therapy, and determining whether the damage to liver lobules is predominantly toxic or virus-induced, which is crucial for establishing pharmacotherapy priorities.

CONCLUSIONS

1. Patients with chronic liver disease (CLD) and moderate opioid consumption (up to 15 ml daily) exhibit deposits of lipogranules in the centrolobular zone of the lobules, increased intensity of lipogranule degradation, a rise in the number of lipophagosomes, and signs of surface layer degradation of lipogranules. In this patient group, there is preservation of the granular and smooth endoplasmic reticulum, enlargement of mitochondria, a decrease in glycogen content in the cytoplasm of hepatocytes, and a moderate increase in Kupffer cell activity.

2. In drug-dependent patients with significant daily opioid consumption (more than 15 ml daily), there was pronounced deposition of steatotic granules in hepatocytes not only in the centrolobular but also in the periportal zone, disruption of lipogranule degradation, destruction of mitochondrial crystals, reduction of glycogen levels in the cytoplasm of hepatocytes, decreased area of granular endoplasmic reticulum, significant increase in Kupffer cell activity, and transformation of Ito cells into fibrocytes, along with collagen fiber deposition in the perisinusoidal space. Significant profibrogenic factors in patients with CLD without comorbid chronic hepatitis C (CHC) include the progression of steatotic granule deposits in hepatocytes, activation of Kupffer cells, and consequently, the transformation of Ito cells into fibrocytes.

3. Analyzing the morphological changes in the liver tissue of patients with CLD and low histological activity of comorbid CHC reveals signs of productive inflammation in the liver tissue, moderate lymphomonocytic infiltration of portal tracts, an increase in the number and activity of Kupffer cells, and a decrease in the number of granules in Ito cells. In the centrolobular zone, hepatocytes show large and dense lipogranules, a reduced area of granular endoplasmic reticulum, and glycogen deposits.

4. In patients with opioid dependence and moderate activity of comorbid chronic hepatitis C (CHC), there is a significant increase in necrotic and apoptotic changes in hepatocytes in the portal and periportal zones. In these hepatocytes, there is a notable increase in the quantity and density of lipid granules, as well as an increase in the area of the smooth endoplasmic reticulum. The progression of histological activity of CHC in opioid-dependent patients is accompanied by a significant increase in collagen deposits in the perisinusoidal space, as well as in the periportal and centrolobular zones of liver lobules. Moderate activity of CHC in opioid dependence is associated with an increase in the number and activity of lymphocytes in the portal and periportal zones, along with pronounced steatosis in hepatocytes specifically in the periportal zone.

5. Electron microscopy studies of the liver in patients with opioid dependence – both those without comorbid CHC and those with minimal to moderate activity of concurrent CHC – allow for an objective assessment of the severity of necrotic changes in hepatocytes, the predominance of toxic or viral origins of liver damage in each examined patient, the intensity of productive inflammation, and the degree of steatosis, which are factors promoting fibrosis. The progression of fibrotic changes in liver tissue also helps to evaluate the prognosis of the connective progression of opioid dependence and chronic hepatitis C.

Prospects for further research include the comparison of morphological changes in liver tissue in patients with opioid dependence and chronic hepatitis C with laboratory algorithms for fibrosis verification, particularly with NASH-fibrotest and FIB-4.

COMPLIANCE WITH ETHICAL REQUIREMENTS

The study has been approved by the Biomedical Ethics Commission of Luhansk State Medical University and was conducted in accordance with the principles of bioethics outlined in the Helsinki Declaration «Ethical Principles for Medical Research Involving Human Subjects» (1975), which was revised in 2000; the «Universal Declaration on Bioethics and Human Rights» (UNESCO); and the Council of Europe Convention on Human Rights and Biomedicine (2007); as well as the Recommendations of the Bioethics Committee of the Presidium of the National Academy of Medical Sciences of Ukraine (2002). All participants were fully informed about the research, and their written informed consent was obtained prior to the commencement of the study. All research methods were carried out following the established guidelines and regulations.

FUNDING AND CONFLICT OF INTEREST

The entire research was conducted at the authors' own expense without the involvement of additional funding sources. The authors declare no conflict of interest or financial interest.

AUTHORS' CONTRIBUTIONS TO THE ARTICLE

Ovcharenko Mykola Oleksiyovych – creation of the research concept and design, collection of research materials, writing the text of the article, editing of conclusions. Linskyi Ihor Volodymyrovych – formulation of the work's conclusions. Holubovska Olha Anatoliivna – review of materials on patients with chronic hepatitis C. Khaytovych Mykola Valentynovych – manuscript editing. Mishiev Viachyslav Danylovych – processing of materials on patients with opioid dependence. Radchenko Tetiana Mykolaivna – collection of research materials. Pinsky Leonid Leonidovych – collection of research materials, writing of the text of the article.

REFERENCES

1. Iversen Jenny, Wand Handan, McManus Hamish, Dore Gregory J., Maher Lisa (2023). Incidence of primary hepatitis C virus infection among people who inject drugs in Australia pre- and post-unrestricted availability of direct acting antiviral therapies. Addiction,118(5), 901-911. https://doi.org/10.1111/add.16113.
2. Druckrey-Fiskaaen Karl Trygve, Vold Jørn Henrik, Madebo Tesfaye, Midgard Håvard, Dalgard Olav, Leiva Rafael Alexander, Fadnes Lars T. (2024). Liver stiffness and associated risk factors among people with a history of injecting drugs: a pro-spective cohort study Subst Abuse Treat Prev Policy, Mar 26, 19(1), 21. https://doi.org/10.1186/s13011-024-00603-z.
3. Wissel Kerstin, Vernazza Pietro, Kuster Stefan, Hensel-Koch Katharina, Bregenzer Andrea (2024). Hepatitis C prevalence and cascade of care among patients in the decentralised opioid agonist therapy programme of the canton of St Gallen, Switzerland: a cross-sectional study Swiss Med Wkl,. Feb 29, 154, 3352. https://doi.org/10.57187/s.3352.
4. Schwarz M., Schwarz C., Schütz A., Schwanke C., Krabb E., Schubert R., Liebich S.-T., Bauer D., Burghart L., Brinkmann L., Gutic E., Reiberger T., Haltmayer H., Gschwantler M. (2023). Combining treatment for chronic hepatitis C with opioid agonist therapy is an effective microelimination strategy for people who inject drugs with hgh risk of non-adherence to direct-acting antiviral therapy J Virus Erad., Mar 2, 9(1), 100319. https://doi.org/ 10.1016/j.jve.2023.100319.
5. Tsui Judith I., Lum Paula J., Taylor Lynn E., Mehta Shrut H., Feinberg Judith, Kim Arthur Y., Norton Brianna L., Niu Jiajing, Heo Moonseong, Arnsten Julia, Pericot-Valverde Irene, Thomas Aurielle, Blalock Kendra L., Radick Andrea, Murray-Krezan Cristina, Page Kimberly, Litwin Alain H. (2023). Injecting practices during and after hepatitis C treatment and associations with not achieving cure among persons who inject drugs Randomized Controlled Trial Drug Alcohol Depend., Jun 1, 247, 109878. https://doi.org/10.1016/j.drugalcdep.2023.109878.
6. O'Sullivan Margaret, Anna-Marie Jones, Adele Mourad, Yazan Haddadin, Sumita Verma (2024). Excellent hepatitis C virus cure rates despite increasing complexity of people who use drugs: Integrated-Test-stage Treat study final outcomes J Viral Hepat., Feb, 31(2), 66-77. https://doi.org/10.1111/jvh.13897.
7. Chi-Ming Tai, Ming-Lung Yu (2024). Hepatitis C virus micro-elimination in people who inject drugs: Challenges and chance in Taiwan and worldwide Review Kaohsiung J Med Sci. Feb, 40(2), 112-118. https://doi.org/10.1002/kjm2.12788.
8. Anna Jerkeman, Johan Westin, Martin Lagging, Gunnar Norkrans, Christer Lidman, Jan Frimand, Christian Simonsberg, Johan Kakko, Anders Widell, Per Björkman (2014). Chronic hepatitis C in Swedish subjects receiving opiate substitution therapy--factors associated with advanced fibrosis Scand J Infect Dis., May, 46(5), 340-7. https://doi.org/10.3109/00365548.2013.879994.
9. Lim Aaron Guanliang, Aas Christer Frode, Çağlar Ege Su, Vold Jørn Henrik, Fadnes Lars Thore, Vickerman Peter, Johansson Kjell Arne (2023). Cost-effectiveness of integrated treatment for hepatitis C virus (HCV) among people who inject drugs in Norway: An economic evaluation of the INTRO-HCV trial Addiction, Dec, 118(12), 2424-2439. https://doi.org/10.1111/add.16305.
10. Dalgard Olav, Litwin Alain H., Shibolet Oren, Grebely Jason, Nahass Ronald, Altice Frederick L., Conway Brian, Gane Edward J., Luetkemeyer Anne F., Peng Cheng-Yuan, Iser David, Gendrano Isaias Noel, Kelly Michelle M., Haber Barbara A., Platt Heather, Puenpatom Amy (2023). Health-related quality of life in people receiving opioid agonist treatment and treatment for hepatitis C virus infection Randomized Controlled Trial J Addict Dis., Jul-Sep, 41(3), 213-224. https://doi.org/10.1080/10550887.2022.2088978.
11. Amaddeo Giuliana, Trung Cong Nguyen, Maillé Pascale, Mulé Sebastien, Luciani Alain, Machou Camilia, Rodrigues Aurélie, Regnault Hélène, Mallat Ariane, Laurent Alexis, Lafdil Fouad, Hézode Christophe, Pawlotsky Jean-Michel, Calderaro Julien (2020). Intrahepatic immune changes after hepatitis C virus eradication by direct-acting antiviral therapy Liver Int., Jan, 40(1), 74-82. https://doi.org/10.1111/liv.14226.

12. Ferreira Joana, Oliveira Mariana, Bicho Manuel, Serejo Fátima (2023). Role of Inflammatory Immune Response and Cytokine Polymorphisms in the Severity of Chronic Hepatitis C (CHC) before and after Direct Acting Antiviral (DAAs) Treatment Int. J. Mol. Sci., Jan 10, 24(2), 1380. https://doi.org/10.3390/ijms24021380.
13. Sufletel Rada Teodora, Melincovici Carmen Stanca, Orășan Olga Hilda, Zaharie Toader, Bogdan Alexandru Gheban, Istrate Alexandru, Constantin Anne-Marie, Mihu Carmen Mihaela (2023). Activated Hepatic Stellate Cells (Ito Cells) - Marker of Advanced Fibrosis in Chronic Viral Hepatitis C: A Pilot Study J Gastrointestin Liver Dis., Jun 22,32(2), 170-181. https://doi.org/10.15403/jgld-4726.
14. Wang Wei, Huang Xuelian, Fan Xuzhou, Yan Jingmei, Luan Jianfeng (2020). Progress in evaluating the status of hepatitis C infection based on the functional changes of hepatic stellate cells (Review) Review Mol Med Rep., Nov, 22(5), 4116-4124. https://doi.org/10.3892/mmr.2020.11516.
15. Baiocchini Andrea, Nonno Franca Del, Taibi Chiara, Visco-Comandini Ubaldo, D'Offizi Gianpiero, Piacentini Mauro, Falasca Laura (2019). Liver sinusoidal endothelial cells (LSECs) modifications in patients with chronic hepatitis C Clinical Trial Sci Rep., Jun 19, 9(1), 8760. https://doi.org/10.1038/s41598-019-45114-1.
16. Kawassaki Aline, Beltrame Farina Ana Paula, Santos Cinthya dos, Alda, Venâncio Avancini Ferreira (2022). Immuno-histochemical assessment of lymphatic vessels in human livers with chronic hepatitis C - relation to histological variables Arq Gastroenterol., Jan-Mar, 59(1), 58-64. https://doi.org/10.1590/S0004-2803.202200001-11.
17. Puchtler Holde, Sweat Faye (1964). Histochemical specifity of staining methods for connective tissue fibers: resorcin-fuchsin and Van Gieson's picro-fuchsin Z. Zellforch Microsk Anat Histoche, 79, 24-34. https://doi.org/10.1007/BF00304175.
18. Bedossa P., Poynard T. (1996). An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group Hepatology., Aug, 24(2), 289-93. https://doi.org/10.1002/hep.510240201.
19. Knodell Robert G., Ishak Kamal G., Black William C., Chen Thomas S., Craig Robert, Kaplowitz Neil, Kiernan Thomas W., Wollman Jerome (1981). Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis Hepatology, Sep-Oct,1(5), 431-5. https://doi.org/ 10.1002/hep.1840010511.
20. Wisse Eddie, Braet Filip, Duimel Hans, Vreuls Celien, Koek Ger, Steven WM Olde Damink, Maartje AJ van den Broek, Bart De Geest, Cees HC Dejong, Chise Tateno, Peter Frederik, Wisse E, Braet F, Duimel H, Vreuls C, Koek G, Olde Damink SW, van den Broek MA, De Geest B, Dejong CH, Tateno C, Frederik P. (2010). Fixation methods for electron microscopy of human and other liver Review World J Gastroenterol., Jun 21, 16(23), 2851-66. https://doi.org/10.3748/wjg.v16.i23.2851.

Резюме

МОРФОЛОГІЧНІ ЗМІНИ В ПЕЧІНЦІ У ХВОРИХ НА ОПІОЇДНУ ЗАЛЕЖНІСТЬ ЗА ВІДСУТНОСТІ ТА НАЯВНОСТІ СУПУТНЬОГО ХРОНІЧНОГО ГЕПАТИТУ С

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Мета. Визначити клінічну значущість морфологічних ознак в оцінці токсичного або вірусного генезу ураження печінки у хворих із коморбідним перебігом опіоїдної залежності та хронічного гепатиту С.
Матеріали та методи. Гістологічні препарати тканини печінки 48 хворих на опіоїдну залежність за критеріями МКБ.10 (F 11.30), з них – 18 пацієнтів із опіоїдною залежністю без хронічного гепатиту С у віці від 22 до 40 років (16 осіб чоловічої статі і 2 – жіночої) та 30 хворих із опіоїдною залежністю та наявністю хронічного гепатиту С за критеріями МКБ.10 (В18.2) віком від 22 до 38 років (27 чоловіків та 3 жінки). Ультратонкі зрізи тканини печінки вивчали в електронному мікроскопі ЕМ-100 при прискорювальній напрузі 75 кВ та збільшенні ×12000.
Результати. При високопрогредієнтному перебізі опіоїдної залежності без хронічного гепатиту С значущою була наявність великих стеатозних гранул в центролобулярній та перипортальній зонах, порушення процесів деградації ліпідних гранул, значне зростання активності клітин Купфера та трансформація клітин Ітo до фіброцитів.
Наявність малої гістологічної активності коморбідного хронічного гепатиту С обумовлює: помірну лімфомоноцитарну інфільтрацію саме портальних трактів, збільшену активність процесів руйнації ліпідних гранул в центролобулярній зоні печінкових часточок. При помірній активності коморбідного хронічного гепатиту С у наркозалежних хворих суттєво зростають некротичні та апоптотичні зміни в гепатоцитах портальної та перипортальної зон, зростання кількості та щільності ліпідних гранул, значне збільшення відкладень колагену в перисинусоїдальному просторі, перипортальній та центролобулярній зонах печінкових часточок.
Висновки. 1. В клінічній практиці доцільними є використання морфологічних досліджень печінки у хворих на опіоїдну залежність та хронічний гепатит С для верифікації значущих профіброгенних факторів: прогресування відкладень стеатозних гранул в гепатоцитах, порушення процесів їх деградації, активацію клітин Купфера, трансформацію клітин Ітo до фіброцитів. 2. Морфологічні дослідження печінки у хворих на опіоїдну залежність з наявністю та відсутністю коморбідного хронічного гепатиту С дозволяють об'єктивно оцінити переважання токсичного або вірусного генезу ураження печінки у кожного з обстежених хворих та визначити пріоритетність в призначенні лікування.

Ключові слова: **розлади, пов'язані з опіоїдами, хронічний гепатит С, фіброз, стеатоз печінки**