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COMPARATIVE MORPHOLOGICAL CHARACTERIZATION OF VIRAL AND VIRAL-ALCOHOLIC LIVER CIRRHOSIS (BASED ON AUTOPSY DATA)

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Pathomorphological comparison of viral liver cirrhosis (induced by hepatitis B virus, hepatitis C virus or both) and viral-alcoholic liver cirrhosis is presented. It was shown that patients with viral-alcoholic cirrhosis decease in younger age (p = 0,004). Occurrence of steatosis (93% vs 74%, p = 0,011) and cholestasis (67% vs 45%, p = 0,048) is significantly increased in these patients.
Keywords: liver cirrhosis, alcohol, hepatitis B virus, hepatitis C virus, steatosis, cholestasis

Представлена сравнительная морфологическая характеристика циррозов печени вирусной (вызванной вирусами гепатитов B,C или B+C) и вирусно-алкогольной этиологии. Показано, что больные вирусно-алкогольным циррозом погибают в более молодом возрасте (p = 0,004). В этой группе пациентов значимо чаще встречается стеатоз (93% против 74%, p = 0,011) и холестаз печени (67% против 45%, p = 0,048).
Ключевые слова: цирроз печени, алкоголь, вирус гепатита B, вирус гепатита C, стеатоз, холестаз

Problem of chronic viral hepatites is acute due to high prevalence and progradient flow of infection leading to cirrhotic transformation in some patients [1]. Combination of alcoholic liver damage and chronic viral infection increases risk of liver cirrhosis and hepatocellular carcinoma exacerbating morphological changes associated with viral infection [2,3]. Morphological analysis of liver tissues in hepatitis of different aetiology is widely elucidated in the literature [1,4-6]. Nevertheless, it is not yet clear, whether severity of liver tissue morphological changes at the moment of death is identical in patients with viral and viral-alcoholic cirrhosis, died from ascitis-peritonitis, hepatic encephalopathy, oesophageal/gastric bleeding and other causes associated with liver pathology or not.

Purpose: our aim was to provide comparative morphological analysis of autopsy material from deceased patients with cirrhosis of viral (hepatitis B virus (HBV), hepatitis C virus (HCV) or HBV+HCV) and viral-alcoholic aetiology.

Materials and methods

Clinical records, autopsy protocols and histological preparations of liver tissue from 91 patients with chronic viral hepatitis with clinical signs of cirrhosis, died in clinical hospital of infectious diseases named after S. P. Botkin in Saint-Petersburg in 2004-2007 were analysed.

Specimens with signs of autolysis or morphological lesions characteristic for infections other than HBV- or HCV-infection, patients with systemic diseases (amyloidosis, dermatomyositis, systemic lupus erythematosus, etc.) and patients who have undergone antiviral therapy (interferon, ribavirin, entecavir, telbivudine) were excluded from analysis.

Type of viral hepatitis (B, C or B+C), age at death, sex, histological activity index (HAI – Knodell score) [7], Desmet score [8], presence, severity and prevalence of circulatory disorders in liver tissue, presence and severity of cholestasis and steatosis were considered. Etiology of viral hepatitis was determined by means of solid-phase ELISA of sera for specific markers of HBV and HCV (HBsAg, HBcAb, HCVAb).

I group (n = 60) included patients with regular alcohol consumption according to clinical records (more than 50 g of alcohol per day, consultive examination by hospital narcologist), II group (n = 31) consisted of patients with no regular alcohol consumption in anamnesis, proved by clinical records.

Statistical analysis was performed in SPSS v17.0. Critical significance level was 0,05 for null hypothesis (no differences between groups). Sample mean (M) and standard deviation (SD) were calculated. Pearson's χ^2 test was used in analysis of qualitative variables. Distribution was tested for normality using Kolmogorov-Smirnov test, Lilliefors test and Wilk-Shapiro test. For normally distributed data independent sample's Student's t-test was used. Non-parametric Mann-Whitney U test was used for data with unknown distribution.

Results

The average age of patients in group I was 42,5±10,6 years, male:female ratio = 30:30. Chronic viral hepatitis B was found in 40% of case (24 patients), chronic viral hepatitis C — in 33% (20 patients), mixed viral hepatitis (B+C) — in 27% (16 patients). The average age of patients in group II was 50,5±12,8, 48% male, 52% female. Chronic viral hepatitis B was found in 42% of case (13 patients), chronic viral hepatitis C — in 39% (12 patients), mixed viral hepatitis (B+C) — in 19% (6 patients). Significant differences in age between groups were observed: death age of patients with regular alcohol consumption was lower (p = 0,004). There were no significant difference in sex or type of viral hepatitis between groups.

There were no significant difference in mean HAI score between groups: 10,6±2,5 in group I and 10,3±2,7 in group II (p = 0,469). No difference in observed frequency of different degrees of intensity of histological activity was found. Low histological activity (HAI 4-8) was observed in 23% of deceased patients in group I and in 32% — in group II, moderate histological activity (HAI 9-12) — in 48% deceased in group I, and 45% in group II, high histological activity (HAI 13-18) — in 26% and 19% of deceased patients in group I and II, respectively.

Reliable signs of complete cirrhotic transformation of liver (fibrosis score 13-16) were observed in 55% of patients in group I and 68% of patients in group II (χ^2 = 1,375, p = 0,241). Remaining deceased patients had fibrosis with different degree of intensity (fibrosis score 1-12).

In some cases disease was accompanied by circulatory disorders (50% in group I, 58% in group II, χ^2 = 0,533, p = 0,465) like venous engorgement with necrosis of hepatocytes around central veins. Analysis of subgroup of deceased patients with circulatory disorders (n = 48) showed that in most cases microcirculatory disturbances affected less than 1/3 of observed liver lobules (73% in group I, 89% in group II). Mostly inside each affected lobule microcirculatory disturbancies occupied up to 1/3 of the lobule.

Presence of steatosis was observed more frequently in patients with regular alcohol consumption in anamnesis (93%, n = 56/60) than in patient without it ((74%, n = 23/31), χ^2 = 6,541, p = 0,011). Large-droplet (93% against 71%, χ^2 = 8,350, p = 0,004) and medium-droplet (90% against 61%, χ^2 = 10,617, p = 0,001) steatosis frequency was significantly higher in group I. Differences in occurrence of small-droplet steatosis between groups were not found (12% и 3%, χ^2 = 1,816, p = 0,178). It should be noted that small-droplet steatosis was identified only in patients with large- and medium-droplet steatosis. In group I signs of fatty degeneration of hepatocytes was more severe (χ^2 = 8,432, p = 0,015. Table 1).

Table 1

Degree of steatosis intensity (n=79)

Group	Number of lobules with signs of steatosis in autopsy material, abs. (%)		
	Less than 1/3 of lobules	From 1/3 to 2/3 of lobules	More than 2/3 of lobules
Group I, n = 56	19(34)	23(41)	14(25)
Group II, n = 23	16(70)	4(17)	3(13)

Inflammatory alterations of ducts were observed in 37% of patients in group I and 29% of patients in group II (χ^2 = 0,530, p = 0,466).

Cholestatic disturbancies were more frequently observed in group I patients: intracellular cholestasis (67% and 45% in group I and II, respectively, $\chi^2 = 3,918$, $p = 0,048$), canalicular cholestasis (65% and 35,5%, $\chi^2 = 7,193$, $p = 0,007$), ductular (20% and 3,2% in group I and II, respectively, $\chi^2 = 4,697$ $p = 0,03$). Isolated ductular cholestasis was found in one case, in woman with signs of cholangitis. In the rest of cases canalicular and ductular cholestasis were combined with intracellular cholestasis.

Discussion

Obtained data show that natural course of chronic viral and viral-alcoholic hepatitis in observed Saint-Petersburg population of patients (in the absence of antiviral treatment) to the stage of cirrhotic transformation with decompensation and fatal outcome falls on employable age. The average age of patients with viral cirrhosis was 8 year less than the average age of patients with viral-alcoholic cirrhosis. Data shown agree with literature data indicating that patients with chronic viral hepatitis and regular alcohol consumption develop liver cirrhosis earlier [1,2,5].

Most of the patients in our study had moderate activity of pathological process in the liver. There were no significant differences in HAI between patients with and without alcohol abuse. D.L.Nepomnyashchikh et al. [5], Z.G.Aprosina, V.V.Serov [9] estimating histological activity in HCV-infected patients with alcoholic disease found an increase in histological activity index (HAI). Maximal HAI score was observed in HCV- and HBV-coinfected patients with alcohol abuse [5,9].

It should be noted that in 45% of patients from group I and 32% of patients from group II with clinical signs of cirrhosis (ascites, oesophageal varices, etc.) had no reliable morphological signs of liver cirrhotic transformation (fibrosis score according V.J.Desmet et al. was less than 12). We have not found in the literature studies elucidating such facts. To make situation clear thorough clinical-anamnestic analysis of clinical records of this group of patients is required. Presumably, emergence of relievable portal hypertension may be associated with reversible changes in liver during hepatitis exacerbation (oedema, inflammatory infiltration of portal tracts stroma, blood vessel walls, changes in endothelial lining) with marked fibrotic changes leading to blood flow decrease in portal vein branches.

Microcirculatory disturbancies inside liver lobules were found in half of all cases in both groups. Diagnostic significance of changes in portal and, particularly, hepatic vein branches in viral hepatitis was pointed out by Ju.N.Darkshevich who was the head of pathological anatomy service in clinical hospital of infectious diseases named after S.P.Botkin in Saint-Petersburg for a long time [4]. Followers of Ju.N.Darkshevich have studied and described circulatory disturbances in the liver in detail [4]. Other researchers also report circulatory disturbances in chronic viral hepatitis [1,5]. Microcirculatory disturbances exacerbate tissue hypoxia that in turn plays significant role in steatosis development.

Liver steatosis was observed more frequently in alcohol abusers (93% vs. 74%), with a predominance of large- and medium-droplet steatosis. In studies on biopsy material from patients with chronic hepatitis steatosis is identified in 46-87% of cases of HCV infection [5,10-13] and in 14-60% of cases of HBV infection [11,14-16]. Association between presence and severity of steatosis and fibrosis progression and development of cirrhosis has been already shown [13,16,17]. It should be noted that in repeated morphological studies severity of steatosis increased [13]. According to literature small-droplet steatosis of hepatocyte cytoplasm is an indication of acute oxygen deficiency, tissue hypoxia of different origin. However, large-droplet steatosis is often a consequence of chronic alcoholic intoxication, and less infrequently of viral infection [4,5,18,19]. So it is no wonder in observed number of patients with steatosis and it's severity in patients with cirrhosis died from complications of liver disease.

Inflammation in bile ducts was identified in 1/3 of patients in both groups. Inflammation of bile ducts and gallbladder is common for patients with viral and viral-alcoholic hepatitis [4,20] and is associated with liver steatosis and abdominal obesity [20].

Intracellular, canalicular, ductular and often combined forms of cholestasis were more frequently observed in patients with alcohol abuse. Cholestatic disturbances in chronic hepatitis in the form of bile pigmentation of hepatocytes, cholestasis in canaliculi and ducts, proliferation and sclerosis of bile ducts are widely reported in literature [1,4,5]. It appear that cholestatic phenomena are associated with pathology of bilirubin metabolism and membranous transport caused by toxicity. Cholestasis is regarded as an unfavourable factor for disease progression prognosis and fatal outcome [21].

Conclusion

Patients with viral-alcoholic cirrhosis decease in younger age. Liver steatosis and cholestasis, usually of toxic origin, are observed in this group of patients more frequently. Apparently unfavorable exogenic influences lead patients with clinical signs of cirrhosis but incomplete cirrhotic transformation of liver (according to morphological data) to fatal outcome.

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