AJPMHS GLOBAL RESEARCH NETWORK

**AMERICAN Journal of Pediatric Medicine and Health Sciences**
*Volume 01, Issue 07, 2023 ISSN (E): 2993-2149*

# Progression of Fibrosis and the Formation of Cirrhosis of the Liver in Chronic Viral Hepatitis

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**Abstract:** The paper examines the literature data on factors affecting the process of fibrogenesis and cirrhosis in chronic viral hepatitis. It is shown that the course of fibrogenesis depends not only on the microorganism and the duration of the infection, but also on the genetic predisposition and characteristics of the macroorganism, the activity of the pathological process, the effects of hepatotoxic agents (primarily ethanol), etc.

**Keywords:** chronic viral hepatitis, fibrosis, cirrhosis of the liver.

Chronic viral hepatitis (HCG) is an urgent problem of modern healthcare. Currently, at least four pathotropic viruses are known to cause the development of chronic hepatitis and cirrhosis of the liver (CP) — B, C, D and

G. From a practical point of view, the question of risk factors for the progression of fibrosis and the formation of cirrhosis of the liver in viral hepatitis deserves attention.

Features of the microorganism. According to world statistics, the frequency of CP formation depends on the causes of liver damage, including in viral hepatitis from the type of hepatotropic virus. Thus, the frequency of CP formation in HBV monoinfection reaches 4% [I], whereas in HBV/HDV mixed infection it increases to 40% [2]. In HCV infection, CP, according to various authors, develops in 1.5 — 58% of cases [3, 4].

There are indications of the dependence of the formation of CP in HCG on the genotype of the hepatotropic virus. Thus, J. N. Kao et al.

[5] provide data on the prevalence of the HBV genotype among patients with CP compared with asymptomatic carriers (60 and 23%, respectively). H. Sumi et al. [6] also believe that the HBV genotype is more associated with severe liver fibrosis (74/224 vs. 4/30 for genotypes B and C, respectively). At the same time, according to M. F. Yuen. et al. [7], in patients infected with the HBV genotype, higher levels of AlAT and bilirubin and lower levels of albumin were recorded, and, accordingly, higher mortality rates due to decompensation of liver function compared to individuals with HBV infection caused by geno type C. Brazilian researchers believe that infection, caused by hepatitis B virus with a mutation in the pre core region, it leads to an increase in the index of histological activity and the severity of liver fibrosis [8].

It is believed that patients with HCV having genotype 1b have the most unfavorable course of the disease, and CP is formed more often than with HCV caused by other genotypes of the pathogen. In contrast, there is an opinion that accelerated fibrosis progression is associated with not 1 HCV genotypes, in particular, with genotype 3 [9, 10]. However, other authors believe that the formation of CP does not depend on the HCV genotype [11]. In a study by M. Guido et al. [12] In children, the HCV gene type also did not correlate with the degree of liver fibrosis.

There are indications that in chronic hepatitis D y patients with HDV genotype I, compared with patients with II, IV and unclassified HDV genotype, complete remission is less often recorded (15.2 vs. 40.2%) and unfavorable outcomes of the disease (liver cirrhosis and hepatocellular carcinoma) are more often noted (52.2 vs. 25%) [13].

The concentration (titer) of the pathogen in blood serum and tissues is considered as one of the factors that aggravate the course of hepatitis and lead to accelerated progression of liver fibrosis. According to D. K. Wong et al.

[14] the titers of HBV DNA detected in liver tissue correlate with the concentration of HBV DNA in blood serum and with the degree of liver fibrosis. It is believed that a significant progression of fibrosis in HCV is associated with the concentration of HCV RNA in the blood serum exceeding 8 × 106 copies/ml [15]. At the same time, the negative HCV RNA status of the blood serum of y patients with HCV corresponds to the absence of progression of liver fibrosis [16]. According to other data, viral load is not associated with the progression of fibrosis. Thus, N. Saleem et al. [17] it is believed that the concentration of HCV RNA in the blood serum does not correlate with the activity of the pathological process, nor with the degree of liver fibrosis, nor with ca kim or another indicator of the Knodell histological activity index.

The course and outcomes of mixed infections of various hepatotropic viruses depend on these viruses. Thus, E. Sagnelli et al. [18] it is believed that mixed HBV/HCV infection proceeds with more serious histological changes (including fibrosis) compared to monoinfection with one of these viruses. The histological activity index and the degree of liver fibrosis of y patients with HBV/HCV mixed infection exceeded those of y individuals with HCV mono infection (3.5-1.1 and 3.0 - 1.1 points versus 3.5 - 0.8 and 2.3 - 1.1 points, respectively). At the same time, according to S. Silva et al. [19] HBV infection does not lead to a worsening of the course and severity of liver fibrosis and does not affect the effectiveness of antiviral therapy in patients with HCV. It is also well known that a mixed infection of HBV and HDV leads to a heavier clinical, laboratory and histological manifestations of the disease and a significant increase in fibrosis and cirrhosis of the liver [20].

Mixed infection with HIV leads to an acceleration of the processes of fibrogenesis and the formation of CP in persons with HCV. It is believed that since the improvement of HCV retroviral therapy, CP has become one of the main causes of death of HIV patients. In a study

by D. Fuster et al. [21] it was shown that y patients with mixed HCV/HIV infection of the 3rd and 4th degrees of fibrosis were recorded significantly more often than with HCV mono infection (46.7 and 12%, respectively). In contrast, the Polish authors believe that in patients with HCV infection with HIV does not lead to a deterioration of the histological picture of the liver, both with regard to the inflammatory activity of the process and fibrosis [22].

The path of infection. Most literary sources agree that the path of infection does not play a decisive role in terms of fibrosis progression and CP formation. Despite this, R. R. Joya Vazquez et al. [23] it is believed that the progression of fibrosis is associated with such infection pathways as blood transfusion, extensive surgical interventions and hemodialysis. S. Rerksuppaphol et al. [24] did not note any differences in the outcomes of NS infection in y children depending on the path of infection (vertical or transfusion): y of all patients (n = 31) during the follow-up period (on average, 13 years, range from 9 to 16.8 years), the disease proceeded without clinical symptoms; CP not a single patient was formed.

Features of the macroorganism. First of all, y adult patients have indications of a high frequency of CP formation in y males. The cause of this phenomenon may be an inhibitory effect on the process of fibrogenesis of female sex hormones. In the experiment, the administration of estradiol to rats exposed to a hepatotoxic agent — carbon tetrachloride (CCC) led to a decrease in the level of AsAT, AlAT, hyaluronic acid and type IV collagen in the blood serum, as well as to a decrease in the content of activated stellate cells and collagen in the tissue liver [25]. The connection of the fibrosis process with female sex hormones is confirmed by the fact that the

progression of fibrosis in HCV was higher in post-menopausal women and was accompanied by greater histological activity of the process. In post-menopausal women who received hormone replacement therapy, the degree of fibrosis increase was less (0.099 - 0.016 versus 0.133 - 0.006 units/year on the METAVIR scale) and the corresponding y of women of the preclimacteric period (0.093 - 0.012 units/year on the METAVIR scale) [26]. In accordance with this, sex differences in the severity of liver fibrosis in HCV are manifested only in patients younger than 50 years [27].

However, according to other data, the degree of liver fibrosis is not related to gender [28]. In children with HCV, the degree of fibrosis is also not related to gender [12]. However, there is evidence that the most severe course of HBV CP is observed in girls [29].

There are racial and national differences in the prevalence of severe fibrosis and cirrhosis of the liver. According to North American authors, the severity of necro-inflammatory changes and liver fibrosis in HCV was lower in Blacks compared to white Americans [30]. In another work, it was calculated that y Spanish-speaking North Americans biochemical and histological activity of the process in HCV exceeded those of y Blacks and white Americans; the frequency of CP formation of y Spanish-speaking North Americans was higher than y Blacks and tended to exceed that of y whites [31]. According to the Australian authors, among the numerous ethnic groups living in Australia, pronounced liver fibrosis in CHB is registered with the greatest frequency in persons of the so-called Mediterranean ethnicity [2].

Data on genetic predisposition to increased fibrogenesis and the formation of CP were also traced by the HLA system. According to A. L. Bondarenko [33], the development of CP is associated with HLA antigens A1, B8 and haplotypes A10, B8; B8, Cw3; B8, DR3; A1, B8, DR3; A1, B8, Cw2, DR5; A3, B8, Cw3, DR2. At work

E. V. Volchkova and S. A. Potekaeva [34] in patients with HBV CP, compared with HCV, HLA antigen B27 was significantly more common (71.4 and 9.5%, respectively). According to G. V. Volynets [29], in children with HCV, HLA antigen A9 is associated with the most severe liver damage with the formation of CP.

Associations between chronic HDV infection and HLA antigens have been established. In patients with chronic delta infection of Russian nationality, HLA B8 and B35 antigens are registered in the phenotype with increased frequency. The presence of haplotypes A1/B8 and A1/B35 increases the risk of formation of both HDV and HBV positive HCG. In persons of Kazakh nationality, delta infection is associated with HLA B35 and B40 antigens, A2/B35, A1/B35 haplotypes.

In patients with HCV, the average values of the histological activity index were lower than in patients with the DQB 1*0301 haplotype [3], whereas the DRB 1*0301 haplotype was associated with progressive liver disease [37]. According to other data, although patients with HCV CP compared with HCV had a lower frequency of occurrence of the DRB 1*11 allele (5.6 vs. 14.5%) and a higher frequency — DRB1*03 and DQ1*0201 (18.1 and 37.5% vs. 9.6 and 23.4%, respectively), ultimately, Class II HLA alleles showed a weak association with the severity of liver fibrosis [3].

A statistically significant relationship was found between the inheritance of a genotype with a high production of TGF-1 (transforming growth factor -1) and angiotensin, and the development of progressive liver fibrosis. The discovery of a reliable relationship between the genotype with high angiotensin production and fibrosis suggests a mediator role of angiotensin in extracellular matrix production in the liver [39]. It was shown that in the experiment of y mice with a genetic deficiency of angiotensin I receptors after the effect of a damaging factor on the liver (ligation of the external bile ducts), a reduced content of various pro-inflammatory cytokines, profibrogenetic cytokines (in particular TGF-1) and lipid peroxidation products in the liver tissue was noted, and a lower severity of fibrotic changes in liver compared with the wild type of mice [10]. To confirm the role of the renin angiotensin system in the process of fibrogenesis, there is

evidence that angiotensin converting enzyme (ACE) inhibitors inhibit the processes of fibrogenesis. In a pilot study, it was shown that in patients with HCV who received ACE— losartan — 50 mg per day for 6 months, there was a decrease in the severity of liver fibrosis compared to those who did not receive losartan [11].

A mutation of the gene encoding the synthesis of TGF □1 at codon position 10 is associated with the development of CP in CHB [22]. There is information about the role of homo and heterozygous carriers of deficient S and Z alleles of the alpha 1 antithrypsin gene in the formation of CP in HCV [23]. According to other data, heterozygous carriage of the Z allele of the alpha-1 antitrypsin gene does not affect the severity of liver fibrosis in HCV [14].

The frequency of HBV CP development is associated with the genotypes of GSTM1 and GSTP1 Val (105) glutathione 8 transferase, whereas the genotype of GSTT1 occurs with equal frequency in patients with CP, HCG and "healthy" carriers of HBV [15].

Data on the dependence of the fibroge process were obtained

The risk and frequency of CP development in HCV infection depends on the polymorphism of genes encoding the synthesis of matrix metalloproteinases (MMP) — MMP 1, MMP 3 and MMP 9 — enzymes directly involved in the processes of connective tissue remodeling [16]. High levels of serum iron, ferritin and transferrin saturation coefficient are associated with severe fibrosis and cirrhosis of the liver in HCV. In turn, with a high content of jelly heterozygosity according to the gene of hereditary hemochromatosis is associated with increased fibrosis in liver tissue in HCV. Moreover, heterozygous carriage of mutation in the C282Y and H63D genes was found in the work of German authors in patients with HCV in 4.2 and 21.3% of cases, respectively [7]. Iron overload leads to an increase in the level of liver fibrosis in patients with thalassemia infected with HCV, compared with patients with HCV without thalassemia and patients with thalassemia uninfected with HCV [8]. According to other data, the serum ferritin level and the iron content in the liver of the night tissue do not play a significant role in liver damage in HCG [9].

Increased body weight is also a risk factor for the rapid progression of liver fibrosis in HCV. Thus, in a study by A. D. Clouston et al. [50] it was shown that in HCV, the average body mass index (body weight, kg/height 2, cm) was higher in y patients with localized (28.4 - 4.7 kg/m2) or extensive (29.6 - 5.9 kg/m2) fibrosis than in y patients without fibrosis (25.5 - 3.7 kg/m2). Obesity and diabetes mellitus are directly related to the development of liver steatosis. Steatosis can occur not only due to metabolic disorders, but also as a result of the cytopathic effect of HCV (especially geno type 3) [1]. HCV ultimately disrupts lipid metabolism and leads to impaired formation and release of very low-density lipoproteins and the accumulation of triglycerides in hepatocytes. Another factor associated with the development of steatosis in HCV infection is alcohol consumption. Steatosis, regardless of other factors, is associated with the severity of inflammation and the progression of liver fibrosis. Possible mechanisms of this effect are associated with an increasing sensitivity of the liver affected by steatosis to oxidative stress and cytokine-induced damage [2]. On the other hand, the Turkish authors did not find a relationship between body mass index and the severity of liver fibrosis [3]. The literature provides information that a high level of glucose in blood serum is associated with an increased risk of significant liver fibrosis in HCV [1]. A correlation between serum glucose levels and fibrosis was also found in children with HCV [54]. It has also been shown that insulin-resistant diabetes is associated with severe fibrosis and cirrhosis of the liver in HCV [5].

The age of the patient at the time of infection. There are indications of the importance of the age of infection of patients in the pathogenesis of infection caused by hepatotropic viruses. Thus, chronic HBV infection develops in 90-98% of children born to HBeAg positive mothers as a result of perinatal infection. In infants, this figure decreases to 40-70%, in children aged 4-6 years — to 10-40%, while in adults, HBV persistence occurs only in 5-10% of individuals [5]. At the same time, there is an opinion that the chronization of the process and the progression of

fibrosis in adults is the higher the older the age of infection of a person. Bye It is proved that the increase in liver fibrosis occurs faster in persons infected after 40 years [2]. Among people infected with HCV during hemotransfusion at the age of 50 years or more, the average duration of time from hemotransfusion to the development of CP was 9.8 years, whereas among patients infected with hemo transfusion before the age of 50, the average period of time before the development of CP was 23.6 years prospective follow-up of patients did not exceed 20 years. All calculations of the expected time of CPU formation are based on mathematical models and are, accordingly, likely. Therefore, the question of the frequency and timing of CPU development remains open.

Activity of the pathological process. There is evidence that the growth of fibrosis and the formation of cirrhosis of the liver in viral hepatitis occurs with a greater frequency in persons with increased activity of the pathological process and a high degree of necro-inflammatory changes in the liver. In accordance with this, the normal level of AlAT in the blood serum is associated with the absence of progression of liver fibrosis [18], whereas the level of AlAT, at least 1.5 times higher than normal, is associated with rapid progression of liver fibrosis [6]. The Brazilian authors indicate that the level of aminotransferases exceeding three norms is associated with 2-4 degrees of liver fibrosis [11]. According to

H. Fonlaine et al. [7] in HCV, an increase in the level of fibrosis was noted in y 13.3% of y patients with low and y 43.8% of patients with high indicators of the activity of the pathological process. S. Herve et al the HCV RNA group of positive individuals with normal serum AlAT levels (80 people) CP was observed significantly higher than in the group of patients with elevated AlAT content (455 people) — 4 and 13%, respectively; at the same time, according to histological examination of liver tissue, the progression of fibrosis in the second group of patients was more pronounced, and the normal histological picture of the liver was more common in the first group (9 and 1%, respectively). R. Mathurin et al. [2] in their study, HCV patients were divided into two groups of 102 patients with normal (on average, 25 units/l) and elevated (on average, 127 units/l) AlAT levels. The authors found that in the first group, the degree of fibrosis (0.95 versus 1.8) and the average level of fibrosis progression (0.05 versus 0.13 units on the METAVIR scale per year) were lower than in the second.

At the same time, there is an opinion that there is no correlation between the level of cytokine transaminases and the activity of the pathological process with liver fibrosis. I. Kyrlagkitsis et al. [3] in the examination of 99 patients with HCV with a normal Conclusion

Thus, the data presented in the literature show that, despite a fairly large number of studies concerning the problem of CP in viral hepatitis, there is no definitive clarity on the factors contributing to fibrogenesis and the development of CP. The available data are sufficiently contradictory. Nevertheless, from the presented material, it is possible to distinguish the following factors that affect the course of fibrogenesis with the greatest frequency in the works of different authors: etiology of viral hepatitis, mixed infection of various hepatotropic viruses and HIV, genetic predisposition and features of the macroorganism, duration of infection, activity of the pathological process and the effect hepatotoxic agents (primarily ethanol). In the literature, only a few works are devoted to the problem of the CPU of y children. We have previously shown that in childhood, the formation of CP in the outcome of viral hepatitis, regardless of the etiology of the disease, occurs at a fairly early time from the moment of infection, is associated with increased activity of the pathologic process and does not depend on the age and method of infection, the presence and nature of previous and concomitant diseases, the genotype of the pathogen (with HCV infection) and the duration of the infection [83]. The totality of the above data gives reason to believe that the process of cirrhosis in chronic viral hepatitis is realized depending on the peculiarities of the macroorganism in specific environmental conditions.

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