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Research Article

Plasmapheresis in the Treatment of Chronic Liver Diseases

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Abstract

Chronic liver diseases are one of the most common diseases affecting hundreds of millions of people. Despite all the achievements of modern drug therapy, many of them are characterized by a progressive course with a high mortality rate. First of all, it is about viral hepatitis, the treatment of which is not always successful and results in liver cirrhosis and hepatocellular carcinomas. In their pathogenesis, the key role is played by accumulation of autoantibodies and other high-molecular toxic products that are not removed by the kidneys, which requires extracorporeal apheresis treatment, mainly plasmapheresis, which allows at least to stop the progression of such diseases, prescribing less toxic doses of drugs.

Keywords: Virus Hepatitis; Cirrhosis; Autoimmune Hepatitis; Toxic Hepatitis; Fatty Hepatosis; Cholestatic Hepatosis; Plasmapheresis

Introduction

Chronic liver diseases are a fairly large group of diseases that combine viral and other infectious and toxic liver damage, autoimmune and metabolic disorders, passing into liver cirrhosis and even hepatocellular cancer. Most of them are difficult to drug therapy and are one of the main causes of deaths. This manual explains the need for apheresis therapy, mainly plasmapheresis, in such liver diseases.

Virus hepatitis

Chronic hepatitis B is one of the most severe types of autoimmune diseases. It is known that after the acute hepatitis B chronicity occurs in 5-10% of patients, and according to U.S. statistics in the U.S. the number of patients with chronic hepatitis B was 1.25 million people and, in the world, reaches 180-350 million people [1]. Viral hepatitis B is the leading cause of death, reaching 786,000 per year due to complications such as cirrhosis, liver failure and hepatocellular carcinoma [2]. At the same time, deaths from chronic hepatitis B in 5 to 10 times higher than from acute, entering the top ten causes of death, 50 times greater than the frequency of deaths of HIV infection. Despite the introduction of vaccination, hepatitis B remains a major problem, as many patients are not even aware of its existence. However, the quality of life in chronic hepatitis B is significantly reduced.

On the scale of the Earth are infected with hepatitis B virus more than one third of the population (approximately 1 billion people) and about ¼ of them will develop chronic hepatitis, cirrhosis and primary liver cancer. Thus 1-2 million people die annually. In Europe, each year 1 million people are infected, of which about 90,000 will be chronically ill and 22,000 will die from cirrhosis or cancer. Unfortunately, HBV is not curable with today's medicine.

Approximately 15 million HBV patients have developed a hepatitis delta (HDV) infection on top of their HBV infection. The patients superinfected with this satellite virus suffer from a more severe disease development. Chronic HDV infection commonly results in the most rapidly progressive form of viral hepatitis; it is the chronic viral infection that is most likely to lead to cirrhosis, and it is associated with an increased risk of hepatocellular carcinoma. HDV infection is the only chronic human hepatitis virus infection without a therapy approved by the US Food and Drug Administration. Peginterferon alfa is the only recommended therapy, but it produces unsatisfactory results [3].

Chronic forms of hepatitis C in the United States affects about 4.6 million people [4]. Its effects are more severe because the hepatitis C virus (HCV) has the highest chronicity potential being the main reason for the formation of the whole group of chronic liver disease – chronic hepatitis, cirrhosis and hepatocellular carcinoma. Mortality from hepatitis C is 3 times higher than from hepatitis B. Across the Earth by patients with hepatitis C, there are much higher than in AIDS patients (40 million people), despite the fact that this hepatitis is the same incurable disease. Globally, HCV infection imposes a very high economic burden. It has been estimated that treatment of viral hepatitis C was worth $ 6.5 billion in 2012 and will reach $ 9.1 billion by 2024 [5].

There are cases of development and chronic hepatitis E, especially in people with immune disorders. Its manifestations may be jaundice, weakness, subfebrile.

Both acute, and chronic hepatitis can be caused also herpes viruses (a cytomegalovirus, Epstein-Barre's virus and herpes virus-6) with the same consequences, up to the fulminant forms.

What are the causes of such chronic viral hepatitis? It has been suggested that this viral infection "starts" and mechanisms of autoimmune hepatitis also. There is much evidence that viral infection, no matter how serious or, alternatively, it may mild course, causing a cascade of immune-pathogenicity reactions, leading eventually to the formation of autoimmune hepatitis. Confirming the autoimmune nature of chronic hepatitis (especially infection with the hepatitis C virus) is almost regular its combination with other types of autoimmune disease – vasculitis, glomerulonephritis, cryoglobulinemia, polymyositis, pulmonary fibrosis, porphyria, uveitis, cataract, keratitis, thrombocytopenia, etc. [6].

In particular, in the genesis of renal lesions leading consider circulating immune complexes containing antigen C. Very often, hepatitis C triggers the formation of membranoproliferative glomeruldonephritis, which is accompanied by the development and progression of renal failure. At the same time, such severe manifestations of renal failure may develop, which will require hemodialysis. Even after liver transplantation when immunosuppressive therapy helps build-level viremia HCV, symptoms may recur and nephrotic syndrome also [7]. Nevertheless, and against the background of hepatitis B severe membranoproliferative glomerulonephritis can develop also with quickly progressing renal failure.

Nevertheless, and at hepatitis B the serious membrano-proliferative glomerulonephritis with quickly progressing renal failure can develop that demanded carrying out intensive courses of a plasmapheresis [8].

HCV infection is often accompanied and cutaneous manifestations also, such as pruritus, urticaria, porphyria, lichen planus and even ulcers. In addition, these dermatoses long time can be the only manifestations of the underlying disease. Patients with chronic hepatitis C is often found autoantibodies – rheumatoid factor, an antithyroid immunoglobulin, autoantibodies to specific human hepatic lipoprotein, antinuclear and other mitochondrial antibodies.

Brain metabolic disorders are also common. In patients with hypertrophic cardiomyopathy, signs of HCV infection are found much more often than in the control groups. Signs of atherosclerosis are also revealed with increasing thickness of carotid artery intima and epicardial fat. The HCV infection can promote also lymphoproliferation, up to development of a non-Hodgkin lymphoma. Since HCV is lymphotropic, it can be a trigger of clonal B-cell proliferation. Indeed, markers of hepatitis C are often found in non-Hodgkin B-cell lymphoma. HCV could play a direct role in cellular transformation, particularly in de novo large B-cell lymphoma. On the other hand, the toxic effects of chemotherapy at this type of lymphoma are also the most severe with concomitant chronic hepatitis C.

It is quite often possible to observe also cases of infection with a hepatitis C virus against a chronic hemodialysis. Thus the risk of a lethal outcome considerably increases, and antiviral therapy in such cases is connected with serious side complications.

HCV viral infection is involved in the pathogenesis and mixed cryoglobulinemia, both through direct formation of immune complexes, leading to vasculitis and exciting lymphoproliferative processes underlying this disease. Cryoglobulinemia accompanies chronic hepatitis C in 36-45% [9]. This is associated with a particular lymph-tropism HCV and may also be responsible for the transformation of mixed cryoglobulinemia in malignant lymphoma. HCV-infection apparently also involved in the pathogenesis of idiopathic B-cell non-Hodgkin's lymphoma in the same pathogenic mechanisms. At the same time, cryoglobulinemic vasculitis may be accompanied by multiple fingers necrosis, moreover, in chronic hepatitis C, both arterial and venous thrombosis develop. There-

fore, in the treatment of this complication, plasmapheresis also finds its application. The plasma exchange is indicated also at accession of Waldenström macroglobulinemia.

Anti-HCV antibodies can be detected in 72% (!) of patients with "autoimmune" hepatitis, 50% of patients with alcoholic hepatitis, 66% of drug addicts and in 2.4% of healthy individuals. In addition, 21.3% for HBsAg positive patients with chronic hepatitis were positive and HCV-viruses, which means more significant than you might think, the spread of this kind of viral infection.

Virus hepatitis treatment

It was established that interferon is widely used in the treatment of viral infections may even induce autoimmune processes and cause exacerbations in 4-19% of patients. On the background of interferon in these patients showed a twofold increase in the frequency of formation of autoantibodies to human hepatic lipoprotein, antinuclear and mitochondrial autoantibodies. Interferon possesses cardiotoxicity and can trigger the development of pericarditis. Interferon may contribute to ischemic retinopathy, retinal hemorrhages, optic neuritis, keratoconjunctivitis, uveitis, sometimes with loss of vision [10].

Moreover, in patients with autoimmune predisposition interferon can trigger the development of autoimmune thyroiditis, the damage of the eye muscle, chronic inflammatory demyelinating polyneuropathy and multiple need sclerosis: It was described the formation of severe polyradiculopathy with the advent of anti-ganglioside antibodies in the treatment of hepatitis B using interferon-alpha, which was stopped only after a course of cascade plasmapheresis [11].

In the experiment on mice application of γ-interferon animal skin causes the formation of antinuclear (anti-DNA) autoantibodies, which were postponed in the vessels of the glomeruli of the kidneys and lead to severe proliferative glomerulonephritis. K.-P. Maier [12] explicitly states that the use of interferon in patients with autoimmune hepatitis may lead to severe course and even death.

Among the factors that trigger the formation of autoantibodies, are cytokines IL-1β and TNF-α that often present in the formulations of interferon-α and can stimulate an autoimmune disorder with interferon. Their level increases even when vaccination against viral hepatitis A and B, as well as against staph, proteus and Pseudomonas infections. There are also reports of no effect of interferon-α in concomitant HCV- and HBV-infection [13].

Many patients can not tolerate interferon therapy because of the large number of side effects. In particular, reported a significant increase in levels of total cholesterol, triglycerides, very low density lipoproteins, while reducing high-density lipoprotein in the treatment of interferon-α. Other side effects of interferon describe cutaneous manifestations (skin dryness and itching, erythema, seals, reversible alopecia, psoriasis and Herpes labialis provocation).

Interferon therapy can contribute to the development of ischemic retinopathy, retinal hemorrhage, optic neuritis, keratoconjunctivitis, uveitis, sometimes with loss of vision. And in addition, vasculitis, glomerulonephritis, cryoglobulinemia, thyroiditis and other autoimmune diseases can be developed also.

At least 50% of patients remain chronically infected. IFN-α therapy was effective in only 25% of patients with HCV. Assuming that the CD8+ T-cells prevented the therapeutic effect, they have involved the incorporation of monoclonal antibodies to CD8+, leading to a high ratio CD4+/CD8+ from 1.6 to 3.0 during treatment with a gradual decline to 2.3 after 1 year following the last infusion of monoclonal antibodies. In these patients gradually decreased ALT and clinical improvement occurred, which could not be achieved by interferon α, β and γ [14].

HCV have multiple genotypes, with genotype 1b is the most chronicity and it is more resistant to interferon. Even more modern concomitant therapy with INF-alpha-2a and ribavirin does not always lead to success, especially in elderly patients. More than half of patients with chronic hepatitis C are insensitive to interferon.

On the other hand, should take into account the enormous cost of an intensive course of treatment with interferon, which can reach £30.000 to £100.000 [15].

Based only on clinical and laboratory criteria for chronic hepatitis C is virtually indistinguishable from autoimmune hepatitis. It must be borne in mind that the absence of antinuclear or antibod-

ies to smooth muscle does not exclude the presence of autoimmune hepatitis. That is why we must be careful in appointing interferon for hepatitis C patients who have not excluded autoimmune hepatitis. At the same time, as in chronic hepatitis C can never exclude its autoimmune character, it becomes clear high risk of interferon in such cases.

However, the classical approach to the treatment of such patients as having autoimmune pathology with chronic hepatitis C may result in an increase in virus replication with the risk of deterioration of the clinical course. Besides, there are no certificates also that the interferon therapy reduces risk of the subsequent emergence of a hepatocellular carcinoma.

There is a serious clinical dilemma – both interferon and corticosteroids almost impossible to use. However, only plasmapheresis is a decent alternative antiviral therapy for hepatitis C [16]. Removing autoantibodies plasmapheresis helps restore reparative possibilities of hepatocytes, and, on the other hand, removing the "toxic press" from the immune system should stimulate its normalization.

In recent years, more widespread acquire liver transplantation for chronic hepatitis, cirrhosis and liver tumors. However, even after such operations HCV persists, leading to relapse of chronic hepatitis in 50-60% of patients. Three-month course of ribavirin promotes normalization of aminotransferase levels and histological improvement, but after the cessation of such therapy biochemical signs of hepatitis return again, indicating that the inability even of ribavirin prevent the progression of fibrosis in patients with autoimmune hepatitis C [17].

Intrigue HCV-infection is prolonged "light gap" from infection to clinical manifestations of liver disease – up to 10-20 years up to the development of cirrhosis or hepatocellular carcinoma. However, such "asymptomatic" is quite relative. Indeed, may not hyperbilirubinemia and signs of portal hypertension. However, careful analysis of these patients reveals a less optimistic picture. In such patients, a significant fatigue observed in 78%, depression in 53%, joint pain – in 53%, weakness – 51%, a sleep disorder in 51%, abdominal discomfort – 51%, weight loss in 43%, headaches – 39%, itching in 39%, ikterus in 20% cases. This suggests that these patients have a significant deterioration in the quality of life, which contradicts the common opinion that chronic hepatitis is virtually asymptomatic until signs of cirrhosis. It is possible that such practices contribute to the above other autoimmune related diseases, are also still in the subclinical phase.

Nevertheless, we must not forget that in the coming years, millions of carriers of hepatitis C virus become seriously ill with a sharp increase in mortality from chronic hepatitis and cirrhosis.

In recent years, the treatment of hepatitis C is actively implemented direct-acting antiviral (DAA) therapy, based on a combination of drugs such as sofosbuvir, ledipasvir, simeprevir, paritaprevir, dasabuvir. This increased the effectiveness of drug therapy from less than 50% to more than 90%. However, the full recovery of liver function is quite illusory. The levels of urea, nitric oxide, methionine and cyclic polyamines remain elevated. Often, after viral eradication, tests remain, indicating continued disturbances in the liver [18]. There is another limitation of the use of DAA-therapy – in the presence of concomitant membrano-proliferative glomerulonephritis some drugs of direct action, such as sofosbuvir, are contraindicated, because they have nephrotoxic effect. Therefore, such therapy should be combined with plasmapheresis, corticosteroids and rituximab.

However, in hepatitis C, there are multiple extrahepatic concomitant diseases associated with the appearance of systemic immune disorders – diabetes, cryoglobulinemia, vasculitis with kidney damage, cardiovascular and neuro-psychiatric disorders, not to mention the actual liver lesions – fibrosis and cirrhosis of the liver, fatty hepatosis, hepatocellular carcinoma [19]. And how much viral eradication will contribute to the reverse development of the already occurred disorders is not yet clear [20]. Such patients still have a risk of developing hepatocellular carcinoma, which requires constant monitoring – control of α-fetoprotein and elastography, especially in cases of advanced fibrosis and in elderly people. And with the existing hepatocellular carcinoma hepatitis C treatment is less successful.

There are observations that accompanied reactivation of hepatitis B and autoimmune hepatitis against the background of such DAA-therapy [21]. With the effectiveness of viral eradication, signs

of fibrosis and fatty hepatosis are also preserved. In the treatment of hepatitis C using pegylated interferon alpha may develop rhabdomyolysis with increasing levels of creatinine phosphokinase [22].

Thus, and more modern anti-virus therapy of direct action is not a complete guarantee of both the recovery of already occurred before liver lesions and the risk of hepatocellular carcinoma.

All the above facts convincingly prove autoimmune nature of chronic hepatitis, almost naturally developing after suffering the viral hepatitis B, C and D, and if so, it only plasmapheresis helps to mitigate its manifestations and postpone the inevitable outcome. This raises the question of the appointment of preventive courses of plasmapheresis in the very early rehabilitation period after acute viral hepatitis (especially C and D), as there is no guarantee that will avoid chronic process [23]. Because the occurrence of autoantibodies is provoked both the viral infection, and the changes in the antigenic structure of hepatocytes, which occurred at the height of the disease. "Random" HCV detection must also raise the question of holding such preventive courses of plasmapheresis. Given the same factual incurable viral infection of this kind, even when 10-20 years asymptomatic develop signs of chronic hepatitis, it is necessary to repeat such courses of plasmapheresis at least once a year for the rest of life [24]. On the background of improvement of the general state, there was a decrease in the levels of bilirubin, ALT, ESR, circulating immune complexes, alkaline phosphatase, medium-sized molecules. Sessions of plasmapheresis were combined with extracorporeal laser (HeNe) irradiation of blood and external irradiation of the liver area. Repeated courses of plasmapheresis provided more long-term remission. At aggravations of chronic hepatitis results of use of a plasma exchange were the best, than at drug treatment by means of an entecavir [25].

In cases of advanced chronic hepatitis C with the development of hepatic encephalopathy plasmapheresis also contributed to the improvement of overall health and eliminate the symptoms of intoxication with a decrease in the levels of bilirubin and transaminase almost back to normal.

As an additional illustration we give an example from our own clinical practice

Patient V., 80 years old. 33 years ago, in 1985, 10-fold increase of the ALT level incidentally was revealed, and at ultrasonic research the increase and consolidation of a liver with symptoms of portal hypertensia and increase in diameter of a vena porta to 15 mm is revealed. Only in 1993 became clear an etiology – antibodies to hepatitis C are found. Nevertheless, since 1985 a plasma exchange course on 4 sessions with removal up to 1–1,5 liters of plasma each time was annually performed. The ALT levels were all this time at the normal or subnormal levels, and ultrasonic research in 2012 showed normalization of the sizes and structure of a liver with reduction of the vena porta diameter to 12 mm. There were no signs HCV viremia also though the HCV test was constantly positive. All this period the health was satisfactory. Any special medicamentous therapy it wasn't carried out.

The given example confirms our concept of preventive carrying out courses of a plasma exchange right after detection of viral hepatitis C.

However, liver transplant patients with chronic hepatitis C does not eliminate the prospects injury donor liver. Moreover, often the development of cirrhosis in the transplanted liver is more intensive than before transplantation. In such cases, used a cascade plasmapheresis method there were not only selectively removed autoantibodies but do complex HCV therapy (interferon, ribavirin, including cascade plasmapheresis), HCV RNA caused a reduction to 8.2% and 0.7% on the 5th and 30th days of treatment, respectively. In three patients, to whom such therapy was carried out as a preventive measure, did not show recurrence of the disease even one year after treatment, and the patient who has already developed signs of fibrous cholestatic hepatitis has been fast inverse dynamics transplanted liver lesions. There was sharp decline of amount of hepatitis C viruses in the blood (and without the additional use of antiviral drugs) using cascade plasmapheresis. The cascade plasma exchange was used even in the presence of an acute renal failure against the background of a hemodialysis that promoted also decrease in level of a viremiya.

Cascade plasmapheresis was used for the purpose of viral decontamination and in patients who have previously undertaken therapy with interferon or its combination with ribavirin was unsuccessful [26]. Nevertheless, how many wouldn't delete these vi-

ruses but if at least the part of them remains, it doesn't prevent a repeated exacerbation of a disease.

Alcoholic chronic hepatitis and liver cirrhosis

They occur as a result of the formation of free radicals under the action of ethanol with damage to cell membranes and organelles. The oxidation product of alcohol – acetaldehyde – is also providing free radicals. Alcohol also helps to release cytotoxic cytokines (IL-1, IL-6, IL-8, TNF-α). The number of cytotoxic T-lymphocytes in the liver also increases, contributing to the development of necrosis, fibrosis, and then cirrhosis [27]. In addition, alcohol contributes to the progression of other forms of chronic hepatitis.

We should also note the leading role of chronic alcohol intoxication in the development of both primary chronic hepatitis and alcoholic cirrhosis. Moreover, there is evidence that chronic alcoholism develops immunosuppression with suppression ability to fight against hepatitis, contributing to a more severe course of illness and chronicity. Found that drinking more than 90 g of alcohol per day, significantly increasing the severity of chronic hepatitis. This underlines the need for abstinence all kinds of alcoholic beverages in already developed chronic liver disease and even in those cases when you can expect a high probability of such process in HCV- infected individuals.

In chronic hepatitis of alcoholic genesis, plasma exchange courses also contribute to the stabilization of the state with a decrease in the levels of bilirubin, ALT, ESR, alkaline phosphatase and a decrease in the size of the liver according to ultrasound. In the future, when the use of hepatic and diet (elimination of alcohol) it is possible to achieve quite persistent and prolonged remission.

Fatty hepatosis (steatosis)

It is a growing health problem in many countries of the world associated with increasing morbidity and mortality [28]. It is also defined as non-alcoholic fatty hepatosis. It occurs in 30% of the total population and in 40% to 70% of obese [29]. It often accompanies other metabolic disorders – obesity, diabetes. With insufficient control of sugar level in dibet, the accumulation of excess glycogen in hepatocytes (glycogenic hepatopathy) is possible. Possible its connection and with the consequences of Helicobacter pyloti infection and inflammatory bowel disease (Crohn's disease, ulcerous-necrotic colitis), when, due to the greater porosity of the intestinal wall to the liver go toxic metabolites [30]. The development of fatty hepatosis and as a result of the general irradiation of the body of children in the treatment of tumors is described. At the same time developing insulin resistance, dyslipidemia involving and liver.

It is accompanied by fibrosis with hepatocyte apoptosis, leading to endothelial dysfunction with increased ALT and AST levels followed by the development of cirrhosis and in the near future it is expected to be the main indication for liver transplantation. But even after transplantation, there is a high risk of re-development of fatty hepatosis in the transplant, if its main causes are not removed. The frequency of hepatocellular carcinoma associated with fatty hepatosis is also increasing [31]. Fatty hepatosis also contributes to the development of atherosclerosis and cardiovascular diseases. Since there are no specific methods of treatment or prevention of fatty hepatosis, it puts the testimony and to conduct preventative plasmapheresis at the first signs of this pathology.

Liver cirrhosis

A serious complication of viral hepatitis is the development of liver cirrhosis with imminent portal hypertension and profuse bleeding from the varicose veins of the esophagus and stomach [32]. But against the background of developing cirrhosis with severe chronic liver insufficiency courses of plasmapheresis and cryo-plasmasorption also contribute some stabilization of the patients. Thus, in these patients as a result of the treatment of hepatic insufficiency it was stoped encephalopathy phenomenon, decreased ascites, decreased level of cholestasis, and prothrombin index rose more than 60%. Partial reimbursement of plasma after cryo-treatment helped stabilize the level of total protein in the blood. Plasmapheresis also helps in alleviating itching which often accompanies cirrhosis, for up to 6 months [12].

In liver cirrhosis complicated by diuretic resistant ascites plasmapheresis was performed, and as a replacing solution, it was used ascites derived with paracentesis, which was subjected to ultrafiltration and cryosorbtion. It restored the blood circulating volume, reduced protein loss, reduced bilirubin and transaminases level. In extremely severe hepatic insufficiency positive results obtained using the system MARS, when the plasma obtained by membrane plasmapheresis further passes through a special column, wherein

the albumin adsorbed related toxins are then removed by dialysis, and then returned to the patient a purified.

It was reported the case that after removal of the right lobe of the liver for primary hepatocellular carcinoma on a background of already developed cirrhosis of the liver due to hepatitis B the manifestations of cirrhosis increased with the accretion of ascites, but plasmapheresis sessions allowed the restoration of liver function and reduce portal hypertension at the significant period. Such experience has been used and later [33].

Hepatocellular carcinoma (HCC)

It is the most frequent (up to 90%) of all primary liver tumors with a frequency of up to 20 per 100,000 population. HCC is the leading cause of liver-related mortality in the world [34]. Even when transarterial chemoembolization and radiofrequency ablation are performed, the median survival is 22.8 months. The main causes are viral hepatitis B and C. At the same time, even after the cure and disappearance of viral particles in the blood remains a risk of 7 to 13.5% of HCC [35].

Autoimmune hepatitis

"Primary" autoimmune hepatitis is chronic progressive necroinflammatory liver disease as a result of autoantibodies: to a specific hepatic lipoprotein, antinuclear, anti-smooth-muscles, antineutrophil cytoplasmic, and several others. It occurs in both adults (mostly women) and children. Autoimmune hepatitis, as mentioned above, may occur as a result of interferon-treatment viral hepatitis. Under the influence of a number of drugs, viral infections and even previous surgical operations, acute liver damage may develop as the first manifestation of the development of autoimmune chronic hepatitis [36]. The pathogenesis of autoimmune hepatitis involves cytotoxic T-lymphocytes, whose concentration in the liver increases. Natural killer cells contribute to the development of chronic hepatitis and in the presence of viral hepatitis B. Plasma exchange allow in 85% of cases to improve the overall condition of the patients and significantly reduce the level of bilirubin, ALT and AST in remission up to 10 months.

Wilson's disease

It may be development of chronic hepatitis and in some metabolic disorders involving the accumulation and deposition of copper in the liver and brain in Wilson's disease. There may be different degrees of liver damage, up to fulminant hepatic failure. Cerebral manifestations are characterized by rigid-hyperkinetic symptoms. There are perhaps the development of hemolysis with hemolytic anemia, hemolytic jaundice, thrombocytopenia and leukopenia. Used in the treatment of this disease chelates (D-penicillamine, kuprenil) have hepato- and nephrotoxicity and often lead to serious complications. Plasmapheresis helps to reduce the copper content in the body and to stop developing complications. Plasmapheresis was used also as an adjunctive treatment modality in cases of fulminant liver failure due to Wilson's disease [37].

Idiopathic hemochromatosis

Close pathology is idiopathic hemochromatosis, accompanied by the accumulation of iron. Therapeutic apheresis in these cases may also be useful, and in this case more effective removal of iron-containing red blood cells, ie, regular bloodletting. To reduce iron levels can be used erythrocytapheresis and plasmapheresis were done every 3 weeks, the number of procedures and volume of red cells or plasma removed determined on the basis of each patient's haemoglobin, haematocrit, and serum ferritin concentration [38].

Exogenous toxic hepatitis

Drug induced htpatitis is a form of jatrogenic illnesses. Essentially there is no medication that would not cause damage to the liver. Protein P450 system in the metabolism of drugs contributes to the formation of toxic metabolites. Pregnancy increases the risk of drugs toxicity. Hepatotoxic are many anticancer drugs – methotrexate, anthracyclines, as well as a number of other drugs (allopurinol, coumarin, diclofenac, methyldopa, minocycline, fentoin, sulfosalicil). Widely used in hypertension, nifedipine is hydralazine and can also cause severe liver damage, requiring many months for treatment. At the same degenerative processes in the liver can lead to the development of cholestasis and veno-occlusive disease of the liver. All this makes once again refer to the methods of extracorporeal detoxification [39].

Exogenous toxic hepatitis often develops when receiving such a tuberculosis drug isoniazid. Especially dangerous is the combination of the latter with rifampicin. Evolving with hepatocyte necrosis accompanied mortality is 10 times greater than in viral hepatitis. Although rare (1 in 10,000 anesthesias) but may develop severe liver damage as a result of inhalation of halothane. Even such a "harmless" drug like paracetamol, at doses above 10 g can cause necrosis of hepatocytes fatal. Described the development of severe acute hepatitis also omeprazole used in the treatment of hyperacidity gastritis. Cholestasis can develop and owing to regular reception of contraceptive preparations also. The plasma exchange course to 9 sessions allowed to normalize this pathology [40].

Development of an acute damage of a liver with a fulminant liver failure after reception of the paracetamol (acetaminofen) which is already mentioned above is frequent that in some cases demanded even transplantation of a liver. Timely use of courses of a plasma exchange in such cases promotes restoration of functions of a liver [41].

These data also underscore the advisability timely excretion of these hepatotoxic drugs by means of a plasmapheresis to reduce the scale of injury and prevent the progression of pathological disorders of the liver. All this forces to address to methods of an extracorporeal detoxification once again [42].

Primary biliary cirrhosis

It is a chronic, progressive autoimmune cholestatic disease. Occurs mainly in middle-aged women with a frequency of 3.9 - 15 per 1 million population. At this disease occurs degradation small intralobular bile ducts with the transition fibrosis and cirrhosis with portal hypertension development. Manifested yellowness of the skin, weakness, persistent pruritus, osteoporosis, hypercholesterolemia with xanthomas and xanthelasma. At laboratory monitoring revealed marked cholestasis with increased levels of bilirubin, transaminases, immunoglobulin M, detect antibodies against mitochondria.

Important role in the pathogenesis of oxidative stress plays a significant accumulation of free radicals, malondialdehyde and 8-isoprostane due to lower antioxidant activity, vitamin A and selenium.

The common treatment of the first line is ursodeoxycholic acid, but this does not always have the proper effect. However, 95% of patients have highly specific antimitochondrial autoantibodies. As a leading etiological factor of the disease is also accumulation of autoantibodies, the substantial assistance to patients may have plasmapheresis. Indeed, as a result of the plasmapheresis course total bilirubin decreased by 25-30%, ALT and AST – by 12-15%, and normalized levels of CIC and medium-sized molecules, which helped to reduce the itching and asthenoneurotic manifestations [43]. According to recommendations of ASFA, in some cases, knocking over of a persistent skin itch requires carrying out a course of a plasma exchange 2-3 times a week on an extent of about four weeks [44].

Close to this liver disease also is primary sclerosing autoimmune cholangitis –chronic cholestatic liver disease of unknown etiology. As at patients with autoimmune hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis can have anti-mitochondrial (AMA), anti-neutrophil cytoplasmic (ANCA), intestinal antibodies anti-ribosomal antibody (ARA). Sclerosing cholangitis is often accompanied by IgG4-antibodies with infiltration of T-lymphocytes and the concomitant development of cholecystitis, retroperitoneal fibrosis, tubulo-interstitial nephritis, interstitial pneumonia, prostatitis, and lymphadenopathy.

Often, development and combinations of autoimmune hepatitis with primary biliary cirrhosis and primary sclerosing cholangitis, and sometimes with ulcerative colitis and Crohn's disease. In particular, inflammatory bowel diseases are found in 75% of patients with primary sclerosing cholangitis. At the same time, most drugs prescribed for ulcerative colitis and Crohn's disease (in particular – methotrexate and thiopurines), are highly toxic to the liver [30]. In all such cases therapeutic apheresis also helps to smooth the general toxic effect, as in the development of acute hepatitis, and chronic exposure to toxicants hepatotropic.

Budd-Chiari syndrome

It occurs more frequently in antiphospholipid syndrome and is characterized by progressive obstruction of the hepatic veins from the lobular vein to the confluence of the inferior vena cava into the right atrium. Manifested hepatomegaly, abdominal pain, ascites. It can occur acutely and malignant, but mostly for its chronic and asymptomatic. In the latter case, there is an insignificant increase of

the liver by increasing the background activity of transaminase and alkaline phosphatase in conjunction with hypoalbuminemia. Nevertheless, such a chronic metabolic disorder of the liver cells leads to fibrosis and cirrhosis [45].

Autoimmune nature of the disease involves the use of plasmapheresis to remove as antibody and vaso-active and pathological metabolites. At an intensive course of plasmapheresis in the treatment of acute proceeds Budd-Chiari syndrome with obstruction of blood flow in the hepatic veins and rapid progression of ascites and oliguria due to high levels of AST, ALT, LDH and bilirubinemia. As a result, the treatment of positive dynamics – reduction in liver size and ascites with incomplete recanalization of hepatic veins.

Crigler-Najjar syndrome

It is characterized by sharp increase of level of non-conjugated bilirubin, up to development of encephalopathy, owing to a congenital lack of the enzymes promoting bilirubin elimination (uridine diphosphate glycosyltransferases) [46]. The plasma exchange in such cases also promoted knocking over of such serious manifestations of an illness [47].

Conclusion

Thus, the picture of homeostasis disorders, leading to an increase in organ disorders, is becoming increasingly clear. The presented materials indicate a variety of causes of liver damage, but they are all combined pathogenetic mechanisms associated with the accumulation of a number of toxic products that damage the liver parenchyma. In this case, many pathological substances accumulate, the size of molecules which does not allow their excretion by the kidneys, while the liver is also unable to destroy them. On the other hand, the fact of their accumulation suggests that no drugs can help them to leave the body.

To date, significant progress has been made in the treatment of viral infections, but these drugs themselves are not safe and are not always able to interrupt the already existing pathological liver disorders that still require the use of plasmapheresis. Therefore, in all these cases, plasmapheresis is a pathogenetically justified method of treatment and prevention of progression of liver damage.

In such cases, it is sufficient to remove up to 1 liter of plasma with the replacement of only crystalloid solutions for 4 such sessions of plasmapheresis, held every other day, which can be provided even in outpatient settings. In the future, it is necessary to regularly repeat such courses up to two times a year. Thus, it is possible to effectively interrupt the progression of the disease and the transition to the development of irreversible liver damage in cirrhosis and hepatocellular carcinoma. But even with far-reaching processes, plasmapheresis can significantly improve the condition of patients.

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