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Infection with hepatitis C virus as a cause of nervous system disorders

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ABSTRACT: Hepatitis C is a disease caused by hepatitis C virus (HCV), which prevalence may reach over 5% in some countries. Untreated infection may lead to death due to cirrhosis or hepatocellular carcinoma. Almost 80% of infected patients occurs as asymptomatic. Symptoms of hepatitis C may include jaundice, nausea, vomiting, fever or muscle and joint pains. Even half of the patients experience nervous system disorders, due to the affinity of some types of HCV to nerve cells. It is also estimated that up to 30% of patients with chronic hepatitis C will develop cirrhosis within 25-30 years. Currently, the vast majority of infected patients can be cured thanks to the introduction of direct-acting antivirals (DAAs).

Key words: hepatitis C virus, HCV, neurocognitive disorders, nervous system disorders

1. INTRODUCTION

Hepatitis C virus (HCV) belongs to the Flaviviridae family and hepacivirus genus. The virus was discovered in 1989 by using molecular methods and it was then ascribed with responsibility for more than half of the cases of chronic hepatitis [1-3].

HCV is a small virus containing capsid with genetic material (single-stranded RNA) [4]. The capsid is surrounded by the envelope with glycoproteins E1 and E2. Glycoproteins allow the virus to enter the host cell by attaching to the receptor and fusing the envelope with the cell [5]. The sequence of nucleotides in the genetic material can vary by as much as 30-50%. Despite such differentiation, all known types are hepatotropic and pathogenic. There are 11 genotypes with a different nucleotide sequence, of which six are major. Genotype 1 is the most widespread (46% of all HCV infections). They differ among themselves, inter alia, the speed of disease progression or resistance to treatment [1, 3, 6].

It is estimated that around 71 million people in the world are chronically infected with HCV and it is unevenly distributed between countries [1, 7]. Over 350,000 people with HCV

die each year in the world, mostly due to the liver cirrhosis or hepatocellular carcinoma (HCC) [8, 9]. The percentage of people infected ranges between 0.5% (in Australia) up to 6.5% (in Pakistan). In the case of pregnant women, the risk of infection of the newborn babies is low and amounts to less than 5%, which is not of great epidemiological significance [1].

2. DIAGNOSTICS

It is estimated that only 15-20% of people infected with HCV are aware of the disease [7]. WHO adopted a strategy that aims to achieve 90% reduction of morbidity and 65% reduction of mortality by 2030, which would be realistic if the screening algorithm was simplified [8, 10]. It is worth to point out that the infection may not show symptoms in up to 80% of patients, therefore the main method of diagnosis is to examine high-risk groups for anti-HCV antibodies [6].

There are three different diagnostic methods. The first is based on the detection of IgG antibodies in the ELISA test, the second relies on the detection of HCV core antigen (HCV-Ag), the last one is based on the detection of viral RNA by PCR method (nucleic acid testing- NAT) [7].

Detection of anti-HCV antibodies does not distinguish between past infection and active infection, it allows detection of HCV RNA by testing nucleic acids. Due to the cost of doing NAT, its use is limited. An alternative method is to test the HCV core antigen (HCV-Ag). It is reliable in most cases, but its sensitivity is reduced with viral loads under 104 IU / ml. It allows you to quickly and cheaply diagnose active infection, and to evaluate the antiviral treatment [7, 11]. In addition, the genotype should be determined, which will allow to determine drug doses, virological monitoring procedure and treatment time [4].

3. ROUTES OF TRANSMISSION

Hepatitis C virus is transmitted to the main parenteral path. The highest risk of infection have people using drugs with non-sterile equipment. Another cause of infection are an absence of aseptic in a dental or medical treatment. High risk are blood transfusion or organ transplantation [12, 13]. Transmission of the virus by sexual means between a monogamous heterosexual couple is small and amounts to 0-0.6%/year. Having many sexual partners increases the risk of 0.4-1.8%/year. The type of sexual practices used is significant: in couples using traumatic forms of intercourse (unprotected anal sex, fisting) significantly increases the risk of getting sick [14]. Vertical infections are 1% of pregnancies from HCV-positive mother [15]. Living with an HCV positive person in one flat does not increase the risk of infection, provided that appropriate precautions are taken in dealing with blood and devices that may be in contact with it, such as razors, toothbrushes. An important aspect is the fact that 40% of patients fail to determine the risk factor that could lead to infection with the virus [16].

4. SYMPTOMS

Chronic hepatitis C causes ca. 27% of all cirrhosis in the world [17]. It is estimated that about 20-30% of infected people develop cirrhosis with its complications in 20 years: portal hypertension, esophageal varices, liver failure. Symptoms, mainly caused by decompensation of liver failure are jaundice, ascites, spontaneous bacterial peritonitis, pruritus, hepatic encephalopathy [12, 13, 18-20]. Cirrhosis is a strong risk factor for the development of hepatocellular carcinoma (HCC). The risk of developing HCC increases by 1-4% with each year of the disease [13]. 40% of patients with chronic hepatitis C die from liver cancer. Chronic infection with this virus is one of the main reasons for the need for liver transplantation in patients around the world [16].

The extrahepatic symptoms of chronic hepatitis C are more often manifested in people who have not developed hepatic symptoms. At first glance, they are not characteristic of hepatitis C, which may cause delay in establishing the correct diagnosis and implementation of treatment [17]. One such manifestation is the lymphatic system diseases. HCV is lymphotropic, resulting in continuous sensitization of B lymphocytes and their proliferation, which is the cause of non-Hodgkin's lymphoma B cells. Another common disorder is cryoglobulinemia, mainly type II. It is caused by the formation of pathological antibodies, mainly monoclonal IgM and polyclonal IgG in the patient's plasma. Antibodies are detectable in up to 60% of HCV infected patients, with clinical picture such as purpura, dry eye syndrome, nephropathy or arthralgia miałgia occur in only 4 - 40% of patients [18, 20, 21]. Other extrahepatic symptoms are kidney diseases (mainly membranous-proliferative glomerulonephritis), endocrine disorders (hypothyroidism, Hashimoto's disease), metabolic disorders (insulin resistance, type 2 diabetes) and rheumatic diseases (rheumatic arthritis) [12, 18, 21] Chronic inflammation in the organism can also lead to an increased risk of cardiovascular events [22].

About half of patients with Hepatitis C virus have symptoms associated with the central nervous system (CNS) [23, 24]. The variety of viral sequences in brain and liver tissue suggests an independent virus evolution in the CNS, which means that the brain appears to be a suitable place for replication virus [25-27]. Among CNS symptoms in patients with hepatitis C, cerebrovascular events, encephalopathy, encephalomyelitis and psychiatric and cognitive disorders can be found [28, 29].

5. IMPACT OF HCV ON NERVOUS SYSTEM

Cerebrovascular events

In the majority of cases, cerebrovascular events are associated with the presence of mixed cryoglobulinaemia [30, 31]. In chronic hepatitis C infection, cerebrovascular events are more frequent than the majority of the general population [32]. Enger et al., Gutierrez et al. and Hsu et al. have shown that people infected with hepatitis C have a higher risk of stroke than healthy people, which means direct involvement of cerebral vessels through their chronic inflammation [33-35]. In addition, HCV infection is proving to be an independent factor of stroke [32]. On the other hand Younossi et al. did not find a relationship between stroke and hepatitis C infection [36]. However, it should be noted that this study was not standardized in terms of race, sex or hypertension in the subject [32].

In chronic hepatitis C infection, there is an increased risk of hepatitis C receptor molecules on the surface of the blood-brain barrier endothelial cells [37]. Which means that this virus can theoretically cause obstructive vascular disorders [32]. A role in remodeling of the arteries causing destabilization of the atherosclerotic plaque by cracking and erosion [38]. Inflammation is a key mediator of thromboembolism [39]. This may suggest an increased risk of ischemic stroke during chronic hepatitis C [40].

Inflammation and CNS symptoms

Inflammatory disorders of the central nervous system in the course of hepatitis C infection are undisputable [32]. Histopathologically manifested by infiltration of perivascular T lymphocytes, microglial nodules, loss of neurons as well as acute demyelination with infiltration of parenchymal cells [32, 41, 42]. For clinical symptoms of central nervous system inflammation include: spastic quadrilateral paresis sphincteric dysfunction, loss of sensation as well as change of consciousness, psychomotor agitation, hemiparesis, hemianopausal urinary retention and other neurological defects [32, 43].

Cognitive and mental disorders

Cognitive and mental disorders occur in approximately 30% of patients infected with hepatitis C. Cognitive disorders are most often mild disorders [44]. They manifest inadequate concentration rate or decreased ability to learn [45]. There are also symptoms much heavier, for example, impairment of executive functions, such as lack of reasoning ability, abstraction, inhibition of verbal response or dementia [45-48]. Despite the huge amount of evidence for possible association with hepatitis C virus infection and cognitive impairment Hilsabeck et al. and Córdoba et al. did not find any evidence between infection and cognitive impairment [49,50] However, test results may be questionable due to the small number of subjects [32].

Referring to mental disorders caused by chronic hepatitis C infection, they cause impairment of quality of life due to chronic fatigue manifested by physical and mental exhaustion, frequent headaches, osteoarticular pain and sleep disorders [51, 52]. Other symptoms include depression in about 15% of patients and anxiety and panic in about 6% of patients [53, 54]. There have been reports of patients treated unsuccessfully in a psychiatric center due to an undiagnosed or incorrectly diagnosed mental illness in whom the correct diagnosis showed infection with the hepatitis C virus, and after the inclusion of appropriate treatment the patient's mental state improved [55].

Psychiatric disorders during the treatment of hepatitis C

Viruses that, parallel to other symptoms, cause mental disorders are rare. Also worth to consider is the earlier mental basis of these disorders - patients diagnosed with HCV may already present personality disorders such as drug addiction, alcoholism, mood disorders, and hypersexuality before the infection. Also, as it was previously mentioned, some kinds of HCV [56].

Treatment with interferon (IFN), which is very effective in the treatment of hepatitis, is also not indifferent to the patient's psyche - up to 70% of patients treated with IFN develops depression. Probable cause is a disorder of monoamine synthesis and altered function of altered hypothalamus-pituitary-adrena caused by interferon. McMahon et al., Found prevalence of interferon and ribavirin [57]. Usually, depressive episodes develops after 4 weeks of the treatment with IFN. Patients who have been diagnosed with bipolar disorder or depression in the past are more susceptible to develop psychiatric disorders during the treatment [56, 57].

6. TREATMENT OF CHRONIC HEPATITIS C

The main goal of therapy is eradication of the virus, stop or reverse histological changes and prevention complications associated with HCV infection. Hepatic and extrahepatic effects of hepatitis C include hepatic necroinflammation, fibrosis, cirrhosis, decompensation of cirrhosis, hepatocellular carcinoma, severe extrahepatic manifestations and even death. Sustained virologic response is the endpoint of therapy – undetectable HCV RNA (< 15 IU/ml) in blood 12 weeks or 24 weeks after the end of treatment [58, 59].

Pre-therapeutic procedure must contain assessment of the severity of the disease, baseline virological parameters and other possible causes of chronic liver dysfunction. It is necessary to adapt appropriate and individual therapy to the patient. There are many factors affecting the progression and history of the disease. All patients should be tested for hepatitis B virus (HBV) and human immunodeficiency virus (HIV). It is absolutely necessary to limit alcohol consumption and smoking. The occurrence of comorbidities should be assessed, mainly alcoholism, cardiovascular disease, renal failure, autoimmunity, other liver diseases, diabetes or obesity [58, 60].

Particular importance is an earlier assessment of the severity of the disease. Patients with cirrhosis or advanced fibrosis are a high-risk group, because the choice of the treatment

regimen and the post-treatment prognosis depend on the stage of disease. If clinical evidence of liver cirrhosis is present, assessment of the stage of fibrosis is not required, but assessment of portal hypertension, including oesophageal varices is obligatory [61].

All patients who want to be treated and those who have no contraindications for therapy should start antiviral treatment. Treatment regimens should be implemented immediately in patients with significant fibrosis or cirrhosis, including decompensated cirrhosis. The beginning of medication is priority in groups of patients presents extrahepatic symptoms, such as vasculitis associated with mixed cryoglobulinaemia, HCV immune complex-related nephropathy and non-Hodgkin B cell lymphoma. Treatment is recommended in patients with HCV recurrence after liver transplantation, risk of a rapid evolution of liver disease, active injection drug users, men who have sex with men with high-risk sexual practices, women who wish to get pregnant and haemodialysis patients [58, 62].

The evaluation of HCV genotype should take place before the start of treatment, including the separation of subtype 1a and 1b. Recently this procedure was essential and determined the selection of proper therapy for patients. In the light of current knowledge, this is not required but recommended [63]. Other factors determining the choice of treatment regimen are advancement of fibrosis, diagnosis of cirrhosis, previous antiviral treatment and its effect, comorbidities, drug interactions and local determinants [62].

Direct-acting antivirals (DAAs) allowed for the potential recovery of the majority of patients with chronic hepatitis C infection. Oral interferon-free regimens are based on 2-4 DDAs. The purpose of these drugs are various stages of the HCV replication process. There are the following classes of drugs: protease inhibitors, anti-NS3 (glecaprevir, grazoprevir, paritaprevir, simeprevir, voxilaprevir), RNA-dependent polymerase inhibitors, anti-NS5B (dasabuvir, sofosbuvir) and anti-NS5A inhibitors (daclatasvir, elbasvir, ledipasvir, ombitasvir, pibrentasvir, velpatasvir). The drugs, that are used, have different antiviral activity and resistance so they are combined in different treatment regimens. Modern treatment with the use of DDA has allowed for the cure of patients at the level of 95% which is undoubtedly a success and a breakthrough in HCV infection. The withdrawal of interferon in HCV therapy allowed for safer and more effective treatment of patients for whom antiviral treatment was contraindicated, such as decompensated cirrhosis [64, 65].

DDA monotherapy is unacceptable due to the risk of selection resistant strains. The majority of drug combinations is in the form of one tablet. The recommended treatment regimens are: glecaprevir (GLE)/pibrentasvir (PIB), sofosbuvir (SOF)/velpatasvir (VEL), sofosbuvir (SOF)/velpatasvir (VEL) /voxilaprevir (VOX), sofosbuvir (SOF)/ ledipasvir (LDV), elbasvir (EBR)/grazoprevir (GZR), ombitasvir (OBV)/paritaprevir (PTV)/ritonavir [66]. Nowadays, there are no absolute comorbidities for the use of DAAs therapy. Caution should be exercised in the treatment of sofosbuvir in patients with severe renal impairment and in patients receiving treatment with amiodarone. Simeprevir, ritonavir-boosted paritaprevir or grazoprevir are contraindicated in patients with decompensated cirrhosis or previous episodes of decompensation. Limited life expectancy due to non-liver-related comorbidities is contraindication to treatment [58].

7. PROGNOSIS AND COMPLICATIONS

About 55% to 85% of patients have a persistence of HCV RNA in the blood more than 6 months after the onset of acute infection. This condition of the disease is called chronic hepatitis C. Untreated resolution is rare when the infection goes into a chronic phase. Liver cirrhosis and hepatocellular carcinoma (HCC) are among the most common complications of HCV infection. It is estimated that approximately 20-30% of patients with chronic HCV will develop cirrhosis within 25-30 years. Annually, 1-4% of infected people will get HCC [67].

Cirrhosis is the final stage of many chronic liver diseases. The causes of cirrhosis are mainly dependent on geographical distribution. In western European countries the main reason is alcoholism, chronic hepatitis C and nonalcoholic fatty lives disease (NAFLD). Liver cirrhosis has many other causes, including chronic hepatitis B, inherited diseases, primary sclerosing cholangitis, autoimmune hepatitis [68-70]. Although the pathogenesis of cirrhosis is multifactorial, changes in the liver are common to these diseases and include degeneration and necrosis of hepatocytes, replacement of liver parenchyma by fibrotic tissues, regenerative nodules. The result of these processes is a gradual loss of liver function [71]. The precursor of liver cirrhosis and a key process in organ degeneration is fibrosis. Progress and monitoring of fibrosis are a reliable determinant of the course of the disease, in particular development cirrhosis, clinical outcomes, need for liver transplantation and liver-related death [72].

Clinical manifestation of symptoms of liver cirrhosis is associated mainly with disorders of organ functions and structures of the vascular system. This leads to increased pressure in portal vein (> 12 mm Hg) which results in the development of collateral circulation within the esophagus, anus and abdominal wall, enlargement of the spleen and hypersplenism, ascites and portal gastropathy. Symptoms depend on the duration of the disease, the amount of active liver parenchyma, portal circulatory disorders and administered medicines. The progressive nature of cirrhosis leads to laboratory and clinical signs of decomposition. For this purpose, the Child-Pugh score is used in clinical practice. Progress from an early stage, detectable only in histological examination, to extreme liver failure, lasts individually and depends on the etiology and administered medicines. From the onset of the first symptoms of decompensation, 45% of patients survive 5 years, and only 10-20% of patients – 10 years [73-75].

Hepatitis C virus is a leading etiology of HCC and a growing clinical problem, especially in developed countries. The increasing risk of HCC, in chronic HCV, is caused by the fibrosis stage. The annual incidence of HCC in the group of people with liver cirrhosis is high and estimated to be around 1-7 percent and in patients with a lower stage of fibrosis, it develops relatively less frequently. The risk of HCC decreases to 1% in the group of patients treated highly effective DDA for chronic HCV infection, however, even a sustained virological response does not eliminate the total risk of cancer [76]. Symptoms of advanced cancer include progressive wasting, pain and enlargement of the abdominal girth, swelling of the lower limbs, jaundice, fever, haemorrhage into the peritoneal cavity or into the inside of the tumor. Monitoring for hepatocellular carcinoma is recommended for patients with liver cirrhosis, chronic hepatitis B and without cirrhosis but with bridging fibrosis of unknown cause. For this purpose, abdominal ultrasound with alpha-fetoprotein (AFP) determination is performed every six months [77].

The most frequently extrahepatic manifestations of chronic HCV infection are renal (glomerulonephritis, from asymptomatic hematuria and proteinuria to nephrotic syndrome and chronic kidney disease), cutaneous (inflammation of small vessels, lichen planus, late porphyria, psoriasis), hematological (immunological thrombocytopenic purpura), neurological (peripheral neuropathy, cerebral vasculitis) and rheumatological changes (arthritis, Sjögren syndrome, antiphospholipid syndrome, systemic lupus erythematosus) [78, 79].

8. PREVENTION

Primary prevention of new infections and adequate control of confirmed infections is a fundamental activity in the HCV epidemic. Despite the revolution in the treatment of the virus, it is still a major public health problem, due to limitations in access to therapy. Among various prevention solutions, vaccines prove to be the most effective method of prophylaxis. Developing a vaccine against HCV would be an excellent tool to combat the spread of this

disease. Despite numerous attempts, it has not been possible to develop an effective solution to this problem. There are several reasons for failures, including high genetic diversity and variability. Non-specific prophylactic methods are similar to those of acute hepatitis C. The basic method is to observe the general principles of preventing infections transmitted by blood, which include avoiding the use of personal items that may be contaminated with blood, such as a toothbrush, a razor and in the case of drug addicts - a needle and a syringe. During sexual contact should be used condoms, due to the decreased risk of infection [80, 81].

9. CONCLUSIONS

It took about 14 years before hepatitis C was officially recognized as a disease. The discovery led to significant improvements in diagnosis and improved antiviral treatments. Untill 2014, those therapies were ineffective. Introducing protease inhibitors turned out to be a huge breakthrough. HCV can induce many extrahepatic symptoms, including many symptoms associated with the central nervous system, causing, inter alia, neurocognitive and mental disorders.

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