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The Neuropsychiatric Aspect of the Chronic Viral Hepatitis

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Abstract: Chronic viral hepatitis is a systemic disease characterized by a wide range of extrahepatic manifestations, such as cognitive impairment, chronic fatigue, sleep disorders, depression, anxiety and a decrease in quality of life. This article presents a summary of the main theories and hypotheses about the occurrence of cognitive impairment, features of treatment of patients with chronic viral hepatitis. Often, extrahepatic manifestations can outstrip the clinical manifestations of liver damage itself, which requires the use of additional diagnostic and treatment methods, and they can also significantly change the treatment tactics and prognosis of the disease. Changes in neuropsychological parameters and cognitive impairments are often recorded in patients with chronic viral hepatitis at stages characterized by the absence of significant liver fibrosis and liver cirrhosis. These changes usually occur regardless of the genotype of the infection and in the absence of structural damage to the brain. The purpose of this review is to study the main aspects of the formation of cognitive impairment in patients with chronic hepatitis, cirrhosis of viral etiology.

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Introduction

In the structure of chronic liver diseases, one of the significant places is assigned to viral hepatitis, which affect the lives of hundreds of millions of people around the world and are the main cause of steadily progressive morbidity and mortality (Torre et al., 2021). According to the latest estimates, more than 257 million people in the world have active viral hepatitis B (HBV) infection, but according to some authors, the number of infected patients reaches 350 million, chronic viral hepatitis accounts for more than 185 million patients, more than 20 million people have chronic viral hepatitis D (HDV) infection (Conde et al., 2017; Komas et al., 2018; Lanini et al., 2019). Prolonged persistence of viral hepatitis B, C and D can lead to the chronization of infection and subsequently lead to transformation into fibrosis and cirrhosis (Conde et al., 2017; Komas et al., 2018). However, at present, chronic viral hepatitis is a systemic disease characterized by a wide range of extrahepatic manifestations, including a number of neurological conditions (Monaco et al., 2015). In patients with chronic viral hepatitis, a number of symptoms are detected in 50% of cases, such as depression, anxiety, sleep disorders, fatigue and neurocognitive disorders, including impaired executive function, working memory, information processing speed, change of attitudes, decision-making and fluency of speech, which significantly affect the quality of life of patients (Adinolfi et al., 2015; Monaco et al., 2015; Yeoh et al., 2018; Tagliapietra and Monaco, 2020). Various scientists have noted the fact that depression, in particular, can be a reaction to increased psychosocial stress, as well as to the physical symptoms of a progressive existing disease (Yeoh et al., 2018). At the same time, patients at an early stage of the disease with minimal liver inflammation may have more pronounced symptoms of depression and fatigue than in the general population of patients (Yeoh et al., 2018). Characteristic neurocognitive deficiency can occur at an early stage of infection and has no connection with depression or encephalopathy, does not depend on the severity of the disease, the rate of replication of the virus, as well as on the stage of liver fibrosis, the genotype of the virus, the absence of visible structural damage to the brain (Monaco et al., 2015; Pawełczyk, 2016; Yeoh et al., 2018).

Chronic viral hepatitis and nervous system

Patients infected with chronic viral hepatitis have numerous extrahepatic manifestations, such as symptoms of central and peripheral nervous system disorders that develop at various times after infection. Hepatitis B and C viruses can directly have a neurotoxic effect on the brain. These processes are based on complex mechanisms associated with both the direct impact of the virus on brain cells and tissues, and with indirect effects resulting from the impact of the virus on the immune system or as a result of the use of antiviral therapy (Ferenci and Staufer, 2008). According to various authors, cognitive function disorders and neuropsychiatric disorders are registered in almost 50% of patients with chronic viral hepatitis, which do not depend on the severity of liver disease or the rate of

replication of viral hepatitis C (HCV) infection. In addition, symptoms such as fatigue, sleep disorders, depression and decreased quality of life are usually associated with neurocognitive changes in patients even with non-cirrhotic chronic HCV infection, regardless of the stage of liver fibrosis, infecting genotype or in the absence of structural damage to the brain and abnormal signals when using conventional magnetic resonance imaging (MRI) the brain (Adinolfi et al., 2015). Chronic viral hepatitis not only the central nervous system can be affected, but also the peripheral one, which leads to the formation of a wide variety of clinical manifestations, such as cerebrovascular phenomena, encephalopathy, myelitis, encephalomyelitis and cognitive disorders. Moreover, HCV infection is known to cause both motor and sensory peripheral neuropathy in the context of mixed cryoglobulinemia, which has recently been recognized as an independent risk factor for stroke (Wu et al., 2015; Sonavane et al., 2018). Approximately 1% of all cases of acute inflammatory demyelinating polyneuropathy associated with viral hepatitis B. Guillain-Barre syndrome is a surprisingly clinically diverse disease with characteristic variants characterized by an immuno-mediated attack on the components of the peripheral nervous system (Sonavane et al., 2018). Recent studies have shown that hepatitis C virus and Parkinson's disease have a common overexpression of inflammatory biomarkers due to the fact that HCV infection may release inflammatory cytokines that may play a role in the pathogenesis of Parkinson's disease (Wu et al., 2015).

Cognitive impairment and chronic viral hepatitis

According to WHO (World Health Organization) data, over 20 million people worldwide have dementia and cognitive impairment, moreover, the number of new cases of diseases is steadily increasing both in senile and elderly people, and in people of working age (Groppell et al., 2019). According to forecasts, the incidence of dementia is expected to increase from 35 million to 70 million by 2030 (Groppell et al., 2019). In turn, cognitive impairments include a decrease in memory, mental performance and other cognitive functions compared to the individual norm. Changes in neuropsychological parameters and cognitive impairments are often recorded in patients with chronic viral hepatitis, at stages characterized by the absence of significant liver fibrosis and liver cirrhosis. These changes usually occur regardless of the genotype of HCV infection and in the absence of structural damage to the brain or a pathological signal when using conventional magnetic resonance imaging (MRI) of the brain (Ferenci and Staufer, 2008). Researchers note that chronic HCV infection itself can cause moderate cognitive impairment, even in the absence of cirrhosis-related hepatic encephalopathy (Yeoh et al., 2018). Patients with chronic viral hepatitis may have impaired memory, attention, executive function, and processing speed at the non-cirrhotic stage of the disease (Yeoh et al., 2018). In addition to neurocognitive disorders, patients with chronic viral hepatitis may experience a number of symptoms, such as depression and fatigue, which worsen the quality of life (Yeoh et al., 2018). Depression in this case can

serve as a response to psychosocial stress and physical symptoms of progressive HCV-infection or concomitant diseases. However, even patients at an early stage of HCV-infection with minimal inflammation or concomitant liver disease report more symptoms of depression and fatigue than the general population. Similarly, specific cognitive impairments occur at an early stage of HCV-infection and do not depend on the presence of depression or encephalopathy (Lowry et al., 2016; Yeoh et al., 2018). Depression and cognitive impairment may be associated with the neurotoxicity of chronic viral hepatitis itself (Adinolfi et al., 2015). Thus, in studies in which interferon-free therapy was used in patients with chronic viral hepatitis, it was found that patients of this category have neuropsychiatric symptoms such as fatigue, insomnia, anxiety, depression and cognitive dysfunction, supporting hypotheses about the neurotoxicity of HCV infection (Gritsenko and Hughes, 2015). According to recent data, clinical and subclinical manifestations of cognitive dysfunction may be detected in 50% of chronic viral hepatitis patients (Barreira et al., 2019).

Risk factors of cognitive impairment

The high level of substance abuse and the prevalence of mental disorders among HCV-infected patients are important factors associated with cognitive impairments that jeopardize adherence and effectiveness of treatment (Więdłocha et al., 2017). Various authors have established a possible relationship in patients with chronic viral hepatitis between gender and cognitive functions. For example, a recent study found that the female gender apparently affects depression, anxiety and some indicators of cognitive functions in patients with chronic viral hepatitis before treatment (Barreira et al., 2019). Chronic viral hepatitis can also cause long-term brain dysfunction, which significantly worsens the quality of life and may even persist after the elimination of the virus (Dirks et al., 2017). With chronic HBV-infection, the quality of life may also be worsened due to the appearance of fatigue, cognitive impairment and sleep disorders (Wang et al., 2019).

Pathogenesis of the cognitive impairment

The theory of the appearance of cognitive impairment in patients at the terminal stage of liver disease is a generally recognized fact. It is known that ammonia is a toxic metabolite present in the blood in relatively low concentrations in a healthy individual, however, even a small increase in its concentration has an adverse effect on the body, and in particular on the brain (Fletcher and McKeating, 2012). Excessive intake of ammonia through the blood-brain barrier leads to depletion of the amount of glutamate, simultaneously leading to excessive accumulation of glutamine in brain tissues, resulting in swelling and swelling of astrocytes, a decrease in gamma-aminobutyric acid and dysfunction of transmembrane electrolyte transfer, thereby contributing to the deterioration of chemical neurotransmission (Fletcher and McKeating, 2012). Ineffective neutralization of ammonia leads to a decrease in the amount of α-ketoglutarate (which is a metabolite of glutamate), suppression

of transamination and a decrease in the synthesis of neurotransmitters (Fletcher and McKeating, 2012). This pathological cascade of reactions, simultaneously with an increase in alkalosis with excessive concentration of ammonia, contribute to increased hypoxia and hypoenergesis of astrocytes, neurons, resulting in the formation of hepatic encephalopathy (Fletcher and McKeating, 2012). However, recent studies indicate that one third of patients with chronic viral hepatitis have cognitive impairment in the absence of liver cirrhosis, at the same time, their connection with laboratory parameters, viral load and genotype is excluded (Wozniak et al., 2016). There is information explaining the possible pathogenesis of the direct effect of hepatitis viruses on brain cells, as a result of which these symptoms appear. It is assumed that neurobiological changes occur as a result of infiltration of the brain by induced cytokines and through the direct neuropathic action of viral particles of chronic viral hepatitis penetrating the blood-brain barrier (Yeoh et al., 2018). Changes that occur in the brain under the action of viral particles lead to increased inflammatory reactions, changes in the level of neurotransmitters, hormonal regulation and the release of neurotoxic substances, which subsequently lead to abnormal neural conduction and functioning in areas of the brain responsible for affective reactions, emotional processing, motivation, attention and concentration (Fletcher and McKeating, 2012; Yeoh et al., 2018). Despite the fact that direct-acting antiviral drugs lead to high rates of elimination of viral agents, intracerebral changes are not regressed, as a result of which the symptoms of neurocognitive deficiency persist (Fletcher and McKeating, 2012; Yeoh et al., 2018). On the other hand, according to the results of the recent study, it was found that replication of chronic viral hepatitis viruses can take place both on the surface of endothelial cells of the blood-brain barrier, and inside, due to the expression of known receptor molecules such as (LDLR, CD81, claudin-1, occludin, and scavenger receptor-B1) (Fletcher et al., 2012). According to these data, theoretically, hepatitis viruses can lead to obstructive vascular disorders, due to the direct involvement of brain vessels in chronic inflammation (Fletcher et al., 2012). The generally recognized facts of the pathogenesis of cognitive disorders in chronic viral hepatitis is the strengthening of the host's immune response, in which autoantibodies, immune complexes and cryoglobulins are produced (Fletcher et al., 2012). But there are alternative mechanisms of cognitive impairment in patients with chronic viral hepatitis, including the release of viral RNA in microglial cells and astrocytes (Fletcher et al., 2012). Researchers have suggested that hepatitis viruses have the ability to penetrate into the brain and multiply in the endothelial cells of the brain, which characterizes their independent life and pathogenic role in the development of cognitive deficits (Fletcher and McKeating, 2012; Fletcher et al., 2012). Despite the expansion of the clinical range of syndromes in chronic viral hepatitis, the exact pathophysiological mechanisms of cognitive impairment are still poorly understood. On the one hand, the detection of defects in the central serotonergic and dopaminergic neurotransmission of patients with cognitive disorders and mild

course of the disease suggests a possible role of chronic viral hepatitis viruses in inducing dysfunction of selective aminergic systems (Weissenborn et al., 2006). On the other hand, patients undergoing interferon therapy the appearance of depression correlates with the depletion of serotonin in platelets, possibly due to the effectiveness of antidepressants that inhibit serotonin reuptake (Stasi et al., 2014). There are other putative mechanisms of cognitive deficits associated with cytokines released during systemic or immune activation of the brain (Stasi et al., 2014). In recent studies, it was found that patients with mild HCV-infection during magnetic resonance spectroscopy have a pronounced dysfunction of choline and creatinine metabolism in the basal ganglia and white matter of the brain compared with patients without a history of hepatitis. In comparison with the process observed in hepatic encephalopathy, higher concentrations of cerebral choline were recorded in patients in this study, which ultimately serves as evidence of the effect on cognitive functions (Stasi et al., 2014).

Chronic fatigue

Chronic fatigue is an important clinical finding in patients with chronic hepatitis virus infection. Fatigue, according to foreign researchers, has 2 main types – central and peripheral, which can occur both in combination and separately (Golabi et al., 2017). Central fatigue is characterized by a lack of self-motivation and can manifest itself in both physical and mental activity. Peripheral fatigue is classically manifested by neuromuscular dysfunction and muscle weakness. Therefore, the difference is often considered as the difference between intention (central fatigue) and ability (peripheral fatigue) (Golabi et al., 2017). Fatigue is characterized as a multi-level structure, the division of which into central and peripheral fatigue makes it possible to better assess the condition and identify potential causes and correlations. The liver occupies a central place in the pathogenesis of peripheral and central fatigue, which, according to researchers, depends on the regulation of energy and crosstalk between the intestine, liver, muscles and brain (Gerber et al., 2019). Fatigue in liver diseases in most cases manifests itself as central fatigue, which does not correlate with traditional markers of activity or with the severity of the disease (Swain, 2006). There is a certain consensus on the nature, mechanisms and degree of immune dysfunction in this pathology, characterized by slightly increased indicators of pro-inflammatory and anti-inflammatory cytokines, such as interleukin-1 (IL), interleukin-6 and tumour necrosis factor (TNF-α), as well as a violation of the function of natural killer cells and a change in the amount of T-lymphocytes (Torgrimson-Ojerio et al., 2014). Several previous studies have also attempted to establish a link between fatigue and various biomarkers, such as IL-6 and TNF-α in cytokine assays. According to the results of the study, no association of TNF-α with fatigue was recorded, while IL-6 and cortisol were reported to be positively associated with fatigue (Jang et al., 2018a). However, other fatigue studies have established a significant negative correlation with cortisol in patients with HBV,

however, a significant positive correlation has been observed with IL-6 and TNF-α. Cortisol, IL-6, and TNF-α were associated with levels of perceived fatigue, especially cognitive impairment in patients with HBV infection. The characteristic of fatigue in patients with chronic liver disease was noted as central fatigue (Wang et al., 2019). Some studies have shown that fatigue is a true and specific sign of HDV-infection that negatively affects the quality of life, while a significant proportion of fatigue in HBV is associated with the presence of autonomic dysfunction (Ekerfors et al., 2019). Other studies have found that muscle dysfunction is a key mechanism of chronic fatigue syndrome. It is noted that the appearance of fatigue in patients directly depended on low muscle performance and a decrease in the level of physical activity, which can serve as a potential for the treatment of chronic fatigue syndrome (Jang et al., 2018a). A recent content analysis revealed that the overall level of cognitive impairment and chronic fatigue syndrome in chronic HCV-infection had a significant negative correlation with age. Consequently, emotional and psychosocial problems associated with fatigue may be more common in patients with chronic viral hepatitis than physical problems (Jang et al., 2018b). Chronic fatigue is also very common in the terminal stage of liver disease, recent studies have shown its connection with physical activity in patients with cirrhosis of the liver, so when conducting a 6-minute walking test in patients, its indicators showed low and a high degree of shortness of breath was found, which were associated with chronic fatigue syndrome (Ahboucha et al., 2008). Chronic fatigue syndrome is also present in a significant number of patients after liver transplantation (21.5%), and almost half of patients suffer from severe fatigue (45.0%). The related factors of the appearance of chronic fatigue syndrome after liver transplantation are still unclear and complex, which requires additional information to reduce the course of the syndrome and improve the quality of life of recipients (Lima et al., 2019). In patients with liver cirrhosis, chronic fatigue syndrome is a common complaint and can be considered as a debilitating symptom that negatively affects the quality of life, and also has a strong correlation with depressive symptoms and quality of life (Hong et al., 2015). However, studies to assess fatigue in patients with chronic viral hepatitis are very limited.

Anxiety and depression

The prevalence of anxiety and depression in patients with chronic viral hepatitis, according to various authors, varies from 37 to 83% (Adinolfi et al., 2017). Patients with chronic viral hepatitis are characterized by the dominance of negative emotions, communication difficulties, a high degree of asthenization, difficulties in obtaining psychological help and social support (Aktuğ Demir et al., 2013; Yeoh et al., 2018). In patients with chronic viral hepatitis, depression is a possible reaction to increased psychosocial stress, to the presence of physical symptoms of progression of chronic viral hepatitis, or to existing concomitant diseases (Tamayo et al., 2016). However, researchers have found that patients even in the early stages of

the disease with minimal liver inflammation or concomitant diseases report more pronounced symptoms of depression and fatigue than in the general population (Fletcher and McKeating, 2012; Zayed et al., 2018; Egmond et al., 2020). The presence of concomitant pathology in patients with chronic hepatitis increases the risk of developing mental complications (Fletcher et al., 2012; Zayed et al., 2018; Egmond et al., 2020). However, according to other authors, depression was not detected in the early stages of the disease, although the fact was noted that in patients with chronic viral hepatitis, depressive mood and cognitive fatigue were critical psychosocial mediators of a decrease in the quality of life (Zayed et al., 2018). Depression is a frequent disorder detected in one third of patients with chronic viral hepatitis C and its prevalence is estimated to be 1.5–4.0 times higher than in patients with chronic infection caused by the hepatitis B virus (Zayed et al., 2018). Currently, an increasing number of studies are focused only on the study of depression, but not on anxiety, although its presence can also significantly correlate with the quality of life associated with health in patients with chronic viral hepatitis (Fletcher and McKeating, 2012).

Modern diagnostic capabilities of cognitive disorders

As is known, neuropsychiatric disorders and neurocognitive dysfunction are registered in almost 50% of patients with chronic viral hepatitis, regardless of the severity of liver disease or the frequency of HCV-infection replication. Fatigue, sleep disturbance, depression and decreased quality of life are usually associated with neurocognitive changes in patients with non-cirrhotic stage of chronic HCV-infection, regardless of the stage of liver fibrosis and the type of virus genotype (Monaco et al., 2015). These manifestations usually occur in the absence of structural brain damage or signal pathology when using conventional MRI of the brain, although metabolic and microstructural changes can be detected with its help (Monaco et al., 2015). It is assumed that chronic viral hepatitis causes neurodegenerative changes through low-severity neuroinflammation, which suggests cortical atrophy. Some researchers have not found a link between fatigue and the thickness of the cortical layer. The total difference in the volume of white and gray matter of the brain was also not detected (Hjerrild et al., 2016). Other researchers also did not establish a connection between chronic viral hepatitis and the volume of gray matter of the brain obtained from 3T neuroimaging. Although a cluster of endothelial cells is reported to be associated with the primary and secondary somatosensory cortex, as well as the temporal and occipital lobes in patients with chronic viral hepatitis. At the same time, a higher average value of endothelial cells in the upper parietal part, adjusted for the average shift in frames, was associated with improved memory and attention indicators, but not with fatigue, depression, viral load or the level of liver fibrosis among patients. These results, according to the researchers, suggest a compensatory mechanism in chronic viral hepatitis and explain the ambiguous results in the literature on cognitive deficits in infected people (Kharabian Masouleh et al.,

2017). HCV-infection affecting the central nervous system (CNS) can lead to various manifestations, such as anxiety, depression, cognitive impairment and vasculitis. In a recent study, patients with HCV-infection were evaluated using the Wexler Adult Intelligence Scale, the Wexler Memory Scale, the Beck Depression Scale and computed tomography (CT) with single-photon emission. The aim of the study was to identify subclinical CNS lesions in patients with chronic viral hepatitis with and without systemic vasculitis. According to the results of the study, it was found that the indicators of the memory scale were lower in HCV patients with vasculitis compared to patients without vasculitis, while block tests and comprehension tests, the indicators of the Beck scale did not differ significantly in both groups. The test scores in patients with and without cirrhosis did not differ significantly. However, some patients had different patterns of cerebral hypoperfusion during CT, while all of them had associated vasculitis, which indicates the possibility of vasculitis developing neuropsychiatric lesions in patients with chronic viral hepatitis (Zayed et al., 2018). An attempt was also made to assess whether neuropsychological disorders in patients infected with chronic viral hepatitis are accompanied by structural changes in the brain, through extensive neuropsychological testing and the use of cranial MRI. The data obtained indicated structural changes in the brains of patients with chronic viral hepatitis. The data obtained indicated structural changes in the brains of patients with chronic HCV-infection. Disorders of the cerebelloalamocortical regions and contours connecting the projections of the cerebellum with the prefrontal cortex through the thalamus, according to the researchers, indicated cognitive dysfunction observed in these patients (Prell et al., 2019). Chronic viral hepatitis can often manifest as a noticeable impairment of attention and executive functions associated with neuropsychiatric symptoms. Neuroimaging methods show the predominance of frontal cortical striated structures and their connections, systems that regulate the interaction between emotional and motivational regulation, executive and motor functions. Unlike metabolic and hepatic encephalopathy, direct brain involvement is observed as an inflammatory reaction in these structures. There is still uncertainty about the clinical significance of this inflammation, and in various studies contradictory data have been obtained on its harmful or protective effects on cognitive functions. According to current hypotheses of brain circuits, altered function is also observed in distant structures associated with the frontal cortical-striatal network, in the absence of signs of inflammation. There is scant evidence for the reversibility of post-treatment imaging changes and their potential use as a biomarker to consider starting treatment. Since effective and well-tolerated treatments are currently available, imaging biomarkers can help clinicians assess cognitive impairment in chronic viral hepatitis (Tagliapietra and Monaco, 2020). The role of HCV hepatitis virus co-infection in cognitive impairment in patients infected with human immunodeficiency virus (HIV) is still being discussed, and there is no functional assessment of neuroimaging on this issue. A recent pilot study demonstrates that there are statistically significant differences in

the types of connections. Thus, it was found that in HCV, the involved areas were the pallidum, the brain stem, lobules 1 and 10 lobes of the right cerebellum. Enlarged frontal-striated dysfunctions have already been reported as consequences of HCV-infection and they may reflect an additive effect. Changes in the cerebellum are associated with HIV-infection, but not with HCV, which indicates a synergistic effect of HCV-infection in the functional modification of the brain associated with HIV (Corgiolu et al., 2018). Several studies have demonstrated evidence of moderate neurocognitive impairment in various areas of ability among a subgroup of people infected with HCV, the severity and exact neurocognitive domains vary depending on the literature, for example, some researchers found only general moderate cognitive impairment in a cohort of HCV-infected patients with specific learning disabilities compared to seronegative participants (Corgiolu et al., 2018). Other evidence suggests that some people infected with HCV may have more diffuse neurocognitive deficits in neuropsychological areas associated with prefrontal systems, including deficits in complex information processing, motor skills, and executive functions. Moreover, approximately 30% of people infected with HCV had difficulties with the test, which required mental flexibility, abstract thinking and concept formation (Posada et al., 2010). It was found that HCV-infection was associated with mild deficiency when performing tasks that assessed inhibition of speech response and fluency of speech. Thus, mild neurocognitive disorders are observed among a subgroup of people with HCV even in the absence of severe liver disease (Posada et al., 2010). In the light of contradictory results in the literature, various complex batteries of tests are used by foreign researchers to study cognitive disorders. The Wexler reading test for adults is a widely used word recognition test, with the help of which it is possible to assess the initial cognitive abilities before the disease (Huckans et al., 2015). It is also possible to use a battery of neuropsychological assessment (NAB), characterized as a well-tested complex set of subtests evaluating a number of cognitive areas, including the modules attention, memory and executive functions, each of which consists of several subtests related to this area. Based on demographically adjusted norms (age, gender, education), standard scores are derived for each subtest, and standard indexes are defined as the total performance indicators for the subtests for each module (Huckans et al., 2015). It is reported about the use of psychiatric questionnaires to identify cognitive impairments in patients with chronic viral hepatitis. The Beck depression scale well confirms the criteria for the severity of depression, consisting of 21 points with which two factors of the disease can be determined, the first of which is the somatic factor (loss of energy, changes in sleep patterns, irritability, changes in appetite, difficulty concentrating, fatigue, loss of interest in sex), and the cognitive affective factor (sadness, pessimism, failure in the past, guilt, sense of punishment, self-dislike, self-criticism, thoughts of suicide, crying, excitement, uselessness) (Bjelland et al., 2002; Zimmerman et al., 2015). Fatigue Severity Scale (FSS) is a 9-point fatigue severity scale previously confirmed for use in patients with HCV, multiple sclerosis

and other chronic diseases (Gavrilov et al., 2018). Although there are many measurement tools available to assess fatigue, there is no tool that can provide both specificity and sensitivity for measuring fatigue. The lack of a tool is part of the problem that leads to underestimation, recognition and treatment of fatigue in patients. Part of the problem is that the tools currently used do not adequately reflect the complexity and dimension of fatigue. None of the commonly used tools addresses all aspects of fatigue. Commonly assessed areas include: descriptions or characteristics of fatigue, feelings of distress associated with fatigue, suspected causes of fatigue, and effects of fatigue. It is important to understand which fatigue components are being evaluated and which fatigue components should be evaluated. Since there are no tools that would cover all these components, it is important for researchers to consider what fatigue is, which is relevant to the current study or patient, and use it to select a specific measure (Gavrilov et al., 2018). When assessing the severity of anxiety, it is possible to use a generalized inventory of anxiety disorders consisting of 18 items (Bjelland et al., 2002). Another equally effective method of diagnosing anxiety and depression is the Hospital Anxiety and Depression Scale (HADS). It is characterized as a tool that measures mental stress among somatic patients. It consists of two subscales: the anxiety subscale (HADS-D A) and the depression subscale (HADS-D D). Each consists of seven questions and must be analysed independently. Higher values indicate a greater deterioration. The average values on the anxiety and depression scales were presented (0–21 n per scale, ≤7 n = normal, ≥11 n = noteworthy symptoms) (Gerber et al., 2019). Cognitive and physical weakness are common in patients with cirrhosis. There is evidence of the use of a combined assessment (MoCA-CFS) developed using the Montreal Cognitive Assessment (MoCA) to assess the severity of hepatic encephalopathy. The MoCA-CFS composite score makes it possible to predict the deterioration of health-related and all-cause quality of life indicators within 6 months. Recent data confirm the prognostic value of the "multidimensional" weakness tool for predicting adverse clinical outcomes and emphasize the potential of a multifaceted approach to therapy aimed at cognitive impairment, physical weakness and depression (Ney et al., 2018).

Conclusion

There is evidence of a wide range of neuropsychiatric disorders at various stages of fibrosis, including early in patients with chronic viral hepatitis. The difficulty of diagnosing cognitive impairment in chronic viral hepatitis is due to the fact that the currently used wide range of neuropsychological tests does not fully reflect the degree and features of cognitive dysfunction in this category of patients. The use of modern diagnostic criteria helps to improve the diagnosis of neuropsychiatric disorders in patients with chronic viral hepatitis, which may be an indication for timely therapeutic measures aimed at improving the quality of life in this category of patients.

References

Adinolfi, L. E., Nevola, R., Lus, G., Restivo, L., Guerrera, B., Romano, C., Zampino, R., Rinaldi, L., Sellitto, A., Giordano, M., Marrone, A. (2015) Chronic hepatitis C virus infection and neurological and psychiatric disorders: An overview. *World J. Gastroenterol*. **21(8)**, 2269–2280.

Adinolfi, L. E., Nevola, R., Rinaldi, L., Romano, C., Giordano, M. (2017) Chronic hepatitis C virus infection and depression. *Clin. Liver Dis.* **21(3)**, 517–534.

Ahboucha, S., Butterworth, R. F., Pomier-Layrargues, G., Vincent, C., Hassoun, Z., Baker, G. B. (2008) Neuroactive steroids and fatigue severity in patients with primary biliary cirrhosis and hepatitis C. *Neurogastroenterol. Motil.* **20(6)**, 671–679.

Aktuğ Demir, N., Çelik, M., Kölgelier, S., Sümer, S., Aksöz, S., Demir, L. S., İnkaya, A. Ç. (2013) Comparison of the level of depression and anxiety in inactive hepatitis B carriers and chronic hepatitis B patients. *Turk Psikiyatri Derg.* **24(4)**, 248–252. (in Turkish)

Barreira, D. P., Marinho, R. T., Bicho, M., Flores, I., Fialho, R., Ouakinin, S. (2019) Hepatitis C pretreatment profile and gender differences: Cognition and disease severity effects. *Front. Psychol.* **10**, 2317.

Bjelland, I., Dahl, A. A., Haug, T. T., Neckelmann, D. (2002) The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J. Psychosom. Res.* **52(2)**, 69–77.

Conde, I., Vinaixa, C., Berenguer, M. (2017) Hepatitis C-related cirrhosis. Current status. Cirrosis por hepatitis C. Estado actual. *Medicina Clínica* **148(2)**, 78–85.

Corgiolu, S., Barberini, L., Suri, J. S., Mandas, A., Costaggiu, D., Piano, P., Zaccagna, F., Lucatelli, P., Balestrieri, A., Saba, L. (2018) Resting-state functional connectivity MRI analysis in human immunodeficiency virus and hepatitis C virus co-infected subjects. A pilot study. *Eur. J. Radiol.* **102**, 220–227.

Dirks, M., Pflugrad, H., Haag, K., Tillmann, H. L., Wedemeyer, H., Arvanitis, D., Hecker, H., Tountopoulou, A., Goldbecker, A., Worthmann, H., Weissenborn, K. (2017) Persistent neuropsychiatric impairment in HCV patients despite clearance of the virus?! *J. Viral Hepat.* **24(7)**, 541–550.

Egmond, E., Mariño, Z., Navines, R., Oriolo, G., Pla, A., Bartres, C., Lens, S., Forns, X., Martin-Santos, R. (2020) Incidence of depression in patients with hepatitis C treated with direct-acting antivirals. *Braz. J. Psychiatry* **42(1)**, 72–76.

Ekerfors, U., Sunnerhagen, K. S., Westin, J., Jakobsson Ung, E., Marschall, H. U., Josefsson, A., Simrén, M. (2019) Muscle performance and fatigue in compensated chronic liver disease. *Scand. J. Gastroenterol.* **54(7)**, 925–933.

Ferenci, P., Staufer, K. (2008) Depression in chronic hepatitis: The virus, the drug, or the ethnic background? *Liver Int.* **28(4)**, 429–431.

Fletcher, N. F., McKeating, J. A. (2012) Hepatitis C virus and the brain. *J. Viral Hepat.* **19(5)**, 301–306.

Fletcher, N. F., Wilson, G. K., Murray, J., Hu, K., Lewis, A., Reynolds, G. M., Stamataki, Z., Meredith, L. W., Rowe, I. A., Luo, G., Lopez-Ramirez, M. A., Baumert, T. F., Weksler, B., Couraud, P. O., Kim, K. S., Romero, I. A., Jopling, C., Morgello, S., Balfe, P., McKeating, J. A. (2012) Hepatitis C virus infects the endothelial cells of the blood-brain barrier. *Gastroenterology* **142(3)**, 634–643.e6.

Gavrilov, Y. V., Shkilnyuk, G. G., Valko, P. O., Stolyarov, I. D., Ivashkova, E. V., Ilves, A. G., Nikiforova, I. G., Shchelkova, O. Y., Vasserman, L. I., Vais, E. E., Valko, Y. (2018) Validation of the Russian version of the Fatigue Impact Scale and Fatigue Severity Scale in multiple sclerosis patients. *Acta Neurol. Scand.* **138(5)**, 408–416.

Gerber, L. H., Weinstein, A. A., Mehta, R., Younossi, Z. M. (2019) Importance of fatigue and its measurement in chronic liver disease. *World J. Gastroenterol*. **25(28)**, 3669–3683.

Golabi, P., Sayiner, M., Bush, H., Gerber, L. H., Younossi, Z. M. (2017) Patient-reported outcomes and fatigue in patients with chronic hepatitis C infection. *Clin. Liver Dis*. **21(3)**, 565–578.

Gritsenko, D., Hughes, G. (2015) Ledipasvir/sofosbuvir (Harvoni): Improving options for hepatitis C virus infection. *P T* **40(4)**, 256–276.

Groppell, S., Soto-Ruiz, K. M., Flores, B., Dawkins, W., Smith, I., Eagleman, D. M., Katz, Y. (2019) A rapid, mobile neurocognitive screening test to aid in identifying cognitive impairment and dementia (BrainCheck): Cohort study. *JMIR Aging* **2(1)**, e12615.

Hjerrild, S., Renvillard, S. G., Leutscher, P., Sørensen, L. H., Østergaard, L., Eskildsen, S. F., Videbech, P. (2016) Reduced cerebral cortical thickness in non-cirrhotic patients with hepatitis C. *Metab. Brain Dis.* **31(2)**, 311–319.

Hong, K., Kim, H., Lee, J. M., Lee, K. W., Yi, N. J., Lee, H. W., Choi, Y., Suh, S. W., Hong, S. K., Yoon, K. C., Kim, H. S., Suh, K. S. (2015) Fatigue and related factors after liver transplantation. *Korean J. Hepatobiliary Pancreat. Surg.* **19(4)**, 149–153.

Huckans, M., Fuller, B., Wheaton, V., Jaehnert, S., Ellis, C., Kolessar, M., Kriz, D., Anderson, J. R., Berggren, K., Olavarria, H., Sasaki, A. W., Chang, M., Flora, K. D., Loftis, J. M. (2015) A longitudinal study evaluating the effects of interferon-alpha therapy on cognitive and psychiatric function in adults with chronic hepatitis C. *J. Psychosom. Res.* **78(2)**, 184–192.

Jang, Y., Boo, S., Yoo, H. (2018a) Hepatitis B virus infection: Fatigue-associated illness experiences among Koreans. *Gastroenterol. Nurs.* **41(5)**, 388–395.

Jang, Y., Kim, J. H., Lee, H., Lee, K., Ahn, S. H. (2018b) A quantile regression approach to explain the relationship of fatigue and cortisol, cytokine among Koreans with hepatitis B. *Sci. Rep.* **8(1)**, 16434.

Kharabian Masouleh, S., Herzig, S., Klose, L., Roggenhofer, E., Tenckhoff, H., Kaiser, T., Thöne-Otto, A., Wiese, M., Berg, T., Schroeter, M. L., Margulies, D. S., Villringer, A. (2017) Functional connectivity alterations in patients with chronic hepatitis C virus infection: A multimodal MRI study. *J. Viral Hepat.* **24(3)**, 216–225.

Komas, N. P., Ghosh, S., Abdou-Chekaraou, M., Pradat, P., Al Hawajri, N., Manirakiza, A., Laghoe, G. L., Bekondi, C., Brichler, S., Ouavéné, J. O., Sépou, A., Yambiyo, B. M., Gody, J. C., Fikouma, V., Gerber, A., Abeywickrama Samarakoon, N., Alfaiate, D., Scholtès, C., Martel, N., Le Gal, F., Lo Pinto, H., Amri, I., Hantz, O., Durantel, D., Lesbordes, J. L., Gordien, E., Merle, P., Drugan, T., Trépo, C., Zoulim, F., Cortay, J. C., Kay, A. C., Dény, P. (2018) Hepatitis B and hepatitis D virus infections in the Central African Republic, twenty-five years after a fulminant hepatitis outbreak, indicate continuing spread in asymptomatic young adults. *PLoS Negl. Trop. Dis.* **12(4)**, e0006377.

Lanini, S., Ustianowski, A., Pisapia, R., Zumla, A., Ippolito, G. (2019) Viral hepatitis: Etiology, epidemiology, transmission, diagnostics, treatment, and prevention. *Infect. Dis. Clin. North Am.* **33(4)**, 1045–1062.

Lima, Y. B., Magalhães, C. B. A., Garcia, J. H. P., Viana, C. F. G., Prudente, G. F. G., Pereira, E. D. B. (2019) Association between fatigue and exercise capacity in patients with chronic liver disease awaiting liver transplantation. *Arq. Gastroenterol.* **56(3)**, 252–255.

Lowry, D., Burke, T., Galvin, Z., Ryan, J. D., Russell, J., Murphy, A., Hegarty, J., Stewart, S., Crowe, J. (2016) Is psychosocial and cognitive dysfunction misattributed to the virus in hepatitis C infection? Select psychosocial contributors identified. *J. Viral Hepat.* **23(8)**, 584–595.

Monaco, S., Mariotto, S., Ferrari, S., Calabrese, M., Zanusso, G., Gajofatto, A., Sansonno, D., Dammacco, F. (2015) Hepatitis C virus-associated neurocognitive and neuropsychiatric disorders: Advances in 2015. *World J. Gastroenterol.* **21(42)**, 11974–11983.

Ney, M., Tangri, N., Dobbs, B., Bajaj, J., Rolfson, D., Ma, M., Ferguson, T., Bhardwaj, P., Bailey, R. J., Abraldes, J., Tandon, P. (2018) Predicting hepatic encephalopathy-related hospitalizations using a composite assessment of cognitive impairment and frailty in 355 patients with cirrhosis. *Am. J. Gastroenterol.* **113(10)**, 1506–1515.

Pawełczyk, A. (2016) Consequences of extrahepatic manifestations of hepatitis C viral infection (HCV). *Postepy Hig. Med. Dosw. (Online)* **70**, 349–359. (in Polish)

Posada, C., Moore, D. J., Woods, S. P., Vigil, O., Ake, C., Perry, W., Hassanein, T. I., Letendre, S. L., Grant, I.; HIV Neurobehavioral Research Center Group (2010) Implications of hepatitis C virus infection for behavioral symptoms and activities of daily living. *J. Clin. Exp. Neuropsychol*. **32(6)**, 637–644.

Prell, T., Dirks, M., Arvanitis, D., Braun, D., Peschel, T., Worthmann, H., Schuppner, R., Raab, P., Grosskreutz, J., Weissenborn, K. (2019) Cerebral patterns of neuropsychological disturbances in hepatitis C patients. *J. Neurovirol.* **25(2)**, 229–238.

Sonavane, A. D., Saigal, S., Kathuria, A., Choudhary, N. S., Saraf, N. (2018) Guillain-Barré syndrome: Rare extra-intestinal manifestation of hepatitis B. *Clin. J. Gastroenterol.* **11(4)**, 312–314.

Stasi, C., Rosselli, M., Zignego, A. L., Laffi, G., Milani, S. (2014) Serotonin and its implication in the side-effects of interferon-based treatment of patients with chronic viral hepatitis: Pharmacological interventions. *Hepatol. Res.* **44(1)**, 9–16.

Swain, M. G. (2006) Fatigue in liver disease: Pathophysiology and clinical management. *Can. J. Gastroenterol.* **20(3)**, 181–188.

Tagliapietra, M., Monaco, S. (2020) Neuroimaging findings in chronic hepatitis C virus infection: Correlation with neurocognitive and neuropsychiatric manifestations. *Int. J. Mol. Sci.* **21(7)**, 2478.

Tamayo, A., Shah, S. R., Bhatia, S., Chowdhury, A., Rao, P. N., Dinh, P., Knox, S. J., Gaggar, A., Subramanian, G. M., Mohan, V. G., Sood, A., Mehta, R., Sarin, S. K. (2016) Correlates of disease-specific knowledge among patients with chronic hepatitis B or hepatitis C infection in India. *Hepatol. Int.* **10(6)**, 988–995.

Torgrimson-Ojerio, B., Ross, R. L., Dieckmann, N. F., Avery, S., Bennett, R. M., Jones, K. D., Guarino, A. J., Wood, L. J. (2014) Preliminary evidence of a blunted anti-inflammatory response to exhaustive exercise in fibromyalgia. *J. Neuroimmunol.* **277(1–2)**, 160–167.

Torre, P., Aglitti, A., Masarone, M., Persico, M. (2021) Viral hepatitis: Milestones, unresolved issues, and future goals. *World J. Gastroenterol.* **27(28)**, 4603–4638.

Wang, H., Zhou, Y., Yan, R., Ru, G. Q., Yu, L. L., Yao, J. (2019) Fatigue in chronic hepatitis B patients is significant and associates with autonomic dysfunction. *Health Qual. Life Outcomes* **17(1)**, 130.

Więdłocha, M., Marcinowicz, P., Sokalla, D., Stańczykiewicz, B. (2017) The neuropsychiatric aspect of the HCV infection. *Adv. Clin. Exp. Med.* **26(1)**, 167–175.

Weissenborn, K., Ennen, J. C., Bokemeyer, M., Ahl, B., Wurster, U., Tillmann, H., Trebst, C., Hecker, H., Berding, G. (2006) Monoaminergic neurotransmission is altered in hepatitis C virus infected patients with chronic fatigue and cognitive impairment. *Gut* **55(11)**, 1624–1630.

Wozniak, M. A., Lugo Iparraguirre, L. M., Dirks, M., Deb-Chatterji, M., Pflugrad, H., Goldbecker, A., Tryc, A. B.,Worthmann, H., Gess, M., Crossey, M. M., Forton, D. M., Taylor-Robinson, S. D., Itzhaki, R. F., Weissenborn, K. (2016) Apolipoprotein E-ε4 deficiency and cognitive function in hepatitis C virus-infected patients. *J. Viral Hepat.* **23(1)**, 39–46.

Wu, W. Y., Kang, K. H., Chen, S. L., Chiu, S. Y., Yen, A. M., Fann, J. C., Su, C. W., Liu, H. C., Lee, C. Z., Fu, W. M., Chen, H. H., Liou, H. H. (2015) Hepatitis C virus infection: A risk factor for Parkinson's disease. *J. Viral Hepat.* **22(10)**, 784–791.

Yeoh, S. W., Holmes, A. C. N., Saling, M. M., Everall, I. P., Nicoll, A. J. (2018) Depression, fatigue and neurocognitive deficits in chronic hepatitis C. *Hepatol. Int.* **12(4)**, 294–304.

Zayed, H. S., Amin, A., Alsirafy, S., Elsayed, N. D., Abo Elfadl, S., Nasreldin, M., Enaba, D., Nawito, Z. (2018) Psychiatric and functional neuroimaging abnormalities in chronic hepatitis C virus patients: Is vasculitis a contributing factor? *Arab J. Gastroenterol.* **19(2)**, 71–75.

Zimmerman, M., Clark, H. L., Multach, M. D., Walsh, E., Rosenstein, L. K., Gazarian, D. (2015) Have treatment studies of depression become even less generalizable? A review of the inclusion and exclusion criteria used in placebo-controlled antidepressant efficacy trials published during the past 20 years. *Mayo Clin. Proc.* **90(9)**, 1180–1186.