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Review

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VIRAL HEPATITIS B AND C AND NEUROLOGICAL IMPAIRMENT

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Abstract

Viral Hepatitis B and C are characterized as systemic diseases with a wide range of extrahepatic manifestations caused by various immunological disorders. Neurological disorders are among the most important extrahepatic manifestations, which can serve as indicators of the presence of viruses and play a major role in the clinical picture of the disease. This review article describes the most frequently manifested neurological disorders detected in patients with chronic viral hepatitis, particularly Hepatitis B and C.

Keywords: Viral hepatitis, Guillain-Barré syndrome, Parkinson's Disease, peripheral neuropathy, cognitive impairment, stroke.

Introduction

Parenteral forms of hepatitis are systemic diseases in which there is a wide range of neurological disorders of manifestations caused by various immunological disorders. Pathological processes in them are caused by the replication of viral agents both in the liver tissue and outside its borders.[1]

Neurological disorders in viral hepatitis, both in acute and chronic form, can manifest not only from the side of the brain but also from the side of the spinal cord and peripheral nervous system, according to the severity from subclinical changes to neurocritical states.[2,3] These disorders are caused by both the direct neurotoxic effect of viral particles on brain cells and the indirect effect caused by the influence of viruses on the immune system or as a result of using antiviral therapy.[4] Neurological disorders and deterioration of the quality of life associated with health in patients with viral hepatitis may occur even at the non-cirrhotic stage of infection, regardless of the stage of fibrogenesis and the genotype of the virus. [5]

Neurologists often participate in the consultation of patients with viral hepatitis, and it is important for them to detect the main neurological symptoms in patients with viral hepatitis in time, which will further facilitate the adoption of timely tactics of diagnostic and therapeutic measures. [2,3]

The present review aims to investigate the neurological impairment of patients with viral Hepatitis B and C. A systematic literature search of English-language studies was performed in Medline, Embase, Web of Science, Scopus and The Cochrane Library from January 2013 to August 2023. The systematic literature search resulted in 589 hits. The screening of titles and abstracts identified 122 potentially eligible articles. Finally, 51 studies were included in this review. The selection algorithm is shown in Figure 1.

Guillain-Barré syndrome

Guillain-Barre syndrome is one of the most frequent and severe acute peripheral neuropathies and is characterized by protein-cytological dissociation, which is detected in the analysis of cerebrospinal fluid.[5-7] The mechanism of formation of Guillain-Barre syndrome is a demyelinating lesion of peripheral nerves, which occurs due to a previous infection, which is the trigger of a further cross-autoimmune reaction.[7] Currently, there are many cases of Guillain-Barre Syndrome associated with many infectious agents, such as Haemophilus influenzae, Campylobacter jejuni, Zika virus, SARS-CoV-2 and universal interest among both scientists and healthcare professionals.[5,7-9] It is noteworthy that most patients report respiratory or gastrointestinal symptoms a few weeks before the development of Guillain-Barre Syndrome.[5]

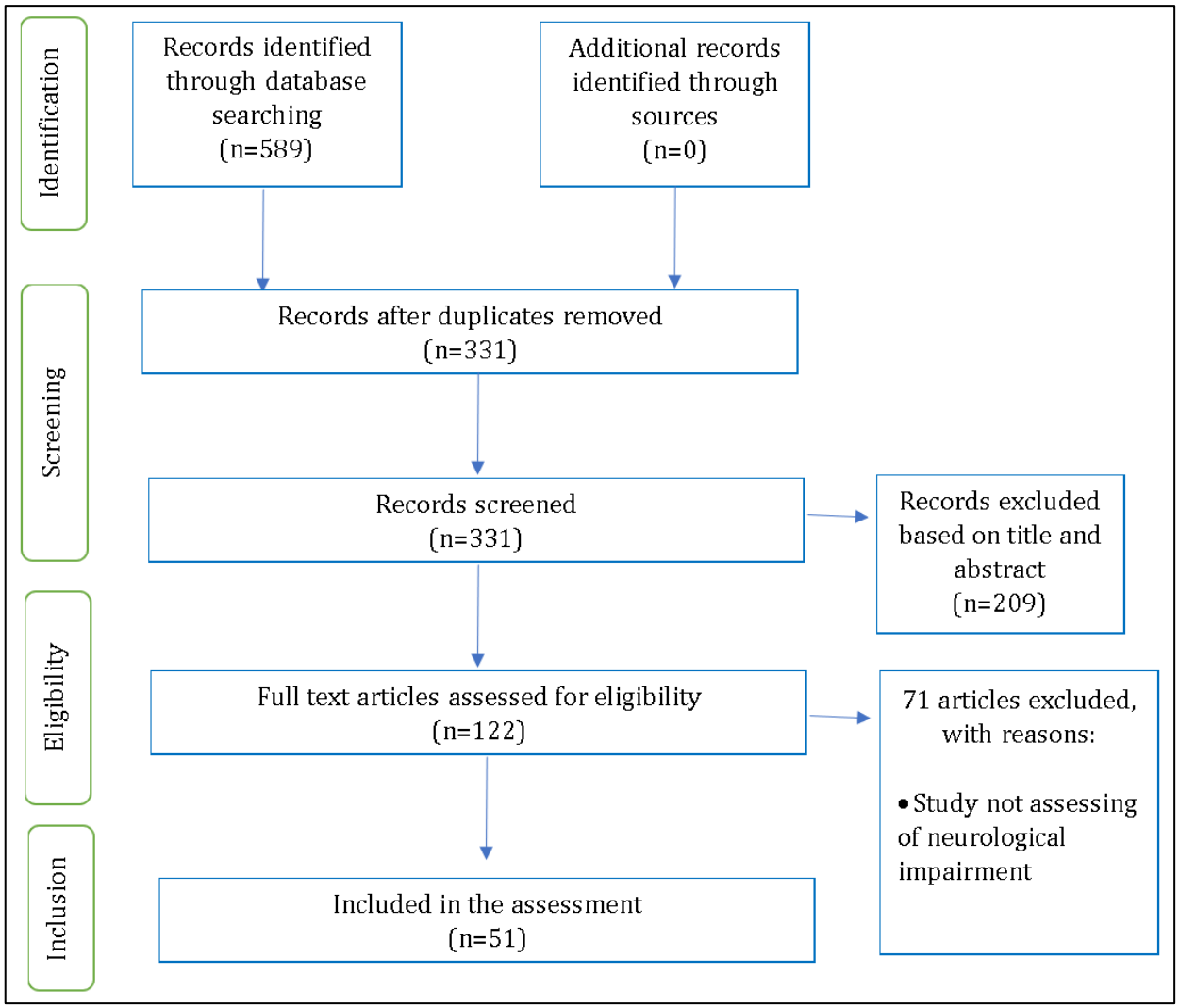

Figure 1. Flow diagram of the of the literature search

Hepatitis viruses can also form postinfectious autoimmune peripheral neuropathy and manifest acute limb paralysis.[6] However, in the modern literature, there are a small number of cases of Guillain-Barre syndrome in viral hepatitis, while most of the research is devoted to the study of the disease after viral hepatitis A and E.[7] However, the rare triggers for the development of Guillain-Barre Syndrome are viral Hepatitis B and C.[5-7,10,11] At the same time, the pathogenesis of the syndrome formation remains completely unexplored. One of the links in the pathogenesis of Guillain-Barre syndrome in viral Hepatitis B is the positive immunofluorescence labeling of HBsAg around endoneural small blood vessels and in the endoneurium of affected individuals, as well as significantly higher levels of HBsAg immune complexes in both serum and cerebrospinal fluid.[7] Besides, immune complexes can be deposited in the endoneurium through the hemato-nervous barrier and damage

nerve fibers, serving as important pathogenic agents. In addition, the Hepatitis B virus has some components similar to peripheral nerves and circulating immune complexes that can cause an imbalance of T-cell subpopulations and reduce the suppressive activity of T-cells in the peripheral blood of patients.[7] The Hepatitis B virus can cause the production of autoantibodies and activation of monocytes through molecular mimicry, leading to immune damage to myelin and axons.[7] It is known that with viral Hepatitis B, Guillain-Barre syndrome manifests itself with a severe course, which responds well to therapy with intravenous immunoglobulin, plasmapheresis, a long course of corticosteroids, immunosuppressants, appropriate antiviral therapy, the use of hepatoprotection, acupuncture, and timely rehabilitation.[5,10-12] According to some authors, there is a link between Guillain-Barre syndrome, viral Hepatitis C and mixed cryoglobulinemia.[7] A case related to acute reactivation of chronic viral Hepatitis C, which led to the formation of Guillain-Barre syndrome, is also described.[5] In addition, according to some authors, the course of Guillain-Barre syndrome can take on a severe character with a coinfection of viral Hepatitis C and HIV infection.[13]

Peripheral neuropathy

According to the latest data, there is no replication of hepatitis viruses in peripheral nerves, unlike brain cells, where this pathological process occurs.[14] Of the total number of peripheral neuropathies, 86% of cases occur in patients with existing mixed cryoglobulinemia associated with HCV infection.[14] However, a recent study found that peripheral neuropathy had a close relationship with age and Hepatitis C virus and not with cryoglobulinemia, while neuropathic pain had a correlation with damage to nociceptive pathways, which was assessed using laser-induced potentials.[15] Many studies also confirm the widespread prevalence of peripheral sensory-motor neuropathy in patients with viral Hepatitis C.[16,17] There are reports that the Hepatitis C virus can lead to peripheral neuropathy associated with eosinophilic infiltration and granuloma formation, which have been confirmed by biopsy.[18] Other studies have evaluated the role of vitamin B12 in the development of peripheral neuropathies in patients infected with viral Hepatitis C. However, as a result, no significant association was found.[19] There is evidence of the role of HCV-E2 glycoprotein in the formation of peripheral neuropathy in patients infected with the Hepatitis C virus, regardless of the presence of cryoglobulin. According to the authors, damage to peripheral nerves occurred due to immune-mediated mechanisms triggered by the Hepatitis C virus.[20] Currently, antiviral therapy used in the treatment of viral hepatitis can have a negative effect on the peripheral nervous system, causing neurological complications, which in some cases limit their use in the future.[21] However, according to other authors, the use of antiviral therapy and the eradication of the virus contributes to the regression of neurological symptoms in patients with viral hepatitis.[16,18,22,23]

Stroke

Cerebrovascular diseases are one of the main causes of mortality among the world's population.[24] Bacteria and viruses can lead to the risk of stroke, in particular, hemorrhagic stroke.[25] However, there are currently few studies on the development of ischemic stroke due to viral hepatitis.[26] The analysis showed that hepatitis viruses are one of the factors in the development of atherosclerosis of the carotid arteries.[26] The pathogenesis of ischemic stroke in patients infected with viral hepatitis includes a complex mechanism, one of the links of which are replication of the hepatitis virus in the walls of arteries, pathological secretion of inflammatory cytokines, oxidative stress, mixed cryoglobulinemia, violations of cellular and humoral immunity.[27,28] Thus, it was found that patients with chronic viral Hepatitis C have a higher level of inflammation in the endothelial cells of the brain, and it was assumed that this category of patients is more at risk of stroke.[24] In a recent study involving 2,444 patients with cirrhosis of the liver, it was found that 160 participants had a history of ischemic stroke, and 32 patients first developed ischemic stroke during hospitalization, which increased the risk of mortality.[29] According to some authors, there is a hypothesis that the elimination of the Hepatitis C virus with interferon therapy helps to reduce the risk of ischemic stroke and, consequently, mortality.[27] Patients with chronic viral hepatitis also have an increased risk of intracerebral hemorrhages, especially in patients with relatively young age.[30] Thus, it was found that patients with a history of chronic viral hepatitis have a 2.33% higher chance of recurrent intracerebral hemorrhage than patients without viral hepatitis.[30] According to the assumption of other authors, patients with decompensated cirrhosis of the liver associated with the Hepatitis B virus have a higher risk of developing countless cerebral microbleeds.[31] There are also reports that patients infected with the Hepatitis B virus have an increased risk of cerebral aneurysm rupture.[32]

Alzheimer's Disease

Alzheimer's disease is a neurodegenerative disease with a complex and multifactorial etiology that leads to irreversible loss of neurons, intellectual abilities, memory and reasoning.[33,34] Many authors confirm the undoubted role of neurotropic viruses in the development of Alzheimer's disease, but in recent years, more and more research has focused on studying the relationship between the Hepatitis C virus and dementia.[35] However, at present, the mechanism of dementia development in viral Hepatitis C remains poorly understood. This is due to the fact that viral agents can both directly and indirectly neurotoxically affect brain cells, causing systemic and/or local inflammation through the action of inflammatory markers.[35] Hepatitis viruses may have the ability to directly infect endothelial cells and penetrate the blood-brain barrier into the central nervous system. During the replication of pathogens, their constituent molecules, called pathogen-associated molecular structures, are released. When the central nervous system is damaged during infection, inflammatory mediators such as TNF-α, IFN-γ, IL-1β, IL-6, IL-18, and chemokines are released.[35] A recent multi-year large-scale study has shown that patients with a history of viral Hepatitis C significantly increase the risk of developing Alzheimer's disease.[36]

Parkinson's Disease

Parkinson's disease is a disease belonging to the group of neurodegenerative diseases and is caused by the progressive death of neurons of the substantia nigra and the formation of Levi's bodies.[37-40] Clinically, the disease includes motor symptoms such as bradykinesia, rigidity, rest tremors, and postural instability.[37] According to modern literature, the development of Parkinson's disease is due to a combination of various factors, such as genetic and environmental.[41] According to various authors, bacteria and viruses can serve as potential triggers for the development of Parkinson's disease, although at the moment, there is a small amount of work devoted to the study of the formation of the disease.[38-41] According to another author, the pathogenesis of Parkinson's disease in viral hepatitis is associated with the potential for penetration through the blood-brain barrier and the ability of hepatitis viruses to multiply in macrophages and microglial cells of the brain, resulting in increased release of pro-inflammatory cytokines and chemokines that have a neurotoxic effect on neurons and cause their death.[37,41] In addition, recent studies conducted on rats have shown that the hepatitis virus leads to the loss of dopaminergic neurons in the brain of rodents.[37,41,42] There are several proven studies in which patients with chronic viral hepatitis had a higher risk of developing Parkinson's disease.[37,43,44] Thus, a large nationwide population-based study conducted in Taiwan with the participation of 49,967 patients infected with viral Hepatitis C, it was found that this category of patients is more vulnerable to Parkinson's disease than patients without a history of viral hepatitis.[45] There are similar data from other researchers who report significant evidence of a more significant vulnerability of patients with viral hepatitis to Parkinson's disease, but the authors recommend conducting further large-scale studies to obtain more reliable data.[37,46] However, according to the results of a study by other authors, no significant link was found between Parkinson's disease and hepatitis viruses. The authors explain this fact by the fact that liver disease, in particular, in its terminal stage, leads to the formation of Parkinsonism, which in turn is mistakenly regarded as Parkinson's disease.[47-49] Despite this, many authors believe that the use of antiviral therapy in patients infected with viral hepatitis leads to a significant reduction in the risk of Parkinson's disease.[50,51]

Conclusion

Most patients with chronic viral Hepatitis B and C may have various neurological manifestations of the existing viral infection. These neurological disorders can be observed in both acute and chronic course of the disease. We recommend that patients with suspected various neurological diseases and without obvious previous acute respiratory or gastrointestinal diseases be screened for viral hepatitis.

Conflict of Interest: The authors declare no conflict of interest.

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