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# Neuropathological and Neuropsychiatric Determinants in HCV-Infected Patients

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## Abstract

Chronic hepatitis C virus (HCV) infection is a growing global health problem. HCV is a leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) and is associated with more than 30 extrahepatic manifestations (EHMs). Although cryoglobulinemia is the main pathological cause of neurologic EHMs, HCV viral replication in the brain itself must also be taken into consideration. The most significant neurological manifestations of HCV chronic infection are stroke, leukoencephalopathy, encephalomyelitis/myelitis, and peripheral neuropathy. The most significant neuropsychological manifestations of HCV infection are fatigue, depression, anxiety, and cognitive dysfunction. Antiviral HCV treatment should be the first-line treatment for managing mild-to-moderate vascular and neurologic symptoms; most of EHMs improve or even resolve if antiviral treatment starts on time.

**Keywords:** hepatitis C virus, extrahepatic manifestations, cryoglobulinemia, neurological manifestations, neuropsychological manifestations, antiviral treatment

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## 1. Introduction

Chronic hepatitis C virus (HCV) infection is a growing global health problem affecting an estimated 185 million people (a prevalence rate of 2.8%) [1]. HCV is a leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) and is associated with more than 30 extrahepatic manifestations (EHMs) [2].

EHMs are immunologic and rheumatologic in their pathophysiology: they are caused by B-cell proliferation, which produce monoclonal and polyclonal autoantibodies and then activate rheumatoid factor or have cryoglobulin properties.

Cryoglobulinemia is the most frequent and best-studied EHM of HCV infection. It is detected in up to 50% of HCV-infected patients. Cryoglobulins (CGs) are cold-precipitable immunoglobulins, which make vascular deposits and then cause inflammation and occlusion of small- and medium-size blood vessels. Typical clinical manifestations of cryoglobulinemia are cutaneous purpura, arthralgias, and membranous proliferative glomerulonephritis. Also, up to 17–60% of patients with cryoglobulinemia develop peripheral neuropathy. Central nervous system (CNS) involvement occurs in approximately 6% of cases. CGs are also a risk factor for carotid plaque formation, hepatic fibrosis, and liver steatosis [3].

Although cryoglobulinemia is the main pathological cause of neurologic EHMs, special consideration must be given to HCV viral replication in brain itself. It is believed that there are specific brain HCV variants that cause neurotoxicity (induce apoptosis). So far, it has been hypothesized that microglial cells (CNS macrophages) are the main targets for HCV entry into the CNS. Detection of replicative intermediate forms of HCV RNA and viral proteins within the CNS has led to this conclusion. Furthermore, sequence analysis of HCV residing in liver and brain has suggested an evolutionary path of a virus to infect the CNS [4].

## 2. Neurological manifestations

HCV-related CNS complications encompass a wide spectrum of disorders ranging from cerebrovascular events to autoimmune syndromes.

1. Acute cerebrovascular events can sometimes be the initial manifestation of HCV infection.
2. Acute or subacute encephalopathic syndromes have been associated with diffuse involvement of the white matter in HCV chronically infected patients with CG and/or circulating anticardiolipin antibodies.
3. The occurrence of an immune-mediated process induced by HCV causes inflammatory disorders such as acute encephalitis, encephalomyelitis, and meningoradiculitis/polyradiculitis; there are reports of patients with rapidly evolving acute leukoencephalitis or fatal progressive acute encephalomyelitic syndromes [3].
4. HCV has been connected with the metabolic syndrome so HCV infection represents an independent risk factor for increased carotid wall thickness and plaque formation, thus contributing to significant cerebrovascular mortality [3].

Neurological manifestations are most often caused by occlusive vasculopathy (due to mixed cryoglobulinemia), ANCA-associated CNS vasculitis or anti-phospholipid associated syndrome. In addition, HCV infection may increase the risk of atherosclerosis and earlier stroke through predisposition to metabolic diseases such as type 2 diabetes [5].

## 3. Neuropsychological manifestations

Fatigue, cognitive dysfunction, and mood alterations display a profound effect on social and physical function of HCV-infected subjects, thus impacting health-related quality of life (HRQL).

Chronic fatigue (often called “brain fog”) is perceived as a sensation of physical and mental exhaustion, and when severe, it is accompanied by deficits of attention tasks, anomia, and word-finding difficulties, in the absence of verbal memory or cognitive ability impairments [6].

It has been found that 28% of chronically HCV-infected subjects have depression [7]. The occurrence of depression has been attributed to psychological factors, or to specific determinants, including immune mechanisms, derangement of the blood–brain-barrier integrity, viral replication within the CNS, iatrogenic factors, or altered dopaminergic and serotonergic transmission [7]. It is very important to diagnose such manifestations because in moderate-to-severe depression it is mandatory to reduce or discontinue interferon treatment.

Investigation of a large population of patients with chronic HCV infection has disclosed the occurrence of subclinical cognitive dysfunction (alterations in verbal and learning skills, concentration, attention, working memory) in 18% of subjects [8].

#### **4. Peripheral neuropathies**

In patients with HCV, the involvement of the peripheral nervous system (PNS) ranges from 26 to 86% in accordance with the disease stage [9]. Peripheral neuropathies occur mostly in the presence of circulating CG which causes ischemic nerve changes, as a consequence of small vessel vasculitis, or, less frequently, necrotizing arteritis of medium-sized vessels [9].

In patients without CG, immune complexes or HCV-induced autoimmune mechanisms may play a pathogenetic role in inducing vascular and perivascular inflammation, which may be driven by an intrinsic nerve population of immunocompetent and potentially phagocytic cells [10].

Many patients develop a symmetrical sensory or sensorimotor axonal-type polyneuropathy, with sensory loss and weakness in distal regions of limbs [11]. Others present with mono-neuropathies and mononeuropathy multiplex or the asymmetrical sensory variants such as large-fiber sensory neuropathy (LFSN) and small-fiber sensory polyneuropathy (SFSN) [12]. Cranial nerves are usually spared.

One must also take into consideration that HCV-infected patients can have multiple neurological/neuropsychological manifestations.

#### **5. Impact of HCV treatment on neurological/neuropsychiatric disorders**

Antiviral HCV treatment is the first-line treatment for managing mild-to-moderate neurologic/neuropsychologic symptoms. However, patients on interferon (IFN) therapy should be monitored as IFN therapy may aggravate the symptoms of peripheral neuropathies (IFN can create the pathogenic inflammatory environment for neuropathy) [4].

Tricyclic antidepressants, local anesthetics, and opioids may be required to the standard antiviral therapy for treatment of acute pain attacks [4].

Rituximab is also useful in treating neuropathic pain, as it acts by inhibiting cryoglobulin production and its pathogenic cascade [4].

If EHMs do not improve after antiviral treatment, the use of immunosuppressants is also a treatment possibility, but only as a last resort in patients not responding to antiviral treatment or with refractory disease (because of possible worsening of viral infection) [4].

Also, when discussing neuropathological and neuropsychiatric manifestations in HCV-infected patients, it is very important to distinguish between neuropsychiatric diseases caused by the virus itself and those caused by the treatment.

There are many neurological side effects of HCV treatment: up to 70% of HCV patients treated with IFN may develop depression [13]. Neurovegetative symptoms like loss of appetite, fatigue, sexual impairment, and psychosomatic symptoms start to occur within 4 weeks of IFN treatment [13]. The confusional state induced by IFN is associated with psychomotor retardation, disorientation, Parkinsonism, psychosis, and manic disorder [14]. As mentioned above, IFN therapy can also aggravate the symptoms of peripheral neuropathies.

## 6. Conclusions

Sometimes EHMs can be the first clinical manifestation of HCV infection. This is why in the diagnostic work-up of a patient with the above reported neurological/psychiatric disorders without more obvious causes, clinicians should always consider screening for HCV infection.

Antiviral HCV treatment should be the first-line treatment for managing mild-to-moderate vascular and neurologic symptoms. Persistence or relapse of neurologic symptoms despite viral clearance suggest the presence of other diseases, so further diagnostic work-up should be undertaken.

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