HCV-associated neurological disorders

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Abstract

Hepatitis C Virus (HCV) infection might be associated with a number of neurological disorders. Neurological symptoms in HCV infection can either be attributed to immune-related mechanisms, e.g. the production of autoantibodies and cryoglobulins, or directly to the effects of viral cytotoxicity. The most common HCV- associated neurological disorders are distal-symmetric peripheral neuropathies and cognitive deficits. Less common manifestations include demyelinating polyneuropathies (e.g. Guillain-Barré-Syndrome) and inflammation of the muscles (myositis). Newer evidence suggests that HCV infection might also be a risk factor for stroke and Parkinson's disease. With the emergence of new antiviral drugs, HCV infection can be cured in over 90% of the patients. Thus, the identification of patients suffering from neurological conditions associated with the infection is of major importance as HCV eradication represents a causal treatment for the symptoms of these patients

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Introduction

Around 180 million people worldwide are chronically infected with the Hepatitis C Virus (HCV)[1]. The virus has been confirmed not only hepatotropic but also lymphotropic [2]. Therefore HCV infection not only causes hepatic inflammation and eventually liver cirrhosis but also a wide range of extrahepatic manifestations termed as HCV syndrome [3]. One major extrahepatic disorder associated with HCV is mixed cryoglobulinemia. Extrahepatic manifestations can either be attributed to immune-related mechanisms including the production of autoantibodies, circulating immune complexes and cryoglobulins or directly to the effects of viral cytotoxicity. These manifestations can affect different organ systems including the nervous system. The most common neurological manifestations are peripheral neuropathies and cognitive impairment. Peripheral neuropathies have an estimated prevalence of around 10%, whereas cognitive impairment seems to affect around 30% of the patients [4, 5]. Due to the lack of systematic research, the exact prevalence of other neurological disorders in the context of HCV infection is not known. Evidence is limited to case reports and smaller scope studies. With the emergence of new Direct Acting Antiviral (DAA) drugs, chronic HCV infection has become curable in over 90% of patients. This article gives an overview of the neurological manifestations of chronic hepatitis C infection in order to enable clinicians to identify patients suffering from neurological sequelae of the HCV infection. HCV eradication might represent a causal treatment for neurological symptoms related to HCV infection. For this reason, DAA treatment should not only be considered for patients with advanced liver disease but also for patients affected by neurological diseases related to HCV.

Peripheral Nervous System manifestations

HCV-related peripheral neuropathies (PN) represent the most common neurological complication of hepatitis C infection and is not necessarily associated to the presence of cryoglobulinemia (CG) [6]. The reported prevalence ranges from 26-86% of CG positive to 28-44% of CG negative patients [7, 8].

The clinical manifestations of PN are heterogeneous, depending on the extent and distribution of nerve involvement. Disease duration is a risk factor for PN but not viral load or genotype, severity of liver disease or cryocrit level [9]. Polyneuropathies can either present as mononeuritis multiplex, distal sensorimotor, sensory or isolated small fiber neuropathies. Acute or chronic inflammatory demyelinating polyneuropathy (AIDP/CIDP)/Guillain-Barré-Syndrome (GBS) or other variants of acquired demyelinating neuropathies such as multifocal motor neuropathies, neuropathies with monoclonal IgM anti MAG antibodies or Lewis-Sumner syndrome are rare HCV related complication.

Polyneuropathies

Axonal sensorimotor polyneuropathy has been described as the most common form of PN in HCV-positive patients with CG [10]. Patients affected by sensorimotor PN typically present with painful distal-symmetric paresthesia, numbness, distal weakness and sometimes atrophy.

The symptoms might be restricted to small fiber involvement. Small fiber neuropathies

(SFN) affect small unmyelinated peripheral nerve fibers (A-delta and C-fibers) causing paresthesia or pain and an impaired temperature. Patients may complain about tingling or burning feet. The sense for vibration might be slightly reduced, however the muscle strength is completely normal because of the large fiber sparing. As myelinated nerve fibers are not affected, nerve conduction studies and electromyography are unremakable in these patients. SFN can be diagnosed using quantitative sensory testing or by performing a skin biopsy to assess intraepidermal nerve fiber density.

Mononeuritis multiplex is a neuropathy characterized by the involvement of one or more peripheral nerves resulting in asymmetric loss of sensory and motor functions. Depending on the form of PN, nerve conduction studies reveal a specific pattern of axonal damage and/or demyelination pointing to the correct diagnosis.

Patients without CG are at a higher risk of developing mononeuritis multiplex compared to patients with CG [10, 11].

Demyelinating polyneuropathies

Demyelinating polyneuropathies are inflammatory disorders of the PNS characterized by immune-mediated damage to myelin sheaths or axons of peripheral nerves.

AIDP/GBS presents as acute-onset symmetric paresthesia followed by muscle weakness and autonomic dysfunction. It can result in respiratory failure in about one quarter of the patients.

CIDP is closely related to AIDP/GBS and considered as its chronic form as symptoms develop over the course of several weeks. In contrast to AIDP/GBS, symptoms of CIDP reach their maximum 8 weeks or longer after onset.

AIDP/GBS and CIDP have been described in association with both acute and chronic HCV infection [12, 13]. CIDP has been shown to respond to antiviral treatment with Interferon [14].

Pathogenesis of PNS involvement in HCV infection

The pathogenesis of PNS involvement in HCV infection is poorly understood. It is most likely be attributed to host immune response including the production of auto-antibodies, immune complex formation and inflammatory infiltrates.

Irrespective of cryoglobulin occurrence, mild perivascular inflammatory mononuclear cell infiltrates without invasion of epineurial vessel walls is described in sural nerve biopsies [15]. The demonstration of HCV RNA-specific viral sequences underlines the role of hepatitis C virus [15]. However nerve biopsies did not detect replicative forms of HCV RNA making a direct nerve infection unlikely [15-17]. Even though the significantly higher prevalence of PN in CG compared to non-CG patients [10], similar histological and molecular features have been described [18].

Myositis

Inflammatory myopathies are rare diseases. Their diagnosis criteria are based on their clinical phenotype (topography of the muscle weakness, presence of skin lesions and/or of extra-skin/muscle signs), the presence of inflammatory infiltrates on muscle biopsy as well as myositis-specific or -associated antibodies (MSA/MAA) [19]. Most of the patients can be classified among dermatomyositis (with or sine dermatitis),

overlap myositis, immune-mediated necrotizing myopathy (IMNM) or inclusion-body myositis (IBM)

All of these forms of myositis have been described in association with hepatitis C. Especially what was historically called polymyositis seems to be significantly associated with HCV infection [20, 21]. A recent study suggested that IBM might have an even stronger link to hepatitis C with about 28% of IBM patients being seropositive for HCV antibodies [22]. Pathogenesis of myositis in hepatitis C infection is not well understood. However, a combination of autoimmune mechanisms (e.g. complement and T-cell activation) leading to muscular inflammation and damage seem more likely than direct cytotoxic effects of HCV [23-25].

Central Nervous System manifestations

Hepatitis C infection can affect the Central Nervous System (CNS) in different ways. Patients may suffer from neuropsychiatric symptoms such as cognitive impairment and fatigue, but also from stroke, Parkinson's disease and demyelinating diseases. Furthermore, patients with advanced liver disease typically develop symptoms of Hepatic Encephalopathy (HE). HE results from the accumulation of toxic substances in the CNS in the context of impaired liver function. HE will not be discussed in this article as we focus on HCV-specific complications.

Cognitive Impairment/Fatigue

While PNS involvement is a well-established extrahepatic manifestation of the HCV infection, the extent and clinical significance of cognitive impairment remains a controversial subject. The detection of cognitive impairment in HCV patients without liver cirrhosis [26] has resulted in a controversial scientific debate. While many studies could replicate similar patterns of cognitive deficits, a few studies could not detect clinically significant cognitive impairment at all [27].

The pathogenesis of CNS involvement in HCV infection has been extensively studied. In contrast to the immune-mediated mechanisms underlying PNS involvement, direct and indirect viral cytotoxicity plays an important role for CNS manifestations in Hepatitis C infection. Although HCV cannot replicate in neurons, it has been shown to infect and to replicate in microglial cells and astrocytes. This eventually leads to neuroinflammation and axonal loss. Imaging studies using Magnetic resonance spectroscopy (MRS) suggest that frontal and subcortical areas are selectively affected by neuroinflammation. HCV is probably entering the brain by a "Trojan-horse mechanism" using infected monocytes to cross the Blood-Brain-Barrier (BBB). A similar mechanism of CNS penetration has also been described in Human Immunodeficiency Virus (HIV) infection. Interestingly, HCV can also directly infect endothelium cells forming the BBB itself, which results in the disruption of the BBB and the entry of free virus particles and circulating pro-inflammatory cytokines. The replicative infection of the CNS is also reflected by viraemia in the cerebrospinal fluid (CSF)[28]. Recent data even suggest the possibility of compartmentalization and the development of viral quasi-species in the CNS in some patients affected by cognitive deficits [29].

Domains affected by cognitive deficits in Hepatitis C infection are attention, verbal

learning, concentration, working memory, executive functions as well as motor functions. Furthermore, many patients complain about fatigue and depression. Especially fatigue is a well-studied and established complication of chronic Hepatitis C infection. Together with subjective cognitive impairment, these symptoms have an important impact on health related quality of life (HRQL) in Hepatitis C infected patients. Successful HCV therapy leads to an improvement in HRQL and fatigue in cured patients [30]. In parallel, studies demonstrated a positive impact of Interferon-based therapies on cognitive impairment [31]. We recently published data suggesting that Interferon-free DAA-therapies also lead to an improvement in cognitive function and HRQL [32]. This finding is important as Interferon-therapy may cause severe and in some case persisting neuropsychiatric side effects and induce autoimmunity [33]. DAA therapy may therefore not only be considered for patients with advanced liver disease, but also for patients suffering from HCV related neuropsychiatric symptoms.

Stroke

Both ischemic and hemorrhagic events can result in a critical reduction of cerebral blood flow and thereby cause a stroke. Around 90% of strokes are ischemic, mainly resulting from the disruption of atherosclerotic plaques in the carotid arteries. Both types of stroke occur more frequently in Hepatitis C infected patients than in healthy controls. Interestingly, chronic hepatitis C infection has been shown to increase the risk for ischemic stroke independently of cardiovascular risk factors [34]. HCV has been detected in carotid artery plaques and may lead to increased plaque formation and proliferation. Additionally, cryoglobulinemia in HCV infected patients can be associated with CNS vasculitis, another risk factor for ischemic and haemorraghic stroke. It has been suggested that hemorrhagic stroke results from chronic inflammation of cerebral blood vessels due to HCV infection and consecutive vessel wall frailty that eventually leads to haemorrhage. HCV infection should especially be considered in younger patients with haemorrhagic stroke [35]. Furthermore, HCV therapy may offer a possibility to reduce the risk of intracranial haemorrhage in these patients.

Parkinson's disease

Parkinson's disease (PD) is a neuro-degenerative disease affecting the motor system. Symptoms result from the loss of dopaminergic cells in the substantia nigra. Although the majority of patients suffer from idiopathic PD, there are known risk factors for PD including environmental (e.g. head injuries, pesticides) and genetic factors. Recently, two cohort studies revealed a significant correlation between HCV infection and development of PD [36, 37] while one study found no correlation [38]. In addition, it was demonstrated that the Hepatitis C virus can exhibit direct neurotoxicity to dopaminergic neurons in the midbrain [37]. Further research is needed to clarify if the Hepatitis C infection represents a valid risk factor for PD.

Myelitis/Neuromyelitis optica (NMO)

The term Myelitis refers to an inflammation of the spinal cord that can involve both white and grey matter. Depending on the level of the inflammatory lesion, patients present with acute onset motor, sensory and autonomic dysfunction. Acute transverse

myelitis is the most common form of myelitis observed in HCV infected patients. Patients typically present with motor weakness and pyramidal signs, sensory impairment and autonomic dysfunction. Patients were not positive for Aquaporin-4-antibodies (AQP4) that are associated with Neuromyelitis Optica (NMO), although NMO remains an important differential diagnosis. Spinal cord Magnetic Resonance Imaging (MRI) studies revealed multisegmental inflammation [39]. Virus-induced autoimmunity mechanisms seem to play an important role in the pathogenesis of HCV-associated myelitis [40]. Neuronal damage and inflammation can result both from vasculitis and infiltration of the spinal cord by immune cells.

NMO is an autoimmune demyelinating disorder affecting the spinal cord and optic nerves. The presence of circulating antibodies such as AQP4 or others is typical. Kitada et al. reported an HCV patient with central and peripheral demyelination and anti-AQP4 who improved with high dose steroid and plasma exchange [41]. Another case of anti-AQP4 associated NMO is reproteted by Mariotto [42].

Encephalitis/Enceaphalomyelitis

Different forms of inflammatory and demyelinating diseases of the brain have been observed in HCV infected patients. Depending on the affected brain region, patients present with seizures, motor and sensory deficits and a wide range of neuropsychiatric symptoms (e.g. confusion, memory loss, psychosis). Reported cases range from Multiple Sclerosis-like lesions, acute disseminated encephalomyelitis (ADEM) to fulminant and lethal encephalitis [43, 44]. According to different case reports, HCV associated encephalitis can imitate clinical characteristics of Multiple Sclerosis (MS), including the presentation of MS-like lesions in MRI imaging [44, 45]. Cases of ADEM have been reported in patients with both acute and chronic HCV infection [46, 47].

As HCV RNA has been detected in brain biopsies of patients with fulminant encephalitis, inflammation might be caused by HCV itself rather than by immune-mediated mechanisms, an important difference to the suspected pathogenesis of PNS involvement [43].

Conclusion

Hepatitis C is a systemic disease that causes a wide range of extrahepatic manifestations. Neurological sequelae can affect both PNS and CNS and have an important impact on morbidity and health related quality of life. HCV patients might be at higher risk of suffering a stroke or developing Parkinson's disease. As successful and well-tolerated HCV therapies have become available, all symptomatic HCV patients should be considered for DAA treatment.

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