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Hepatitis C virus and neurological damage

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Abstract

Core tip: There is high prevalence rate of neuropsychiatric ailments with respect to patients infected with chronic hepatitis C virus (HCV). Brain inflammatory disorders, cerebrovascular disease peripheral neuropathy, psychiatric disturbs and cognitive symptoms are the complex clinical signs which occurs when infected by chronic HCV infection. HCV prompts psychiatric and neurological symptoms through numerous pathways with imprecise mechanisms, which includes neurotransmitter and metabolic pathway imbalance, immune-mediated responses and direct brain neurotoxicity inflammation. Awareness of HCV-associated neuropsychiatric disorders and its pathogenic mechanisms is vital to understand the clinical manifestations and to introduce an applicable treatment.

INTRODUCTION

Hepatitis C virus (HCV) with a prevalence rate of 2.8% globally, affects around 185 million people[1]. Targeting mainly liver parenchymal cells (hepatocytes), HCV causes severe hepatitis, cirrhosis that could lead to hepatocellular carcinoma if left unattended. It may affect other organs too[2]. The association of hepatitis with insulin resistance and diabetes type 2 is well documented. Nevertheless it has also been correlated to various other organs like eye, gut, kidney, thyroid and cardiovascular complications leading to rheumatic diseases, neuropathology, and dermatological complications[3-8]. Hence, it could be considered a systemic complication, due to its ability to use cellular machinery for replication regardless of the organ[9]. How HCV is correlated with extrahepatic complications is poorly understood. Nevertheless, chronic infections are characterized by hepatic and systemic inflammation through activation of several signaling pathways and through their effect of release of various cytokines and augmented oxidative stress[10]. HCV infection could directly or indirectly cause systemic inflammations by inducing immunological response to the disease and metabolic imbalance.

The correlation of HCV disease covers a wide spectrum of clinical manifestations therefore it necessities the importance of understanding the disease in this context, clinically, to overcome these manifestations in a more robust way. It is reported that chronic HCV infection has been associated with neurological as well as psychiatric conditions in upto about 50% of the cases[11]. Major HCV related neurological ailments comprise of autoimmune disorders, cerebrovascular events, myelitis, encephalopathy, encephalomyelitis, and cognitive impairment; psychiatric disorders include, anxiety depression, and fatigue[12,13]. All the aforementioned complications that are manifested by HCV infection, regardless of the severity of disease[14]. There seems to be a lack of knowledge about how hepatitis is linked to numerous complications though it's certain that the brain can be a suitable site for viral replication[15]. Nevertheless sequence analysis of HCV residing in liver and brain show variability suggesting an evolutionary path that a virus may embark on to be able to infest the central nervous system (CNS)[14,16].

CNS INVOLVEMENT IN HCV INFECTION

HCV infection has been correlated to numerous neurological disorders ranging from meningeal to encephalic inflammation and leukoencephalitis[17,18].

Clinically a wide range of complications have been associated with HCV infection, ranging from encephalomyelitis to loss of neurons though sphincter impairment, spastic quadriparesis and sensory dominate the clinically know complication[17]. Finding the viral genome in brain during postmortem signifies the correlation of disease with neurological pathology. HCV related transverse myelitis and neuronal malfunction has been well documented[19-22].

Severe demyelination in addition to the infiltration of parenchyma and perivascular T cells has been linked to HCV infection by examining spinal cord biopsy. The commencement of the disease in indicated by acute partial transverse and myelopathy transverse myelitis, or else by sensory ataxia or spastic paraplegia. Recurrence and multi-segmental spinal involvement are commonly reported. A patient with no sign of virus but positive for anti-HCV antibodies postulates an immune mediated response leading to neurological complications.

Chronic HCV has also been associated with severe encephalomyelitis[23,24]. Magnetic resonance imaging (MRI) reports point toward CNS injuries in the cerebral and cerebellar white matter. Clinically, dysfunctional psychomotors, consciousness, hemianopsia, urinary retention, hemiparesis and other neurological defects are documented. HCV has been proposed to prompt demyelination *via* an immune-mediated response. These findings proposed that in cases with acute disseminated encephalomyelitis the likelihood of HCV infection increases[11].

NEUROPHYSIOLOGICAL SYMPTOMS

Around 50% HCV infection patients complain of neuropsychiatric symptoms, brain fog, fatigue, and also show quality of life impairment up to some extent, regardless liver disease severity[25]. During the onset of the disease HCV patients report complications like, fatigue, malaise, maintaining attention and forgetfulness. In a study on 37 HCV infected patients without other complications by McAndrews et al[26], verbal learning impairment and lack of attention were observed. A correlation of cognitive impairment and fatigue with HCV infection was observed in half of the patients observed in a study conducted by Weissenborn et al[27], comparing neuropsychological functioning of HCV positive patients with normal liver function; though in another study by Montagnese et al[28], an exceptionally high incidence of fast (β-dominated) electroencephalograms was documented.

REPLICATION OF HCV IN BRAIN

HCV, though primarily infecting the liver, is frequently associated with CNS abnormalities[27]. Neurocognitive defects in chronic HCV infection independent of hepatic encephalopathy is increasingly reported in several studies[10,26,29]. It is however unclear if the CNS itself supports the viral replication. A recent study has shown the expression of HCV receptors in the brain microvascular endothelial cells. Interestingly, the microvascular endothelia are the only cells in the neuronal pool to bear the receptors for HCV[30]. Microvascular endothelial cells, that form integral components of blood brain barrier (BBB), are thus assumed to play critical role in the transit of HCV into CNS[30].

Quantification of HCV RNA in the brain, liver and plasma have shown a 1000-10000 fold lower load in brain compared to the liver. The HCV RNA was detected in a minimum of one region of the brain of four HCV infected subjects, independent of human immunodeficiency virus (HIV) co-infection status. The viral RNA quantities from the brain and liver - however significantly varied between clinical samples, which may be due to a higher postmortem interval resulting in

the degradation of RNA in some sample[30]. The E1 and 5′ untranslated region sequences of HCV also varies between the liver, brain and plasma, further reinforcing the hypothesis of HCV replication and involvement in the brain[31-33].

Visualizing the hepatocytes expressing HCV antigen is difficult due to the low cellular viral[34,35]. Based on the relatively low HCV RNA content in brain to the liver, detection of HCV antigen in the brain is extremely challenging, and existing imaging methodologies are not sensitive enough to detect the cells of CNS that are infected by the virus[29].

Prior studies have shown the presence of HCV RNA in microglia and astrocytes that were also isolated by laser capture microdissection[36,37]. Another study has shown that two independently derived brain endothelial cell lines (hCMEC/D3 and HBMEC) facilitate the entry and replication of the virus. Antibodies specific for CD81, SR-BI, and claudin-1 inhibited the infection, demonstrating a common receptor dependent entry pathway for hepatocytes and hepatoma-derived cell lines[30,38,39]. All these studies have shown that the viral entry may not be limited to hepatocytes. mRNA and protein profile database have shown the expression of CD81, SR-BI, and claudin-1 in epithelial and endothelial cells derived from various tissues[40,41] strongly suggesting that HCV infection may be supported by extrahepatically[29]. Besides, the entry of HCV into the brain endothelial cells, its replication has also been observed. The HCV infected hCMEC/D3 cells release lower level of virus that can potentially infect hepatoma cells, thereby spreading infection which was CD81 dependent.

Studies have also shown that ApoE plays important role in the infection of brain endothelial cell[42,43]. This is evident by the neutralization of HCV infection in hCME/D3 cells by ApoE antibodies, while only partially neutralized Huh 7 further, underlining its role in exacerbation of infection in the hCME/D3 cells[30].

The tight junction between endothelial cells forming the BBB restricts the exchange of substances between the blood and CNS. Moreover, the receptor-mediated efflux transport systems further restrict the entry of hydrophilic molecules into the brain[44]. The presence of multidrug resistance proteins such as the P glycoprotein in the BBB provide a protective niche for the replication of virus by restricting the access of antiviral drugs in patients treated for HCV infection[45]. Studies have also shown the inhibition of HCV replication through antiviral agents targeting NS3 protease and NS5B polymerase enzymes *in vitro*[30].

Disruption of BBB result in enhanced access of pathogens such as the HIV and west Nile virus into the CNS[46,47]. Infection of hCMEC/D3 is associated with enhanced HCV RNA and antigen expression as confirmed by TUNEL staining with increased permeability to FD-70 a paracellular permeability marker.

In conclusion, it was observed that the brain microvascular endothelium, expressing the major viral receptors essentially contribute to the CNS infection of HCV. Specific brain endothelial cell lines have been identified to support the entry and replication of HCV in the brain that may be controlled by antibodies specific for HCV receptor-such as interferon and antiviral agents.

Low level release of virus by HCV-infected hCMEC/D3 cells with cytotoxic properties supports a model in which the BBB provides - an ideal extrahepatic environment for infection, implying a direct role of HCV to induce neuropathology[30].

MECHANISMS CONTRIBUTING TO NEUROLOGICAL DYSFUNCTION

HCV could lead to various CNS complications ranging from cerebrovascular events to autoimmune syndromes. Acute cerebrovascular events which includes transient ischemic

attacks, ischemic stroke and lacunar syndromes have been reported in patients suffering with HCV[13,48,49]. Occurrence of occlusive vasculopathy as well the vasculitis is also the well-known events[50,51]. Isolated CNS vasculitis could lead to the narrowing of cerebral arteries[52]. In few of the patients, the CNS ischemic changes might be possible in the setting of an anti-phospholipid associated syndrome or it might be associated with the anti-neutrophil cytoplasmic antibodies[53]. A recent study has shown the HCV-metabolic syndrome association with an evidence that HCV infection is a great risk factor for an enhanced thickness in the carotid wall and plaque formation, thus is a major contributory factor of cerebrovascular mortality specifically in the patients who have higher levels of HCV-RNA[54].

Encephalopathic syndromes that have been clinically characterized by confusion, altered consciousness, cognitive impairment, dysphagia, and dysarthria are linked with the diffuse involvement of white matter in HCV patients with cryoglobulins and/or circulating anticardiolipin antibodies. The patients suffering with these syndromes have also shown small lesions in the sub-cortical regions and periventricular white matter. Additionally, alterations in severe and diffuse infra and supratentorial white matter that could cause vasculitis have been observed in patients with coincidental systemic vasculitis. Another study has shown that a CNS vasculitis-induced ischemic damage in a patient that also suffering with mixed cryoglobulins (MC), peripheral neuropathy, and relapsing multiinfarct encephalopathy[55]. The neuropathological examination of this patient has shown multiple ischemic lesions (0.5-3 mm in diameter) in the white matter of cerebral hemispheres, cerebellum, parenchymal infiltration, and an accumulation of the lymphocytes around small vessels. Further study has also shown the incidence of vasculitis-induced ischemic changes in a patient that was suffering with chronic HCV, MC, and sensory neuropathy[56].

Besides the encephalopathic syndromes, cognitive decline that has been clinically characterized by an impaired attention, visual constructive, and spatial functions have been associated with an enhanced occurrence of periventricular white matter high intensity signals (WMHISs) on T2-weighted MRI[56]. The patients have shown a relationship between CG level and number of impaired cognitive functions whereas no correlation was observed with systemic manifestations of CG, including peripheral neuropathy. A variation in the WMHIS has shown vessel disease that could lead to chronic hypo-perfusion of white matter and local alterations of blood-brain barrier[57]. Spectrum of CNS syndromes encountered in HCV patients is not restricted to the foregoing vasculitic and vasculopathic forms but also causes inflammatory disorders such as an acute encephalitis, meningoradiculitis and encephalomyelitis. Studies have also shown the patients suffering with leuko-encephalitis and perivascular T-cell infiltration in association with *HCV* genome[18] or fatal progressive encephalomyelitic syndromes[17]. Another study has shown a patient suffering with an acute disseminated encephalomyelitis, an autoimmune post-infectious CNS disease that has been developed after HCV-infection which supports the role of cellular immune-mediated mechanisms in CNS complications of HCV infection[24].

Most of the patients with chronic HCV-infection complain of fatigue, poor memory and impaired concentration. Fatigue, mood alterations and cognitive dysfunction has shown a disturbed social and physical activity of the patients. Few of the HCV patients with severe fatigue also complain of sleep disturbances, restless leg syndrome, muscle and joint pain, and depression. A recent study of 53 HCV-positive patients with neuropsychiatric has shown an increase choline and myo-inositol concentrations in the basal ganglia and white matter, and an increase in the concentration of creatinine, N-acetyl-aspartate (NAA), and N-acetyl-aspartyl-glutamate in basal ganglia[58], these findings are consistent with the HCV-induced chronic cellular inflammation. Another study revealed an increased ratio of choline/creatine (Cho/Cr) in the basal ganglia as well as the frontal white matter of HCV infected patients through magnetic resonance spectroscopy[59]. Further findings have shown[60] a lower level of NAA/Cr ratio in the frontal

grey matter of HCV-patients without any change in the Cho/Cr ratio. Both findings have suggested the occurrence of an increased cell membrane turnover and reduced neuronal function[27]. Use of ondansetron which is a competitive antagonist of serotonin receptors has ameliorated fatigue in HCV infected patient. Also, the placebo controlled randomized study of thirty six HCV infected patients have shown an improved fatigue and depression scores with ondansetron[61]. These studies have shown an important role of serotoninergic pathway dysfunction that causes fatigue, reduced level of serum tryptophan, and a reduced synthesis of serotonin[62,63]. Moreover, findings of fifteen HCV infected patients reporting neuropsychiatric symptoms was carried out through different neuropsychological tests including 18F-fluoro-desoxy-glucose, serotonin, and positron emission tomography. The results have shown significant decrease in striatal and midbrain dopamine availability and decrease metabolism in limbic, parietal, frontal, and temporal cortices. These findings further confirmed significant role for defective dopaminergic transmission in causing cognitive impairment in the HCV[64]. The HCV infection has also been linked with myopathy and a few cases of non-inflammatory and inflammatory myopathies were reported. The clinical features of HCV associated myopathies ranging from progressive weakness to relapsing forms, mild increase in muscle enzymes, and moderate weakness. In non-inflammatory myopathies, pathological features include vacuolar changes[65] and necrotizing myopathy[66] with slow or progressive proximal weakness, and selective atrophy of type 2 fibers in relapsing myopathy. Study has showed the oxidative mitochondrial damage in a patient with severe ptosis, generalized weakness, diplopia and respiratory involvement, and ultra-structural changes of mitochondrial shape, and cristae[67]. Additional findings have showed that HCV promotes tumor necrosis factor - mediated apoptosis in myocytes[68].

CRYOGLOBULINEMIA

Cryoglobulins are immunoglobulins in nature. They are able to clump together at temperatures below 37 °C[69,70] causing organ damage chiefly through two main pathways, vascular sludging (Hyperviscosity syndrome, associated with type I cryoglobulinaemia) or immune-mediated (Vasculitis, associated with mixed cryoglobulinemia)[70]. Causes of cryoglobulinaemia range from, infections, autoimmune disorders and malignancy though the main culprit is HCV[70]. Our understanding of cryoglobulinaemia advocate successive antiviral therapy in conjunction with targeted therapy rather than following a monotherapeutic[71,72].

While our understanding of the disease progression still has loop holes, chronic immune stimulation/lymph proliferation due to increased cryoglobulins production, formation of complex by cryoglobulins or their antigens and their inadequate clearance are considered to be three main causative factors of cryoglobulinemia.

TYPES OF CRYOGLOBULINEMIA

Type I cryoglobulinemia is characterized by monoclonal globulins produced during lymphoproliferative disease. These Igs precipitate during exposure to cold, leading to inflammatory vasculitis and vessel obstruction.

Types II and III cryoglobulinemia is associated with increased production of cryoglobulins by proliferative B-cells clones[72,73]. Chronic HCV infection may trigger hyperactivation of B-cells causing infection *via* CD81, a cell surface protein[74,75].

HCV IN CRYOGLOBULINEMIA

Detection of HCV in 1989[76] significantly changed the course of scientific research from fundamental to HCV-oriented cryoglobulinaemia[77]. Ferri et al[78] detected circulating HCV-RNA in almost 90% of subjects with mixed cryoglobulinemia, though subsequent analyses by other groups discovered wider ecological. HBV is found to be associated with mixed cryoglobulinemia whereas HCV is primarily correlated with type II cryoglobulinaemia[79]. HIV infected patients have low percentage (7%-17%) of cryoglobulinemia but rises to almost 65% in patients coinfected with HCV[78] that can be reduced by anti-retroviral therapies[79]. Apart from viral infections the disease has also been associated with a wide range of other infectious.

HCV infection is an important model to understand the mechanisms that lie behind cryoglobulinaemic etiology. HCV lympho-tropism is the first step in B-cell hyper proliferation, regardless of cryoglobulinaemia[78,80]. E2 an HCV envelope protein interacts with the major extracellular loop of tetraspanin CD81, a signaling protein expressed by hepatocytes, B and T lymphocytes[74]. This interaction purportedly triggers prolonged B-cell stimulation[81]. B-cell clones are found in peripheral blood, bone marrow, and liver HCV patients, predominantly those with type II cryoglobulinaemia. These B-cell clones produce monoclonal IgM with an idiotype, WA that works as a cross-linker, this binds to immunoglobulins directed towards HCV core protein. Precipitates from HCV-related cryoglobulinaemia patients comprise of HCV core proteins and RNA, this means the immune system forms cryoglobulins during chronic HCV infection[82].

PERIPHERAL NEUROPATHY

Peripheral neuropathy (PN) is a complication secondary to large number of common diseases such as diabetes, thyroid disorders, renal failure, vitamin deficiency and treatments, including viral infection. Degradation of sensory or motor axons commonly occurs which disrupts the effective communication between the central and peripheral nervous system[83]. Clinically, PN manifests itself as motor impairment largely resulting in weakness, sensory defects such as numbness, paresthesia, hyperalgesia/allodynia and pain or more severe autonomic dysfunction leading to organ failures. Patients may present with multiple symptoms of varying severity, making it highly heterogeneous, which in turn depends on the underlying trigger[84]. Degeneration of axon, vascular occlusion and inflammation[84] with perivascular trafficking of mononuclear cells are essential pathologic features of the debilitating condition[85]. Demyelization and absence of axonal fascicular differentiation is also reported.

Forty percent to seventy-five percent patients positive for HCV, present with symptomatic PN, being more prominent with HCV associated cryoglobulinemia (CG)[86]. Although presence of serum cryoglobulins is a prognostic marker of severe manifestation of PN, symptoms may be reported even in its absence, underlying a direct role of the virus in precipitating the disease[87]. Yoon et al[88] reported 43.5% prevalence of PN in the absence of CG based on clinical and electrophysiological examination of HCV infected patients.

Involvement of peripheral nervous system in HCV infection is variable depending upon age, duration of infection, CG and other comorbidities[12,88]. Twenty-six percent to eighty-six percent HCV patients positive for CG present with clinical/electrophysiological PN. Pathogenesis is of HCV associated PN is indirect and mostly inflammatory, as the virus itself does not invade the nerve and muscle tissues. Mechanisms proposed to explain the neurologic manifestation of the virus include the vascular deposition of HCV RNA containing CG, direct viral invasion and perivascular inflammation[89].

HCV associated neurologic impairments range from sensory axonopathy to mononeuritis multiplex. Sensory or motor impairment of one or more distal nerves is most frequent, that tends

to become symmetric causing loss of sensation and weakness[90]. Prevalence of sensory and motor neuropathy with HCV was found to be 9% and 10% respectively[91]. Sensory predominant symmetrical polyneuropathy involves perivascular infiltration of lymphocytes and monocytes of small sized vessels. Mononeuritis multiplex, involving one or two non-contagious nerves, has a more systemic effect and involves inflammation of medium sized vessels with myriad of inflammatory cells accompanied with vascular necrosis that is asymmetric[92]. Asymmetrical sensory neuropathies may be large or small fiber. Demyelinating polyneuropathy and polyradiculonephropathy is less frequently encountered with HCV infection. Pure motor neuropathies and autonomic neuropathies are rare in HCV[12].

Abd El-Kader et al[93] estimated the prevalence of PN in patients with HCV related liver disorders based on complete neurologic examination and nerve conduction study[93]. Of the 50 subjects included in the study, 22% had sensory abnormalities, 18% had motor impairment while 10% had a combination of both. Furthermore, PN was found unrelated to serum vitamin B12 levels and severity of disease. Distal sensory loss of pain and reflexes may observe on neurologic examination in otherwise asymptomatic patients.

Biasiotta et al[90] characterized the clinical and neurological features of HCV related neuropathies. Sixty-eight percent (47 out of 69) of patients were diagnosed with peripheral neuropathy with 45 exhibiting a predominantly sensory, distal symmetric polyneuropathy while 2 showing mononeuropathy multiplex. Thermal pain sensitivity was specifically linked to pure small fiber neuropathy while sensory abnormalities observed in both mononeuropathy multiplex and mixed fiber, distal symmetric polyneuropathy.

PN can be considered a manifestation of HCV induced CG[86]. Abnormal immunoglobulin, reversibly precipitating at low temperatures, *i.e*., 4 degrees, with marked rheumatoid factor activity are produced by B cells, form immune complexes that obstruct vessels and trigger vascular inflammation[90]. IgG and IgM are primarily implicated to precipitate HCV associated PN either by their direct binding to myelin inducing an erosive immune attack or as lymphocytic irritant within the vasa nervorum resulting in vasculitis. In one study antibodies against myelin associated glycoprotein were identified to induce the immune trigger[93]. Such demyelinating association is rare with an occurrence of 5 per 10000. Anti MAG neuropathy is clinically characterized with sensory ataxia with motor involvement and hand tremor intention involving large nerve fibers[94].

PSYCHIATRIC DISORDERS IN HCV-INFECTED PATIENTS

HCV like HIV is among the few known infections that cause psychiatric disorders[95]. Illicit drug injection (IDU) is a major factor for HCV infection[96]. IDU is common among patients who have personality disorders besides alcoholism, illicit sexual behavior and mood disorders[97-99]. Alcohol is predominantly associated with increased prevalence of anti-HCV antibody. Synergy between alcohol and HCV aggravates liver disease and lessens the effectiveness of interferon (IFN) treatment. IFNα is increasingly being used to treat HCV because of its effectiveness though it can induce a variable number of psychiatric disorders likes acute confusional state, depressive and agitated manic episode[100]. Up to 70% of HCV patients treated with IFN may develop depression[96]. This could be attributed to numerous pathophysiological complication that are associated with IFN treatment including distorted monoamine metabolism[96], increase in apoptosis, BDNF reduction, and altered hypothalamus-pituitary-adrenal axis function[100]. In one study observing the neurological implication of IFN in conjunction with ribavirin treatment the authors found 1/4 of all the patients developed major depressive disorder (MDD). Higher interleukin 6 concentrations in serum, history of psychiatric condition, depression and low educational level considerably increases the incidence of MDD during antiviral therapy[101].

Symptoms of neuro-vegetative depression start to occur early during treatment though cognitive symptoms start in a span of 4 wk of IFN treatment[96]. Depression, anxiety, and cognitive impairments can be treated through serotonergic antidepressants, while neuro-vegetative symptoms like loss of appetite, fatigue, sexual impairment, and psychosomatic symptoms are not much responsive to treatment by SSRIs[102]. Hence serotonin-norepinephrine reuptake inhibitors, bupropion, methylphenidate or modafinil are used to address neuro-vegetative disorders[100]. Confusional state induced by IFNα is associated with psychomotor retardation, disorientation, Parkinsonism, and psychosis in addition to induction of manic disorder. In case of acute mania mood stabilization and antidepressants are administered[100]. HCV patients with MDD or bipolar symptoms are more prone to psychiatric disorders as compared to patients with no psychiatric illnesses during treatment with IFN[96]. It's not just IFN but HCV itself might be associated with mood disorder. This can be in part linked to factors such as high-risk behavior, stigma and drug abuse. Nevertheless, evidence suggests the association some HCV genotypes such as 3a are related to risk of depression[103]. Neuronal invasion by HCV is another factor that could lead to mental distortion[103-105].

ANTIVIRAL TREATMENT

HCV related CG is clinically challenging. Use of immunosuppressive agents such as glucorticoids and cytotoxic drugs is not recommended to manage CG induced severe neuropathic pain, because of the ensuing viral infection. Interestingly, antiviral agents considerably improve symptoms, underlining pathogenic role of virus in precipitating the secondary symptoms. Targeting the underlying viral infection is thus a reasonable strategy to treat HCV associated CG symptoms, although the response produced would be slow. Additionally, antiviral therapy suppresses B cell proliferation in the bone marrow, thereby controlling CG in more than one way. However, achieving a sustained virologic response is critical for the success of these therapies[86]. Immunosuppression prior to induction of antiviral therapy can be considered in patients with severe symptoms to obtain a reasonable and timely therapeutic response. Ideally, a combination of immunosuppressive and an anti-viral agent is highly desirable that can directly act on the proliferating B cells while simultaneously wiping out the etiologic trigger, *i.e.*, the virus[106].

IFNα is a cytokine produced by cells that primarily modulates the immune response during viral infections[83]. Interferon an in combination with other drugs is an essential component of HCV therapy. Therapeutic utility of IFN lies in their ability to decrease virus replication rate, inhibit lymphocyte proliferation, Ig synthesis with enhanced immune complex competency and macrophage activity[86].

IFNα monotherapy, although active against virus, was associated with heightened autoimmunity[107]. Thus, the IFNα itself is assumed to brew the pathogenic inflammatory environment for neuropathy *via* immune mediated myelin degradation and vessel occlusion causing nerve ischemia, in the absence of CG. Despite its increased high autoimmune titer, IFNα forms the core of HCV therapy. Peg IFNα-ribavirin is clinically, virological, immunologically superior to IFNα-ribavirin and is recommended in mild to severe cryovas with HCV. Moreover, it was associated with shorter duration of therapy, less frequent side effects and deaths producing, sustained virologic response in 60% patients[84]. Therapeutic success of the combination varies between 48%-88% depending upon the HCV genotype. Reduction of neuropathic pain in HCV positive patients was observed form 65.2% to 22.1% after peg IFN and ribavirin therapy[108]. Chronic inflammatory demyelinating polyneuropathy, reported in a minority of HCV infected population, was significantly corrected with IFNα and ribavirin therapy, although a few studies have classified it as a side effect of IFNα[109]. In that case, intravenous Ig administration and plasma exchange were effective for management of PN. The efficacy of

ribavirin in reducing PN is attributed to its viral clearance, decreasing inflammation, circulating cryoglobulins and anti MAG antibodies[83].

In patients not responding to antiviral therapy, addition of protease inhibitors telaprevir/boceprevir significantly enhanced the clinical outcome. Potency of the triple antiviral therapy was comprehensively described by Saadoun et al[110]. In a cohort with genotype 1 HCV and CG. Patients randomly received either telaprevir/boceprevir with peg IFNα/ribavirin for 48 wk and were followed up to 6 mo after treatment. Of the 56.6% patients included in the study with peripheral neuropathy, 47% showed improvement after treatment as clinically assessed by the neuropathy total symptom score. The study further highlighted the clinic considerations for the success of the triple antiviral therapy.

Successes of these trials have driven the direct use antiviral agents to reduce cryoglobulinemia and related symptoms associated with HCV. The NS3/4A inhibitor simeprevir and the NS5B inhibitor sofosbuvir have recently been approved, for their nearly absolute sustained virologic response 95% with minimum toxicities[106]. The magnified therapeutic response is due to their shortened courses of combination IFN free therapy.

Rituximab, a CD 20 monoclonal antibody, directly acts by arresting cryoglobulins production and its subsequent pathogenic cascade[108]. Rituximab monotherapy is thus highly relevant in treating cryovas emergencies such as neuropathic pain[111]. However its sole efficacy in reducing PN has not been satisfactorily assessed. In one study, 36% patients showed a subsidy in peripheral neuropath with rituximab administration.

Studies have reported higher efficacy and safety of rituximab against the conventional immunosuppressive agent's, *i.e*., glucocorticoids, azathioprine and cyclophosphamide to treat cryovas. An early clinical remission of cryovas with rituximab therapy was reported in patients with HCV, who did not show improvement with previous antiviral treatment[111-113]. Patients with liver cirrhosis, not eligible for antiviral treatment, also showed improvement with rituximab therapy, with enhanced protidosynthetic and ascites activity of the liver.

Rituximab monotherapy effectively alleviated MC symptoms in about 71.4%-84% HCV patients[111,112]. Rituximab given in combination peg IFNα-ribavirin was evaluated in patients with severe HCV-cryo, resistant to IFNα combination therapy. Of the 16 patients enrolled, 15 showed marked clinical improvement with 10 complete responders. Efficacy and safety of peg IFNα/ribivarin with and without rituximab was evaluated in two separate studies. Rituximab with the antiviral regimen produced earlier clinical remission[114-116].

Recently, low dose of interleukin 2 (IL2) has emerged as a promising approach based on the presence of defective regulatory T cells in HCV-cryo. $CD4^+$ $CD25^+$ Fox $P3^+$ T cells are assumed to be responsible for disease refraction, after the complete resolution of HCV and vasculitis[117,118]. These are regulatory cells that control the autoimmune response of the body and their deficiency during viral infection account for the expansion of holistic B cells. Efficacy of low dose IL2 in patients with refractory HCV-cryo was assessed in a prospective open labeled phase I/II a trial wherein IL2 increased the percentage of the regulatory T cells while decreasing the B cells[119-121].

DISCUSSION

Antiviral treatment should be the first line treatment for managing mild to moderate vascular and neurologic symptoms. Symptoms usually recede with an optimum sustained virologic response. Rituximab therapy should be opted for patients with severe exacerbations of secondary symptoms. Plasmapheresis may be required before placing patients on the antiviral therapy.

Patients on IFN therapy should be monitored as IFN therapy may aggravate the symptoms. Corticosteroids may be used for temporary relief of minor inflammatory pain. Immunosuppressant should be the last resort opted in patients not responding to antiviral treatment/ refractory disease.

CONCLUSION

Age and duration of HCV infection are the major clinical determinants of PN. Furthermore, it was found that duration of HCV infection and not the presence of cryoglobulins, was related to PN. Clinically, Neuropathic pain with HCV should be approached with a multimodal approach, with the prime objective being reducing the viral load, that automatically resolves secondary symptoms. Treatment should be strategized based on the severity of the disease and patients response. Addition of steroids, tricyclic antidepressants, local anesthetics and opioids may be required to the standard antiviral therapy, in case of acute pain attacks. Persistence or relapse of neurologic symptoms despite viral clearance may be indicative of other seeding conditions.