World Journal of Gastroenterology

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DOI: 10.3748/wjg.v21.i8.2269

World J Gastroenterol 2015 February 28; 21(8): 2269-2280
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Chronic hepatitis C virus infection and neurological and psychiatric disorders: An overview

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Supported by Research grant from Regione Campania, Italy.
Conflict-of-interest: All authors have no conflicts of interest.

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Received: October 1, 2014
Peer-review started: October 3, 2014
First decision: October 29, 2014
Revised: November 11, 2014
Accepted: January 8, 2015
Article in press: January 8, 2015
Published online: February 28, 2015

Abstract

Hepatitis C virus (HCV) infection is considered a systemic disease because of involvement of other organs and tissues concomitantly with liver disease. Among the extrahepatic manifestations, neuropsychiatric disorders have been reported in up to 50% of chronic HCV infected patients. Both the central and peripheral nervous system may be involved with a wide variety of clinical manifestations. Main HCV-associated neurological conditions include cerebrovascular events, encephalopathy, myelitis, encephalomyelitis, and cognitive impairment, whereas "brain fog", depression, anxiety, and fatigue are at the top of the list of psychiatric disorders. Moreover, HCV infection is known to cause both motor and sensory peripheral neuropathy in the context of mixed cryoglobulinemia, and has also been recently recognized as an independent risk factor for stroke. These extrahepatic manifestations are independent of severity of the underlying chronic liver disease and hepatic encephalopathy. The brain is a suitable site for HCV replication, where the virus may directly exert neurotoxicity; other mechanisms proposed to explain the pathogenesis of neuropsychiatric disorders in chronic HCV infection include derangement of metabolic pathways of infected cells, alterations in neurotransmitter circuits, autoimmune disorders, and cerebral or systemic inflammation. A pathogenic role for HCV is also suggested by improvement of neurological and psychiatric symptoms in patients achieving a sustained virologic response following interferon treatment; however, further *ad hoc* trials are needed to fully assess the impact of HCV infection and specific antiviral treatments on associated neuropsychiatric disorders.

Key words: Hepatitis C virus; Neurological disorders; Psychiatric disorders; Stroke; Inflammation

Core tip: High prevalence of neuropsychiatric disorders has been reported in chronic hepatitis C virus (HCV) infected patients. Cerebrovascular disease, brain inflammatory disorders, cognitive symptoms, peripheral neuropathy, and psychiatric disturbs are among the multifaceted clinical manifestations occurring during chronic HCV infection. HCV induces neurological and psychiatric symptoms through several complex and as yet unclear mechanisms, including direct brain neurotoxicity, metabolic and neurotransmitter pathway derangement, inflammation, and immune-mediated responses. Knowledge of HCV-associated neuropsychiatric manifestations and pathogenic mechanisms is paramount to correctly understand the whole clinical picture and to institute an appropriate treatment. Evidence suggests improvement of neurological symptoms following specific antiviral therapy.

Adinolfi LE, Nevola R, Lus G, Restivo L, Guerrera B, Romano C, Zampino R, Rinaldi L, Sellitto A, Giordano M, Marrone A. Chronic hepatitis C virus infection and neurological and psychiatric disorders: An overview. *World J Gastroenterol* 2015; 21(8): 2269-2280 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i8/2269.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i8.2269

INTRODUCTION

Hepatitis C virus (HCV) infection is a worldwide disease affecting about 185 million people, with an estimated prevalence of 2.8%[1]. HCV infection primarily targets the liver, causing acute and chronic hepatitis, cirrhosis, and hepatocellular carcinoma, although other organ systems may be involved[2]. Specifically, HCV infection has been associated with insulin resistance and type 2 diabetes; involvement of kidney, thyroid, eye, gut, and cardiovascular system; induction of rheumatologic, neuropsychiatric, and dermatologic manifestations[3-10]. Thus, HCV infection is increasingly being considered as a systemic disease, this notion further strengthened by accumulating evidence for HCV entry and replication in all major cellular systems of the body[11]. The mechanisms by which HCV may be implicated in extrahepatic manifestations are not yet completely understood. However, it is well known that chronic HCV infection is characterized by both hepatic and systemic inflammation through activation of several pathways, resulting, among other effects, in cytokine release and increased oxidative stress[12]. Thus, HCV may cause systemic manifestations through numerous mechanisms, *e.g.*, directly and/or indirectly *via* local and/or systemic inflammation, through an immune-mediated process, and/or by inducing metabolic derangement.

HCV-associated extrahepatic conditions may result in a wide variety of clinical manifestations capable to aggravate the clinical spectrum of hepatic infection or to even dominate the clinical scenario, regardless of liver disease manifestations. Thus, it is important for clinicians to maintain an updated knowledge of the role of HCV as causative agent in extrahepatic manifestations in order to establish a timely diagnosis and proper treatment.

Chronic hepatitis C has been reported to be associated with neurological and psychiatric disorders in up to 50% of the cases. Different pathogenic mechanisms underlie such alterations. Main HCV-associated neurological conditions include cerebrovascular events, autoimmune disorders, encephalopathy syndromes, myelitis, encephalomyelitis, and cognitive impairment; psychiatric disorders include depression, anxiety, and fatigue[13,14]. Of importance, these disorders do not seem to correlate with severity of the underlying chronic liver disease and are independent of hepatic encephalopathy[15]. If a link exists between HCV and brain damage, current knowledge seems to suggest, at least in part, a direct role for the virus. Indeed, the brain is a suitable site for HCV replication[16]; intriguingly, viral sequence diversity between brain and liver tissue has been reported, possibly suggesting independent HCV evolution in the central nervous system (CNS)[15,17].

The aim of this paper was to review the current knowledge on neurological and psychiatric conditions associated with chronic HCV infection, the presumed underlying pathogenic mechanisms, and the effects of antiviral treatment.

HCV infection and neurological diseases

Several neurological disorders, due to involvement of the central and/or peripheral nervous system, have been described in association with chronic HCV infection.

HCV infection and cerebrovascular events

In chronic HCV infection, cerebrovascular acute and chronic events have been reported with a higher prevalence than that observed in the general population; in many cases, such neurologic conditions were associated with the presence of mixed cryoglobulinemia[14,18-20]. Enger *et al*[21], in the largest retrospective study to date, including 21919 HCV-positive subjects and 67109 HCV-negative control subjects, reported a strict association between HCV and stroke, with a higher adjusted estimated risk of stroke for anti-HCV positive subjects [odds ratio (OR) = 1.76; 95%CI: 1.23-2.52]. Gutierrez *et al*[22] showed a close association between HCV infection and stroke (OR = 9.61; 95%CI: 2.51-35.78) in a retrospective study of subjects from the NHANES cohort during the period 2005-2010. However, it should be underscored that the two above studies have thus far been published only in an abstract form. Nonetheless, in a

prospective study, involving a large population cohort from Taiwan, Liao *et al*[23] established an association between HCV infection and stroke [hazard ratio (HR) = 1.22; 95%CI: 1.13-1.40]. Recently, in a large retrospective cohort from Taiwan, Hsu *et al*[24] also found a higher risk of stroke (HR = 1.23; 95%CI: 1.06-1.42) in HCV infected subjects. Likewise, we recorded a higher prevalence of HCV infection in patients with stroke when compared with a large age- and gender-matched control group (26.8% *vs* 6.6%, respectively, $P = 0.0001$)[18]. In addition, HCV infection turned out to be an independent risk factor for stroke (OR = 2.04; 95%CI: 1.69-2.46, $P = 0.0001$).

In contrast, Younossi *et al*[25] were not able to demonstrate an association between HCV and stroke in a retrospective cohort of subjects enrolled in the NHANES database between 1999 and 2010. However, the study populations were heterogeneous in terms of such factors as gender, race, and hypertension. Finally, a recent meta-analysis[26] concluded for a significantly increased risk of stroke (OR = 1.97; 95%CI: 1.64-2.30) in association with HCV infection.

Overall, data are robust enough to suggest an increased risk of stroke in chronic HCV-infected patients. Moreover, occurrence of stroke at a younger age in HCV-infected patients as well as the negative prognostic impact of HCV RNA serum levels on outcome[27], as opposed to a more limited role for gender and classic predisposing conditions[4,12], emphasizes the important role played by HCV.

How HCV may predispose to ischemic stroke is unclear. Carotid plaque destabilization with subsequent rupture and erosion plays a crucial role in the development of 20%-30% of all cases of ischemic stroke. In this regard, the causal association between chronic HCV infection and atherosclerosis is well documented[4]. Inflammation is the key mediator of plaque rupture and thromboembolism[28,29]. Consistently, chronic HCV infection is characterized by a state of chronic inflammation, which may be instrumental in the pathogenesis of arterial remodeling[12]. Infection may cause atherosclerosis by building up a cascade of immune/inflammatory responses either locally (within vascular tissue) or systemically (through inflammatory mediators)[30,31]. Indeed, HCV core protein positivity has been shown to independently predict development of carotid plaques[32]; specifically, individuals testing positive for HCV core protein had a 5.6 fold higher risk of developing carotid plaques than HCV-negative patients[32-34]. Moreover, HCV has been demonstrated to colonize and replicate within carotid plaques[13,18]. Of particular interest was the discovery of HCV RNA negative strain sequences in plaque tissue, suggesting active infection locally, and, presumably, an active role in carotid atherosclerosis through vascular inflammation and consequent plaque instability[35]. Accordingly, viral load as well as HCV-related steatosis, which result from modulation of atherogenic factors, has been reported as independent risk factors for early and facilitated carotid atherosclerosis[30]. Besides, HCV-induced mitochondrial injury may increase production of reactive oxygen species, which are known to contribute to development and progression of atherosclerosis[36,37]. The close correlation between HCV RNA serum levels and risk of cerebrovascular death lends support to the notion of a stronger inflammatory response ensuing from host-virus interaction, leading to a more accelerated and severe atherosclerosis[27].

Occlusive cerebral vascular diseases can also occur in the context of HCV-related vasculitis, such as mixed cryoglobulinemia[38-41], antiphospholipid syndrome[42,43], and ANCA-associated vasculitis[44]. HCV-related mixed cryoglobulinemia is due to precipitation of complement-fixing immune complexes in vessel walls, with involvement of such small vessels as vasa nervorum and cerebral arterioles[45]. Consistently, involvement of the white substance has been reported, manifesting as acute or sub-acute encephalopathy syndrome. Confusion, cognitive impairment, dysarthria and dysphagia can generally be observed, often in association with multi-infarct encephalopathy, likely due to small ischemic lesions leading to chronic hypoperfusion of subcortical regions and periventricular white matter[13,46]. In addition, it should not be overlooked that HCV infection may increase the risk of atherosclerosis and earlier stroke through predisposition to such metabolic diseases as type 2 diabetes, prevalently by inducing insulin-resistance[18,25,47]. Indeed, HCV has been shown to affect glucose-insulin homeostasis as well as lipid metabolism and lipid synthesis in an atherogenic fashion[3,48].

Recently, all of the known HCV receptor molecules (LDLR, CD81, claudin-1, occludin, and scavenger receptor-B1) have been reported to be expressed on the surface of blood-brain barrier endothelial cells; within these cells, HCV replication has also been documented[49]. Based on these observations, HCV can theoretically cause obstructive vascular disorders *per se*, *i.e.*, by direct involvement of brain vessels through chronic inflammation.

HCV infection and CNS inflammatory disorders

CNS involvement in chronic HCV infection may also result from encephalic and/or meningeal inflammation.

Cases of leukoencephalitis associated with HCV infection have been reported[50,51]. Different clinical patterns have been described, ranging from a rapidly evolving form with perivascular T cells infiltrates and microglial nodules to progressive encephalomyelitis associated with neuronal loss and perivascular lymphocyte infiltrates. Spastic quadriparesis, sphincter dysfunction, and sensory loss have been reported to dominate the clinical scenario[51]. As HCV genome in brain tissue has been reportedly detected at post-mortem evaluation, a possible correlation may be theorized.

Evidence of an association between HCV and transverse myelitis, with attending motor, sensitive, and autonomic dysfunction has been reported[52-55]. Acute demyelination, with parenchymal and perivascular T cell infiltration, has been described on pathological analysis of spinal cord biopsy. Disease onset may be characterized by symptoms indicative of transverse myelitis or acute partial transverse myelopathy, or else by spastic paraplegia or sensory ataxia. A recurrent course and multisegmental spinal involvement have been frequently reported. Since these cases tested positive for anti-HCV antibodies in the liquor, with no evidence of virus in tissue biopsies, an immune-mediated pathogenesis was hypothesized to explain disease pathogenesis.

Acute disseminated encephalomyelitis has also been reported in association with hepatitis C infection[56,57]. magnetic resonance imaging findings included multiple foci of CNS damage, prevalently, but not exclusively, in the cerebral and cerebellar white matter. Clinically, alterations of consciousness, psychomotor agitation, hemiparesis, hemianopsia, urinary retention, and other focal neurological defects have been described. HCV has been suggested to trigger demyelination through immune-mediated mechanisms, as also inferred by the beneficial effect of steroid therapy. These observations suggest that in patients with acute disseminated encephalomyelitis the possibility of HCV infection should not be overlooked.

HCV infection and cognitive disorders

Several studies have reported heterogeneous neuropsychological deficits in chronic HCV infected patients, including inadequate concentration and working memory speed, impaired ability of sustained attention, decreased psychomotor speed[58-61]. Nearly one-third of HCV-positive patients can be diagnosed with cognitive disorders, generally of mild degree. Individuals with poor cognitive reserve appear to be particularly susceptible to virus-induced neurocognitive impairment[62]. Failure in domains depending upon front striatal systems, including fine motor speed[63], learning[64] and information processing efficiency[59], may underlie neurocognitive disorders. An association between HCV and impairment of a range of executive functions, including reasoning, abstraction, mental flexibility[62,63] and verbal response inhibition[65,66] has also been described. Fontana *et al*[67] mainly reported alterations in verbal recall and working memory in 33% of HCV-positive patients with advanced fibrosis. Depression scores were predictive of cognitive impairment[67]. In addition, using neurophysiological tests, like P300 event-related potentials, delayed latency peaks and reduced amplitudes have been disclosed in cognitively impaired HCV-positive individuals[61].

A recent population-based cohort study was conducted to investigate the risk of dementia in chronic HCV-infected patients[68]. A total of 58570 HCV-infected and uninfected matched pairs were enrolled. During a follow-up period of 533861 person-years the incidence rates of dementia was for HCV and non-HCV of 56.0 and 47.7 cases per 10000 person-years, respectively ($P < 0.05$) and the adjusted HR was 1.36 (95%CI: 1.27-1.42) for HCV patients. The results indicate that HCV might increase the risk for dementia; however, the data, although obtained in a large cohort, need to be confirmed in different population settings.

Despite the large body of evidence on the possible relationship between HCV infection and neurologic disorders, studies not confirming such an association also exist. Hilsabeck *et al*[59] did not find a different pattern of cognitive deficits between patients with chronic hepatitis C and those with chronic liver disease of different etiology. In spite of some degree of quality of life impairment, Córdoba *et al*[65] recorded normal neuropsychiatric performance in 40 non-cirrhotic HCV-positive patients, when compared with healthy subjects. Similarly, Abrantes *et al*[69] found no evidence of an association between HCV infection and cognitive impairment. However, the small number of subjects examined in the above studies may have affected result interpretation.

HCV infection and peripheral neuropathy disorders

In contrast to the brain, there is currently no evidence for peripheral nerves as permissive sites for HCV replication; however, a wide variety of motor, sensory or sensorimotor mono- or polyneuropathies has been described during chronic HCV infection. Most peripheral neuropathies have been reported in patients with HCV-related mixed cryoglobulinemia, with prevalence up to 86% of cases[70]. In particular, a sensory motor peripheral neuropathy has been found in up to 30% of HCV-positive cryoglobulinemic patients[71-73]. Such neuropathy is the consequence of ischemic nerve changes, secondary to small-vessel vasculitis or necrotizing arteritis of medium-sized vessels[74]. Frequently, the clinical onset is subacute as a distal, symmetric, sensory or sensorimotor polyneuropathy, although asymmetrical sensory impairment has also been reported[75,76]. Small fiber sensory polyneuropathy (SFSN), a painful condition mainly characterized by burning feet and tingling, is the most frequent neuropathy observed in patients with mild cryoglobulinemia syndrome, whereas the so called large fiber sensory neuropathy (LFSN) has been described less frequently[77]. HCV-associated restless legs syndrome has also been reported as expression of SFSN[78,79]. SFSN may later evolve in LFSN. LFSN symptoms include sensory loss, paresthesias, numbness, and cramps[80].

As mentioned above, the pathogenesis of cryoglobulinemia-related neuropathy is likely due to nerve ischemia secondary to occlusion or vasculitis of the vasa nervorum[74,81], causing fascicular ischemia and axonal degeneration[82-84]. T cell dependent

mechanisms have been documented to be responsible for epineural inflammation[85]. Thus, HCV-related peripheral neuropathy seems to be the result of virus-triggered immune-mediated mechanisms[86,87]. It remains unclear whether deposition of cryoglobulin plays a direct pathogenic role during damage of the vasa nervorum or whether it simply represents an epiphenomenon of the immune response.

Neuropathy has also been reported in HCV patients without cryoglobulinemia[88,89], although with a lower prevalence (9% *vs* 45%, without and with cryoglobulinemia, respectively) and less severity[71,84]. Likewise, immune-mediated mechanisms have been proposed to explain vascular and perivascular inflammation leading to ischemia and fascicular axonal loss[90,91].

Unusual forms of neuropathy have also been reported, such as mononeuritis multiplex with necrotizing vasculitis of medium sized vessels[92], motor polyneuropathies[93], and autonomic neuropathy[94]. In addition, sporadic cases of HCV-related demyelinating peripheral neuropathy have been reported, displaying clinically heterogeneous features, including sensory ataxia[95], Lewis-Sumner syndrome[96], and chronic inflammatory demyelinating polyradiculoneuropathy[97,98].

HCV infection and psychiatric disorders

Psychiatric symptoms such as "brain fog", fatigue, weakness, depression, and anxiety have been reported with high frequency in patients with chronic HCV infection, causing interference with patient ability to perform daily activities and impairment of quality of life[99-107]. Mere knowledge of HCV serological status is itself an important reason for poor health-related quality of life[108,109], due to impairment of intimate and family relationships, changes in dietary habits, reduced sense of well-being because of fear of contagion and prognosis, social marginalization, fatigue, anger, hopelessness, depression, and stigma[110]. Moreover, the possible relation between HCV and psychiatric disorders is further strengthened by the results of studies comparing health-related quality of life between HBV and HCV patients. Specifically, a strong relationship between HCV infection and impaired physical health[111], as well as an inverse correlation between levels of brain-derived neurotrophic factor and physical health, has been documented in patients with HCV but not in those with HBV infection[112].

The most frequent psychiatric symptom reported in chronic HCV infection is fatigue[100], mainly manifesting as physical and mental exhaustion, often in association with attention deficit and word-finding difficulty, depression, headache, osteoarticular pain, and sleep disturbances. Although insomnia has been reported in up to 60% of cases, it can also be dependent on other psychiatric comorbidities, such as depression, or on such medical conditions as anemia and hypothyroidism[113], frequently associated with chronic HCV infection. Old age, female gender, and single status have been found to be predictive of fatigue in HCV patients[111,114]. Metabolic and neurotransmitter alterations in the ascending reticular activating system, limbic system, globus pallidus, and putamen have been hypothesized to play a role in the development of chronic fatigue syndrome[13].

Depression and/or anxiety have been reported in about one third of HCV-infected patients; brief, recurrent episodes of depression or anxiety have been recorded in nearly 15% of patients[115]. Navinés *et al*[116] reported an 18.2% overall prevalence of depressive disorders, as diagnosed according to DSM-IV criteria, in a series of 500 HCV-positive patients. Specifically, major depressive disorder, generalized anxiety, and panic were present in 6.4%, 7.0%, and 5.8% of the patients, respectively.

One report suggested that HCV genotype 3 infected patients might be at increased risk of depression[111]. However, it should be remembered that such patients are often drug users, which itself puts them at risk of depression. Moreover, depression was independently associated with perceived barriers to accessing HCV care, thus creating a vicious circle[117].

HCV infection and pathogenic mechanisms of neurotoxicity

Several mechanisms have been proposed to explain the pathogenesis of neuropsychiatric disorders observed in chronic HCV infection.

HCV and direct neuroinvasion

Although HCV is primarily a hepatotropic virus, HCV RNA has also been detected in peripheral mononuclear blood cells[118] and in the brain of chronically infected patients with neuropathologic abnormalities. Evidence of HCV neuroinvasion is now accumulating[15,119,120]. Seifert *et al*[50] found the viral genome in the brain tissue of a young woman with encephalitis; likewise, Vargas *et al*[121] identified HCV RNA negative strands, *i.e.*, viral replicative forms, in the subcortical white matter and cerebral cortex from two patients. Similarly, Wilkinson *et al*[122] detected HCV RNA in CD68-positive cells of CNS (macrophages/microglia) from 8 patients; HCV RNA negative strands were found in three patients. Microglial cells, a resident CNS macrophage population, have been hypothesized to be the main targets for HCV entry into the CNS[123]. Specifically, macrophages may warrant virus access into the CNS through a 'Trojan horse' mechanism, in a process similar to that hypothesized for HIV. CNS infection may follow HCV virus replication in peripheral blood mononuclear cells, which are able to cross the blood brain barrier and to serve as precursors of CNS microglial cells[17,122,124]. Moreover, tumor necrosis factor-α (TNF-α) and interleukin 8 (IL-8), which are associated with neuropsychiatric disorders, have been found to be secreted by HCV-infected

microglial cells. A close relationship between HCV RNA sequences detected in the brain and cerebrospinal fluid and those found in lymph nodes and peripheral blood mononuclear cells comes in support of this hypothesis[125]. Conversely, the diversity of viral quasispecies between the CNS and liver supports the notion of independent viral evolution in the two sites of replication[15]. Evidence suggests that brain-specific viral variants may favor HCV latency in the CNS, possibly because of mutations in the viral gene IRES, which is known to drive the initial translocation of viral polyproteins[16,17].

Since HCV core and non-structural NS3 and NS5A proteins have been found to activate macrophages/microglia as well as astrocytes of infected patients, HCV proteins have been hypothesized to have a role in inducing neurotoxicity[119,126]. HCV core protein has been described to mediate neuronal injury by suppression of neuronal autophagy and through immune activation[127]. Specifically, HCV core protein has been demonstrated to activate both toll-like receptor 2 (TLR2) signaling and extracellular signal-related kinase (ERK); neurotoxicity has been described to result from prolonged TLR2-mediated activation of ERK[128].

Brain microvascular endothelial cells have been recently demonstrated to support HCV tropism and replication[49]. HCV has been shown to induce apoptosis in these cells, leading to changes in the permeability of the blood brain barrier, microglia activation, and diffusion of pro-inflammatory cytokines into the CNS.

However, evidence for an association between HCV neuroinvasion and neuropsychiatric disorders is currently scarce; indeed, replication of quasispecies occurs at a very low level within the CNS and HCV RNA is almost undetectable in cerebrospinal fluid[129]; finally, a poor correlation between viral load and clinical manifestations has been reported[130].

HCV and changes in metabolic pathways

On proton magnetic resonance spectroscopy, metabolic abnormalities of choline/creatine ratio in basal ganglia and white matter have been detected in patients with histologically proven mild hepatitis C with respect to both healthy volunteers and chronic hepatitis B patients[131], suggesting a role for HCV itself in affecting cerebral functions. Moreover, significant correlations have been reported between cognitive dysfunction and HCV replication and between degree of impairment and the choline/creatine ratio in the basal ganglia and white matter[58]; in contrast to what is commonly observed in hepatic encephalopathy, a higher content in cerebral choline has been recorded in these patients[132]. Although the exact significance of elevated choline in the white matter remains uncertain, it may be implicated in glial activation secondary to oxidative stress; a similar mechanism has been suggested for chronic fatigue syndrome in HIV infection[133,134].

N-acetyl aspartate (NAA) is considered to be a marker of functional integrity of nervous cells and pathways; low levels are indeed associated with memory deficiency[64]. Weissenborn *et al*[130] showed a significantly decreased NAA/creatine ratio in the cerebral cortex, but not changes in the choline/creatine ratio, in chronic HCV infected patients with cognitive impairment, anxiety, and depression, with respect to healthy controls; EEG was slowed in 25% of cases. In a study involving 53 HCV-positive patients with neuropsychiatric symptoms, Bokemeyer *et al*[135] found increased choline and myo-inositol levels in basal ganglia and white matter as well as altered concentrations of creatine and NAA in basal ganglia, indicative of glial activation and macrophage infiltration. These findings were in support of HCV-induced neuro-inflammation and brain dysfunction.

Changes in neurotransmission have also been hypothesized in HCV infected patients with psychiatric disorders. In this context, Weissenborn *et al*[130] reported increased anxiety and depression in parallel with changes in both the midbrain serotoninergic and striatal dopaminergic systems, irrespective of HCV viremia and liver disease severity. Ondansetron, a competitive antagonist of serotonin receptors, has been shown to be effective in reducing HCV-related fatigue and depression[136], thus corroborating the suggestion of serotoninergic pathway dysfunction. Moreover, decreased serum tryptophan levels and serotonin synthesis has been documented in HCV patients[137,138]. However, since ondansetron treatment has been associated with clinical benefit in only a third of cases[136], additional factors are probably involved in HCV-related cognitive impairment. Heeren *et al*[139] reported reduced brain dopamine availability in 15 HCV-positive patients with neuropsychiatric symptoms, thus underscoring the prominent role of defective dopaminergic transmission in determining cognitive impairment in HCV patients.

HCV and cerebral and systemic inflammation

As discussed above, chronic HCV infection is associated with systemic and local inflammation[12] that may play a role in the pathogenesis of neuropsychiatric disorders as well. Huckans *et al*[140] identified a proinflammatory profile in HCV-positive patients, significantly correlated with neuropsychiatric symptoms. In HCV infected patients, a local inflammatory response mediated by IL-8 and TNF-α derived from HCV-infected brain macrophages/microglia has been described[126]. Chronic activation of the immune system results in the production of such cytokines as IL-1, IL-6, IL-4, and TNF-α, which are responsible for the neuronal changes underlying neurological impairment[124]. Peripheral proinflammatory cytokines, like IL-1 and IL-6, can interfere with neurotransmitter systems thus predisposing to neuropsychiatric disorders; indeed, increased levels of IL-6 have been reported to be associated with impairment of memory and spatial

learning in chronic HCV infection[140-142]; moreover, an inverse correlation between plasma levels of IL-6 and both cognitive performance and executive function has been described[143].

In summary, despite a consistent number of studies, the pathogenic mechanisms of HCV-induced neurotoxicity remain still unclear. A complex interaction among different HCV-driven derangements may be hypothesized to contribute to neurologic impairment. Further studies are ongoing and will hopefully shed light on the complex mechanisms of interaction between HCV and the nervous system. Recently, even the endocannabinoid system has been suggested to play a role in liver disease. Specifically, CB1 seems to be upregulated in patients with chronic hepatitis C[144], while CB1 receptor has been found in high concentrations in the brain. Coppola *et al*[145] demonstrated an association between a genetic polymorphism, *i.e.*, CB2-63 QQ variant, and more severe hepatic inflammation in HCV-positive patients, supporting a role for CB2 receptor in HCV-associated inflammation and cellular proliferation. Thus, the role of the endocannabinoid system in HCV-related neuropsychiatric disorders deserves further investigations, particularly in light of the possibility of being therapeutically targeted[12].

Impact of HCV treatment on neuropsychiatric disorders: Present and perspectives

Standard of care for HCV treatment is based on a regimen including pegylated interferon plus ribavirin. An improvement in response rates has been obtained with addition of viral protease inhibitors, namely, boceprevir and telaprevir, to standard of care; recently, new oral drugs, sofosbuvir and simeprevir, have been approved for use. These drugs warrant even higher response rates and can also be used without interferon. Obviously, data are lacking on the impact of these new drugs on neuropsychiatric disorders in chronic hepatitis C patients, whereas evidence is available with regard to the effects of interferon-based therapy.

While interferon-α treatment itself is known to possibly determine neuropsychiatric side effects, on the other hand, the drug ability to improve neurological and psychiatric symptoms in HCV patients achieving a sustained virologic response (SVR) has been frequently reported in the literature[146]. In particular, subjects obtaining a SVR experienced an improvement in quality of life independently of liver disease severity[105,146-149]. Moreover, SVR has also been associated with improvement in cognitive function[150], irrespective of outcome of quality of life. Vitality, social and work functioning, productivity, health distress, HCV-specific distress, and fatigue all have been recorded to ameliorate following response to interferon therapy[92]. However, caution should be exercised when considering the conclusions of these studies, since patient satisfaction due to awareness of being healed from hepatitis C may potentially bias interpretation of study results[90]. Recently, patients achieving a SVR have been shown to display reduced brain inflammation and improved neuropsychological functions, including verbal learning, memory, and visual-spatial memory, when compared to interferon nonresponders[151]; moreover, significantly reduced choline/creatine and myo-inositol/creatine ratios have been detected in the basal ganglia of SVR patients, in contrast to nonresponders or relapsing patients.

Importantly, obtaining a SVR following interferon treatment has been reported to even reduce the risk of stroke in chronic HCV infected patients. Specifically, Hsu *et al*[24] calculated a 61% reduction in the long-term stroke risk after adjusting for known prognostic factors.

Overall, the studies performed thus far, albeit with limitations due to the small number of patients, seem to indicate a beneficial effect of interferon-induced SVR on both neurological and psychiatric disorders; however, further *ad hoc* trials are needed to confirm these results.

Since HCV-related cryoglobulinemia has been associated with impaired neurological and cognitive functions, treatment of cryoglobulinemia should theoretically lead to improvement of neuropsychiatric symptoms. The standard of care for HCV-related mixed cryoglobulinemia is based on the association pegylated interferon plus ribavirin[152]. In HCV cryoglobulinemic patients, a gradual improvement in neurological symptoms has been observed after plasmapheresis and immunosuppressant therapy[153].

CONCLUSION

At the end of this overview, some considerations are due. Interpretation of study results should be done with a note of caution, because of the non-confirmatory nature of some reports, the structure of the studies, and the criteria used for study inclusion. Case-control and longitudinal studies relying on neurocognitive tests, quality-of-life questionnaires, and/or magnetic resonance spectroscopy imaging have been carried out to investigate HCV-related neuropsychiatric features. Several issues may be questioned, including the characteristics of HCV-negative controls used for comparisons and the heterogeneity of HCV-positive populations enrolled in the studies, due to coexistence of potentially confounding factors, namely, comorbidities, addictive behavior, and different stages of liver disease, particularly presence of cirrhosis. All these factors have not always been taken into due consideration. Despite these limitations, HCV seems to play an important role in the development of both cerebrovascular events and peripheral neuropathy. In addition, a

higher prevalence of fatigue, depression, and cognitive impairment has also been reported. However, the majority of HCV-associated neuropsychiatric disorders are mild and not generalizable to the whole HCV population. Indeed, a significant number of infected patients are highly fruitful individuals; besides, neuropsychiatric symptoms are potentially reversible following therapeutic HCV clearance. Further studies are necessary for a better elucidation of the role played by HCV in neuropsychiatric disorders and to specifically institute effective treatments. At present, in the diagnostic work-up of a patient with the above reported neuropsychiatric disorders, clinicians should also consider to screen for HCV infection.

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P- Reviewer: Kim SR, Pazienza V **S- Editor**: Ma YJ **L- Editor**: A **E- Editor**: Zhang DN

World Journal of Gastroenterology

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DOI: 10.3748/wjg.v21.i8.2265

World J Gastroenterol 2015 February 28; 21(8): 2265-2268
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Use of non-selective beta blockers in cirrhosis: The evidence we need before closing (or not) the window

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Conflict-of-interest: No potential conflict of interest relevant to this article to disclose.

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Received: November 8, 2014
Peer-review started: November 8, 2014
First decision: November 26, 2014
Revised: December 17, 2014
Accepted: January 30, 2015
Article in press: January 30, 2015
Published online: February 28, 2015

Abstract

Non selective beta blockers (NSBBs) are used in primary and secondary prophylaxis of portal hypertension-related bleeding in patients with cirrhosis. The efficacy of NSBBs treatment is predicted by hemodynamic response in term of reduction of the hepatic venous pressure gradient (HVPG) below 12 mmHg or at least 20% of the basal value. Nevertheless a relevant number of patients who do not achieve this HVPG reduction during NSBBs therapy do not bleed during follow up; this evidence suggests an additional non-hemodynamic advantage of NSBBs treatment to modify the natural history of cirrhosis. Recent studies have questioned the efficacy and safety of NSBBs in patients with advanced stage of liver disease characterized by refractory ascites and/or spontaneous bacterial peritonitis. These studies have suggested the existence of a defined and limited period to modify the natural history of cirrhosis by NSBBs: the "window hypothesis". According with this hypothesis, patients with cirrhosis benefit from the use of NSBBs from the appearance of varices up to the development of an advanced stage of cirrhosis. Indeed, in patients with refractory ascites and/or spontaneous bacterial peritonitis the hemodynamic effects of NSBBs may expose to a high risk of further complications such as renal insufficiency and/or death. Methodological concerns and contrasting results counterbalance the evidence produced up to now on this issue and are the main topic of this editorial.

Key words: Bleeding prophylaxis; End stage liver disease; Non-selective beta blockers; Portal hypertension; Cirrhosis

Core tip: Non selective beta blockers (NSBBs) treatment in cirrhotic patients is an undisputed strategy for bleeding prophylaxis. Nevertheless recent studies question the efficacy and safety of NSBBs in patient with advanced cirrhosis, particularly in case of refractory ascites and spontaneous bacterial peritonitis. These results suggest that NSBBs have beneficial effects on cirrhosis only in a determinate phase of the liver disease: "window hypothesis". In our opinion, the evidence produced up to now is by far conclusive to contraindicate NSBBs in patients with advanced cirrhosis.

La Mura V, Tosetti G, Primignani M, Salerno F. Use of non-selective beta blockers in cirrhosis: The evidence we need before closing (or not) the window. *World J Gastroenterol* 2015; 21(8): 2265-2268 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i8/2265.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i8.2265

INTRODUCTION

Since their introduction to reduce the re-bleeding risk in-patients with cirrhosis[1], the therapy with non-selective beta blockers (NSBBs) has been widely tested to successfully manage the risk of complications of portal hypertension (PHT) ranging from the first evidence of varices up to the bleeding related mortality[2-5]. Moreover, therapy with NSBBs has been tested to prevent other complications such as the *de novo* appearance or worsening of ascites, spontaneous bacterial peritonitis (SBP), hepato-renal syndrome (HRS), and hepatic encephalopathy[2-6].

The hepatic venous pressure gradient (HVPG), the difference between the wedged and the free hepatic venous pressures, measured by hepatic vein catheterization, is one of the most reliable surrogate markers of clinical outcome in patients with chronic liver disease[7]. A HVPG $\geqslant$ 10mmHg is independently associated with the appearance of esophageal varices and/or ascites in patients with cirrhosis, whereas a HVPG $\geqslant$ 12mmHg is the threshold for the risk of variceal rupture and bleeding[8]. Recently, investigators of PHT proposed a functional classification of cirrhosis according with a progressive multistage mortality risk[9,10]. In line with this patient stratification, the one-year mortality after a variceal bleeding episode is 40%. This risk can be reduced by the chronic treatment with NSBBs[11] mainly in patients achieving a significant reduction of HVPG[2,3].

The therapy with NSBBs was based on the recognition that a hyperkinetic circulation is behind the development of symptoms of PHT. This circulatory state is maintained by a persistent vasodilation of the splanchnic arterial bed with reduction of the central blood volume, increased heart rate and cardiac output, and retention of sodium and fluids by the kidney[12]. The reduction of this hyperkinetic circulation is the main target of therapy with NSBBs for cirrhotic patients. Indeed, the blockade of beta-1 receptors antagonizes the high cardiac output, whereas the blockade of beta-2 receptors allows the alpha-adrenergic tone to blunt the splanchnic arterial vasodilation with a lowering effect on portal pressure. Therefore, these pharmacodynamic effects can prevent a rupture of varices. A reduction of the HVPG below 12 mmHg or at least 20% of its basal value (hemodynamic response) under NSBBs is a highly specific predictor of protection from variceal rupture (good clinical response). Conversely, patients who do not achieve this HVPG reduction despite NSBBs therapy (hemodynamic non-responders) are at the highest risk of variceal rupture, although up to 48% of them does not bleed during a relatively large period of time[13]. This unexpected behavior could be explained assuming that these non-bleeding patients are protected by NSBB therapy even if they do not obtain the sufficient reduction of portal pressure. A few of other hemodynamic and non-hemodynamic effects of NSBB have been evoked to justify this clinical advantage[13]. Among them, the ability of NSBBs to reduce the gastro-intestinal permeability to bacterial by-products is a favorable effect that occurs in both hemodynamic responders and non-responders[14]. This is a crucial issue because the ability to cross intestinal barrier by bacteria and by bacterial by-products [bacterial translocation (BT)] is the main risk factor for the SBP, that in turn is the main trigger of HRS.

The efficacy of NSBBs in preventing SBP has been shown by Turnes *et al*[3] who demonstrated that a partial reduction of HVPG (11% instead of 20%) during NSBB therapy was enough to reduce the risk of SBP for a long period of time; while the meta-analysis made by Senzolo *et al*[15] including data from 5 studies, confirmed that the treatment with NSBBs reduces the risk of SBP.

Recently the French group who demonstrated, for the first time, the efficacy of NSBBs therapy to prevent variceal rupture, published a retrospective cohort study of 151 patients with refractory ascites finding that the treatment with NSBBs was independently associated with mortality [hazard ratio (HR) = 2.61 times, 95%CI: 1.91-3.44][16]. A similar concern for the safety of patients was raised for the risk of developing post-paracentesis circulatory dysfunction (PPCD) after large volume paracentesis[17]. In addition, Mandorfer *et al*[18] reported the outcome of 182 incidental cases of SBP where the chronic treatment with NSBBs (n = 86) had exposed to an elevated cumulative risk of renal failure, either defined with the criteria of HRS (11% *vs* 24%, respectively) either defined as acute kidney injury, AKI (8% *vs* 20%, respectively).

All these observations fostered the hypothesis that patients with cirrhosis and PHT may take advantage from the therapy with NSBBs only if they fall in a well-defined window of the natural story of the disease. This window would be opened by the first appearance of esophageal varices at risk of bleeding and would be closed by the development of refractory ascites or other severe complications like SBP/HRS that are clinical hallmarks of an advanced liver disease[19].

The observation by Ruiz-del-Arbol *et al*[20] that patients with SBP develop renal failure in association with reduction of cardiac output and mean arterial pressure can explain why NSBB therapy would be detrimental for survival of patients with advanced cirrhosis. This study and other similar evidences induced authors to revise the "theory of peripheral vasodilation" adding to the well-known algorithm a final

stage including patients characterized by a hyperkinetic circulation that slows down as a consequence of a relative failure of cardiac output[21]. Accordingly, the inotropic and hypotensive effects of NSBBs could represent a danger for patients with advanced cirrhosis and refractory ascites and/or HRS. By contrast, many other investigators continue to prescribe NSBBs to patients with advanced cirrhosis sustaining that the methodological quality of these recent papers is not enough to making the results reliable[22].

Therefore, the use of NSBBs in patients with advanced cirrhosis has become an issue of debate between those who are concerned upon the safety of NSBBs given to patients with severe cirrhosis and those who critics the quality of the methods used to generate the evidence of negative effects of NSBBs in cirrhosis. The methodological quality of the evidences reported in the papers of Serstè *et al*[17] and Mandorfer *et al*[18] may be too weak for such an important change of treatment in patients with cirrhosis. Indeed a series of flaws can be evidenced and summarized as following: (1) the lack of randomization to the treatment; (2) the retrospective nature of data collection; and (3) the insufficient number of patients included in the final analysis (not always consecutive).

It is noteworthy that patients developing HRS and/or SBP under NSBB therapy are those not totally protected by this class of drugs, in other words, they are clinically non-responders to NSBBs since they develop an event whose risk is reduced by the chronic treatment with NSBBs[2,3]. Therefore, this cohort of patients constitutes a highly selected subgroup of cirrhotic patients with high mortality risk if not transplanted. Recently, Leitheahad *et al*[23] conducted an observational study to explore whether or not the treatment by NSBBs increases the mortality risk of patients with an advanced liver disease. The study included a series of 322 consecutive candidates to liver transplant, 117 had refractory ascites. At exception of the window hypothesis, the survival analysis disclosed a significant mortality reduction for patients receiving NSBBs. This occurred in both categories of patients: those without refractory ascites ($HR_{mortality}$ = 0.55; 95%CI: 0.32-0.95), and those with refractory ascites ($HR_{mortality}$ = 0.35; 95%CI: 0.14-0.86). Noteworthy, the survival advantages were achieved even though patients under NSBBs had a low systemic arterial pressure. Moreover, possible selection biases were controlled by matching the population according with the propensity risk score. These results contradict the opinion that NSBBs are detrimental in patients with an advanced or end-stage liver disease. However, Authors fairly state that their patients were highly selected since they were candidates to liver transplantation.

In conclusion: which is the truth? Since its introduction, the evidenced based approach was used to test the efficacy of drugs against hard clinical end-points such as mortality, in order to replace the empiric approach. The randomized controlled trial (RCT) is the best tool to minimize confounding factors and effect modifiers behind the apparent association between an exposure (*e.g.,* treatment with NSBBs) and an effect (mortality) in a specific clinical setting (patients with advanced liver disease).

The studies supporting the "window hypothesis" challenge a huge amount of papers that consistently demonstrated the beneficial effect of NSBBs in patients with PHT. Therefore, it is now mandatory solving any doubts on the safety of such class of drugs in patients with advanced cirrhosis. This aim should be pursued by a trial including a sufficient number of patients on chronic NSBBs therapy with advanced cirrhosis, such as patients with SBP. The effects of the NSBBs would be compared randomizing these patients to stopping or not the chronic treatment with NSBBs. The preference of patients with SBP for such a trial would be justified by the relatively homogeneity of these patients ensured by objective criteria of diagnosis and high risk of renal failure. Certainly this kind of RCT is demanding, and needs a multicenter cooperation. However, the evidence we will obtain is essential before closing (or not) the window.

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P- Reviewer: Chen WX, Maruyama H, Rodriguez-Castro KI, Sargsyants N **S- Editor**: Qi Y **L- Editor**: A **E- Editor**: Zhang DN

Published by **Baishideng Publishing Group Inc**
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ISSN 1007-9327