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Chapter 11

Neurocognitive Impairments and Depression and Their Relationship to Hepatitis C Virus Infection

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http://dx.doi.org/10.5772/intechopen.74054

Abstract

The hepatitis C virus is a blood-borne virus with a direct cytopathic action. Chronic hepatitis C is a prevalent and costly disease. Studies have shown that it is a significant overlap between hepatitis C virus and mental disorders and that a substantial number of patients infected are suffering from mood disturbances and neurocognitive impairment. Recently, the neurocognitive impairments (attention, memory, and executive function alterations) were recognized as being independent of liver fibrosis and representing the direct effect of hepatitis C virus on neurons. However, until now impairments in neurocognition are not associated with viral replication or overall viral burden. Moreover, interferon alpha is still used to treat patients with hepatitis C. According to various researchers, 30–70% will develop significant psychiatric symptoms, leading to a premature discontinuation of therapy or noncompliance and worsening of quality of life. Several potential mechanisms may be implicated in the onset of a depressive episode following interferon alpha, the most important being the activation of immune-inflammatory pathways. This chapter will present the complex and striking relationships between hepatitis C virus infection and central nervous system symptoms. A variety of approaches, which integrate the extensive research data (including molecular, brain imaging, and neuropsychological findings), will be discussed.

Keywords: hepatitis C, cognitive impairments, psychiatry

1. Introduction

Hepatitis C virus (HCV) infects about 200 million people and is considered a public problem worldwide. Studies suggest that patients with HCV have a high burden of comorbidities such as psychiatric disorders, co-infection with hepatitis B and human immunodeficiency virus

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(HIV), atherosclerosis, chronic kidney disease, mixed cryoglobulinemia, insulin resistance, and several cardiovascular diseases [1, 2]. The extrahepatic manifestation is secondary to HCV-related inflammatory responses and autoimmune reactions. According to a recent meta-analysis, the most frequent extrahepatic manifestation occurring in HCV-infected persons is depression, irrespective of alcohol and drug abuse or antiviral treatment [3].

The issue of a direct relationship between hepatitis C virus (HCV) infection and neuropsychiatric symptoms was raised for some years. Initially, the psychiatric and neurocognitive complaints were considered as the results of impairments in liver function. About 50% of the patients complain of chronic fatigue, deficits in attention, memory, learning, and depression [4–8].

Meanwhile, it has been shown that the reduction of global health-related quality of life (HRQoL) and development of psychiatric and neurocognitive impairments are not correlated with the level of hepatic alterations [9, 10].

Data point to an increasing evidence to support central nervous system (CNS) change in HCV patients. Several studies detected HCV in cerebrospinal fluid and brain. Further evidence was provided by studies using imaging techniques like magnetic resonance spectroscopy (MRS), positron emission tomography (PET), and single photon emission computed tomography (SPECT).

The mechanisms through which HCV entries and replicates in the brain are not fully elucidated yet, but evidences point to microstructural changes, and cerebral metabolite abnormalities [11–13].

Historically, the treatment of hepatitis C with interferon (IFN) was burdensome, complicated, and often was associated with neurocognitive abnormalities, depression, anxiety, and psychosis.

This chapter aims to analyze the current data about the relation between chronic HCV infection, depression, and neurocognitive impairments. Also, the effects of pharmacologic viral clearance on cognitive dysfunction and psychiatric features will be discussed.

2. Neurocognitive impairments and hepatitis C virus

The evidence of CNS infection is supported by the detection of replicative intermediate forms of HCV RNA and viral proteins within the CNS. Additional mechanisms, involved in neurological dysfunction, are possibly related to the consequence of circulating inflammatory cytokines and chemokines in the brain tissues through altered sites of the blood–brain barrier [14–17]. HCV ribonucleic acid (RNA) has been detected in peripheral blood mononuclear cells, cerebrospinal fluid (CSF), and the brain of chronically infected patients with neuropathological abnormalities. The majority of reports supporting HCV in the CNS have used PCR-based approaches to detect viral genomes in brain tissue and CSF. The presence of HCV in the brain was demonstrated using immunostaining and Western blot techniques. The presence of RNA negative strand intermediate is considered as a direct evidence of HCV replication. Until now, it is not clear which cells are involved. Some authors demonstrated that HCV infects microglia/macrophages, astrocytes, brain microvascular endothelial cells,

neuroepithelioma cells, and neuroblastoma cells. More recent studies showed that CSF was found to be HCV positive in more than 50% of patients with HCV [18–23].

A variety of mechanisms have been hypothesized to explain the biological abnormalities in the brain:

a. direct infection of the brain,

b. chronic neuroinflammatory response,

c. indirect stimulation of neurotoxic cytokine pathways, and

d. toxicity mediated by vascular damage.

2.1. Neuroimaging studies

The imaging techniques that have been used to determine the biological abnormalities in HCV patients were: magnetic resonance spectroscopy, positron emission tomography, single photon computed tomography (SPECT), magnetic resonance-perfusion weighted imaging, and diffusion tensor imaging (DTI).

MRS provides noninvasive measures to evidence the metabolite abnormalities concentration in specific brain regions: myoinositol (mI), choline-containing compounds (Cho), creatine and phosphocreatine (Cr), glutathione, and N-acetyl aspartate (NAA). These metabolites are sensitive to changes in neuronal and glial state and density.

In general, metabolites are reported as a ratio to creatine. The evidence of neuroinflammation in HCV-positive patients is underlined by choline/creatine ratios. The choline-containing compound (Cho) peak is considered a marker for cell turnover and membrane metabolism. They were significantly higher in the basal ganglia (BG) and white matter of HCV positive patients. This data was associated with elevated myoinositol/creatine ratios (a marker of glial density). Myoinositol is a cerebral osmolyte and considered a marker for gliosis. Increases are thought to reflect microglial activation and are associated with CNS inflammation. Choline and myoinositol were significantly higher in the BG. N-acetyl aspartate (NAA) is considered a marker for neurons/axons. NAA and N-acetyl-glutamate were also significantly higher in BG.

Alterations in brain metabolism and neurotransmission are presented in **Table 1**.

In spite of the fact that the results vary greatly in the areas of the brain most affected, HCV positive patients with mild liver disease are characterized on MRS by higher mI (or mI/Cr), higher Cho (or Cho/Cr), and often lower NAA (or NAA/Cr). Those results are considered to represent the results of neuronal dysfunction and immune activation of microglia cells.

The main limitations of these studies are represented by:

- small study sizes,
- heterogeneity and varying selection of patients, and
- differences in data acquisition and data analysis.

Author	Year	Technique	Findings	Journal
Forton et al.	2001	MRS	Elevated choline/creatine (Cho/Cr) ratio in the basal ganglia and frontal white matter	Lancet [24]
Forton et al.	2002	MRS	Higher choline in basal ganglia, white matter	Hepatology [10]
Weissenborn et al	2004	MRS	Decrease of the N-acetyl-aspartate (NAA)/Cr ratio in the frontal gray matter no changes of the Cho/Cr ratio	Journal of Hepatology [12]
Bokemeyer et al.	2011	MRS	Increased Cho and myoinositol concentrations in basal ganglia and white matter Increased Cr, NAA, and N-acetyl-aspartyl-glutamate in basal ganglia	Gut [25]
Nagarajan et al.	2012	Localized two-dimensional correlated spectroscopy (L-COSY)	Increased myoinositol and glutathione	International Journal of Hepatology [26]

Table 1. Neuroimaging findings.

Diffusion tensor imaging (DTI) is a technique of magnetic resonance imaging that provides metrics for the speed and direction of water diffusion along the white matter tracts in the brain. DTI is a sensible method for detecting microscopic differences in tissue properties. The common DTI measures are mean diffusivity (MD), fractional anisotropy (FA), radial diffusivity (Dr), and axial diffusivity (Da). Mean diffusivity (MD) is an averaged measure of speed of diffusion in the three main directions. Fractional anisotropy (FA) measures the degree to which diffusion is faster in one direction than others. FA is used to highlight the microstructural changes, but it seems to be not very specific to the type of changes. Reductions in FA and elevations in MD seem to indicate impaired white matter integrity. Microglial state is also assessed using the positron emission tomography (PET) ligand PK11195, which binds to the mitochondrial membrane translocator protein (TPSO) present in endothelial, astroglial, and microglial cells. It is considered a marker for microglial activation. The most important neuroimaging findings are presented in **Table 2**.

2.2. Cognitive impairments

Approximately more than 50% of patients with chronic HCV infection complain of:

- poor memory,
- impaired attention, and
- fatigue.

Despite its potential clinical significance, cognitive impairments are often missed in patients evaluated for HCV, unless the manifestations are overt or interfere with the functionality, leading to impairments in health-related quality of life. When the symptomatology is very

Author	Year	Technique	Findings	Journal
Bladowska et al.	2013	DTI	Decreased FA in all white matter areas measured	Journal of Hepatology [27]
Thames et al.	2015	DTI	Increased FA in striatum, thalamus, and insula	Neurology Neuroimmunology Neuroinflammation [28]
Grover VPB	2012	PET	Significantly higher binding potential in all subcortical areas assessed (caudate, thalamus, pallidum) but in no cortical areas	Journal of Viral Hepatitis [29]
Pflugrad et al.	2016	PET	No differences between patients with mild HCV and healthy controls	Journal of Viral Hepatitis [30]

Table 2. Neuroimaging findings in HCV patients.

severe, the patients could present word finding difficulties, anomia, and significant deficits in attention performance. In general, constructional abilities and nonverbal recall are intact in these patients. Many studies suggest that approximately 30% of patients with chronic HCV exhibit cognitive dysfunctions even in the absence of cirrhosis. It seems that the cognitive performances are unrelated to viral load or viral genotype. The imaging studies showed significant reduction in striatal and midbrain dopamine availability and reduced metabolism in limbic, frontal, parietal, and temporal cortices. Thus, a crucial role of impaired dopaminergic transmission in causing cognitive impairment in HCV-infected patients was suggested. Moreover, pathologic cerebral serotonin and dopamine transporter binding were observed.

Emerging lines of evidence suggest that the profile of neuropsychological dysfunction in HCV-infected patients is characterized by impairment in:

a. executive function,

b. sustained attention,

c. working memory, and

d. verbal learning and verbal recall.

Several cognitive impairments demonstrated in patient with HCV are presented in **Table 3**.

Author	Year	Domains	Journal
Weissenborn et al.	2004	Impaired executive function	Journal of Hepatology [31]
Karaivazoglou et al.	2007	Impairment of verbal learning and memory	Liver international [32]
Fontana et al.	2007	Impairment in verbal recall and working memory	Hepatology [33]
Lowry et al.	2010	Alterations in memory, sustained attention, and delayed auditory recognition	Journal of Viral Hepatitis [34]
Ibrahim et al.	2016	Worse performance in nonverbal reasoning, attention, spatial orientation, age identification, and working memory	Journal of Clinical and Experimental Neuropsychology [35]

Table 3. Summary of major cognitive dysfunctions observed in patients with chronic hepatitis C virus infection.

There is evidence that cognitive dysfunctions in HCV patients have some impact in the reduction of health-related quality of life, chronic fatigue, and impaired functionality. The literature demonstrates evidence of neurocognitive impairment in patients with chronic HCV infection. However, until now, it is not clear that these dysfunctions can be linked, wholly or in part, to the virus itself. The longitudinal evaluation of the cognitive functioning could provide valuable information regarding the persistence of symptoms after the clearance of virus in the periphery.

3. Depression and hepatitis C virus

Depression has long been recognized and associated with many chronic medical conditions. The occurrence of depression is higher in patients with chronic liver disease than that in the general population. The depression is a very common psychiatric comorbidity in HCV patients. The link between HCV and depression has been the focus of many investigations. Several studies have reported variability in the prevalence of depression among the HCV population. The prevalence of depression in HCV patients has been estimated to be 1.5–4 times higher than in general population. Moreover, the prevalence rate seems to be unrelated to liver disease severity and interferon treatment. However, psychiatric comorbidities are usually underdiagnosed or overlooked when patients seek primary care, even though depression affects overall disease progression in the HCV-infected population [36–40].

Understanding the depressive disorder comorbid with HCV may be critical for developing effective intervention strategies. Most patients with depression will suffer noticeable changes in social and physical activities, a loss of interest in work or leisure activities, or poor academic performance. Another important issue is that HCV infection is often associated with behaviors that are condemned by society (e.g., drug use, alcoholism, and high-risk sexual behaviors), promoting prejudice, discrimination, and abuse against patients. Also, these maladaptive behaviors could further exacerbate the depression.

The high prevalence of psychiatric comorbidities in HCV-infected patients has been typically associated with direct effects of the virus on the central nervous system or adverse effects of hepatitis C treatment. The high prevalence of psychiatric comorbidities in HCV-infected patients has been typically associated with direct effects of the virus on the central nervous system or adverse effects of hepatitis C treatment.

The comorbid depression in HCV patients could be:

a. depression that may be pre-existent,

b. a reactive depression to the diagnosis of HCV,

c. a biological effect of HCV infection, or

d. an α-interferon-induced depression.

Both biological and psychosocial factors are important considerations for the effective clinical management of HCV and the prevention of HCV disease progression.

3.1. Psychosocial factors involved in development of depression

It is very important to distinguish between psychological reactions to the knowledge that one has been infected with HCV and the direct effects of the virus itself. Learning that one has contracted HCV infection represents a significant life stressor and will produce emotional stress in most patients, and psychiatric disorder in many. The psychological reasons for the development of depression are illustrated in **Table 4**. The psychosocial factors involved in the development of depression are illustrated in **Table 4**.

Stigma negatively affects the HRQOL, mental health, and social life of the patients, and leads to difficulties with receiving or accepting treatment. Poor social and work adjustment, lower acceptance of the illness, and higher subjective complaints are other problems associated with stigmatization. Researches showed that women generally are prone to experience more stigmatization. The social stigma may cause some HCV individuals to refuse to disclose their HCV diagnosis. Furthermore, HCV-related stigma is an important stressor that leads to poor treatment adherence. In some cases, HCV-infected individuals tend to isolate themselves to prevent stigma-related negative attitudes. Low income is also a socio-demographic factor significantly associated with the appearance of depressive symptoms [41–46].

The most commonly used coping styles by HCV patients are:

- problem-solving behavior,
- distraction and self-revalorization,
- religiousness and search for meaning,
- cognitive avoidance and dissimulation, and
- depressive coping.

Illness perception
Risk of cirrhosis/cancer and other health-related worries
Fear of transmitting the disease
Concerns about the complications of disease/treatment
Functional disability
Impaired quality of life
Fatigue severity
Personality disorders
Low income
Social stigma
Coping styles
Social support

Table 4. Psychosocial factors associated with the development of depression in HCV patients.

Several studies have reported using inappropriate coping strategies in patients with HCV, which may negatively affect several aspects of their management.

Psychosocial interventions that include cognitive, behavioral and lifestyle strategies may influence the negative impact of HCV symptoms and treatment side effects on HRQOL.

3.2. Biological factors

Biological factors appear to play a significant role as well. Major depressive disorder is associated with the increased production of pro-inflammatory cytokines, such as interleukin-1 (IL-1), IL-6, and interferon gamma (IFN-γ). Chronic HCV infection is also known to increase inflammatory cytokines like IL-1, IL-6, and tumor necrosis factor alpha (TNF-α). The inflammatory model of depression provides a possible link between the HCV infection and major depressive disorder. An increased macrophage migration inhibitory factor was also demonstrated in patients with major depression. Elevated pro-inflammatory cytokines have been found in patients with anxiety and depression symptoms and pharmacological agents who specifically inhibit inflammatory mediators seem to determine a reduction in depression and anxiety symptoms. The rise in cytokine levels is associated with fatigue, malaise, lethargy, and depression. Another effect of pro-inflammatory cytokines is the activation of the hypothalamic–pituitary–adrenal (HPA) axis, which represents the regulator of the stress response.

Many studies suggest that the activation of HPA pathways can modify monoamine expression in the CNS, and as a consequence, leading to symptoms of depression. It was demonstrated that the neurochemical imbalance of serotonin (5-HT), norepinephrine (NE), and dopamine (DA) is linked to the development of depression. Studies in HCV-infected patients demonstrate impaired levels of dopamine and serotonin among distinct brain regions.

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IFN-α-induced depression may increase suicidality, impair quality of life, increase, and lead to noncompliance or even treatment withdrawal among patients with chronic HCV infection. Following IFN treatment of patients with HCV, up to 70% may develop depression. Several mechanisms have been proposed:

a. altered monoamine metabolism,

b. altered hypothalamus–pituitary–adrenal axis function,

c. increased rate of apoptosis, and

d. brain-derived neurotrophic factor (BDNF) reduction.

The predictors of development of depression during antiviral treatment are:

1. history of depressive disorder,
2. sub-threshold depressive symptoms,
3. female gender,
4. low educational level, and
5. high baseline serum interleukin 6 (IL6) concentrations.

Specific risk factors for IFN-induced suicide are still unknown.

Standard treatment for CHC was for a period a combination of pegylated interferon (pegIFN) and ribavirin (RBV), which was known to exacerbate fatigue and depressive symptoms. Interferon-based regimens are related to complicated dosing schedules, weekly administration of subcutaneous injections, and many side effects. Interferon alpha combined with ribavirin has been shown to be more effective than interferon alone on obtaining sustained virologic response. Moreover, it seems that SVR achieved with PEG-IFN-α and RBV combination therapy is durable over time [51].

Until now, we do not have sufficient data whether or not the cognitive impairments are irreversible in patients who have eliminated HCV after successful treatment. A study performed by Byrnes et al. concluded that HCV eradication was associated with an improvement in memory (visual and spatial) and verbal learning [52]. Another survey of 168 HCV patients receiving antiviral therapy with interferon and ribavirin evaluated 12 months after the termination of antiviral treatment concluded that in patients with a sustained viral response a significant improvement was observed in three out five cognitive domains (working memory, vigilance, and shared attention) [53, 54].

3.3. Direct-acting antivirals

Approval of direct-acting antivirals (DAA) against the hepatitis C virus has dramatically changed the management of HCV infection due to high cure rates and a favorable safety profile. It was reported that DAA in certain combinations are curing HCV infection in almost 100% of cases [55]. DAA are taken once-daily in oral combinations. Treatment duration has also been shortened considerably in comparison with interferon therapies, making treatment regimens more tolerable. Patient-reported outcomes (PROs) provide the patient's perspective on the physical, functional, and psychological consequences of treatment and the degree and impact of disease symptoms. Recent regimens are interferon-free, and in many cases, RBV-free, and involve a combination of DAA agents. Many studies showed a consistent improvement in the quality of life, fatigue, and work productivity during treatment in patients receiving IFN and RBV-free strategy. Newly approved oral anti-HCV drugs are very safe and effective, but unfortunately, they are very costly. DAAs do not seem to increase the neuropsychiatric risks to patients undergoing HCV triple therapy [56–60].

In the absence of the neurocognitive side effects of interferon, it should be expected a significant improvement in neurocognitive functioning if, as suggested, the impairments are directly attributable to HCV action on CNS.

3.4. Treatment of depression

Several studies have specifically investigated the treatment of depression in HCV patients. The literature suggests that depression, anxiety symptoms, and cognitive complaints are responsive to selective serotonin reuptake inhibitors (SSRIs) antidepressants. However, the neurovegetative symptoms seem to be less sensitive to SSRIs. Some evidence suggests that dual antidepressants neurovegetative symptoms can be better influenced with serotonin-norepinephrine reuptake inhibitors (SNRIs). Although the data are not strong, it does appear that SSRIs might be the first choice for the treatment of interferon-induced MDD and citalopram is recommended as first-line treatment for IFN-induced depression. Antidepressant medication should be continued for at least 12 weeks following the end of IFN treatment. Antidepressant therapy is also indicated for those patients with baseline depressive symptoms and those with a history of IFN-induced depression. Data showed that antidepressant pre-treatment with SSRIs lowers the incidence and severity of IFN-associated depression in patients with chronic hepatitis C infection. But we need to keep in mind that antidepressants are not recommended for all HCV patients, and the indication should be tailored to each patient [54, 61–65].

4. Conclusions

HCV infection causes multiple provocations to practitioners due to nontreatment and especially treatment-related psychiatric comorbidities. The evidence reviewed in this chapter strongly suggests that HCV patients should be carefully monitored for psychiatric side effects of treatment. The psychiatric comorbidities along with the cognitive dysfunctions affect the patient's care significantly and might influence the course of the disease. The mechanisms involved remain mainly not sufficiently understood. Psychological adjustment to illness is determined by a complex interaction of many factors. Psychosocial factors appear to be of significance, particularly concerning the coping mechanisms and perceived stigma. In the long run, the goal is to offer a multidisciplinary approach for optimal medical and psychosocial management of patients with HCV.

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