Cognitive dysfunctions in hepatitis C virus (HCV) infection. A mini review

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Abstract

Hepatitis C virus (HCV) infection is often associated with different neuropsychiatric disturbances including various cognitive symptoms. These impairments, which affect up to 50% of all subjects, are very often reported by the patients, but generally receive poor attention, and are very rarely investigated and measured with standardised tests. This review aims to describe these symptoms, the brain circuits most often involved and their etiology, in order to provide updated information to professionals taking care of the disease. Publications from 2001 to 2012 were searched on Pubmed database through the following keywords: cognitive impairment and HCV, cognitive dysfunction in liver disease, brain and HCV, neuropsychiatric disorders in HCV, liver and brain. HCV subjects essentially show cognitive impairments of the executive functions, that is the brain activities allowing capacities such as the decision making, the planning and the management of non habitual situations. As these functions are relevant in daily life, these impairments entail significant consequences. The hypothesis suggested to explain these impairments i.e. the relationship between HCV infection and cognitive disturbances is a recent topic of research that will probably receive more attention in the future years.

Keywords: Hepatitis C virus, neuropsychiatric, impairment

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Introduction

HCV infection affects about 2% of subjects worldwide and almost 4 million people in the USA. Its natural course is modulated by host and viral factors and typically tends to chronicity, which follows the acute infection in approximately 85% of the cases. In about one third of them HCV infection leads to end stage liver disease, making HCV the primary cause of liver transplants [1]. A wide range of neuropsychiatric disturbances may develop during HCV which include behavioral and cognitive symptoms that may significantly impact daily life, requiring therefore, an early detection. These disturbances were in the past attributed to development of cirrhosis, but now they are recognized to complicate the clinical course in non cirrhotic subjects as well which suggests that the C virus has a direct effect on the central nervous system. The cognitive impairments may affect up to 50% of subjects [2] and are found also in subjects having mild HCV infection.

These patients usually complain of some memory problems or concentration difficulties, but these aspects generally do not receive particular attention, are very rarely investigated, and measured with standardised tests. However, these problems represent an aspect, which has significant impact on the daily life of the subjects, and they do deserve more attention. This review aims to describe these symptoms and the brain circuits that are most often involved, together with their etiology. Moreover, our aim is to highlight the possible consequences of HCV infection on the brain and to provide an updated information for professionals taking care of the disease.

Methods
Publications from 2001 to 2012 were searched through Pubmed database with the following keywords: cognitive impairment and HCV, cognitive dysfunction in liver disease, brain and HCV, neuropsychiatric disorders in HCV, liver and brain.

Results

The results were divided into three sections: (1) The general aspect of HCV infection, (2) The cognitive impairment related to it and (3) The possible etiology of brain dysfunction.

General aspects of HCV infection

HCV is associated with a wide spectrum of extrahepatic manifestations related with the upregulation of the immune system [3]. The most common of them are:

- type 2 cryoglobulinemia, found in 50% of the subjects
- vasculitis, found in 24-30% of the patients having cryoglobulinemia [4] due to the deposition of immune complexes in medium or small vessels
- kidney complications: membranous proliferative glomerulonephritis
- cutaneous manifestations: porphyria, lichen planus
- haematological conditions: non-Hodgkin lymphoma
- Immune disorders: sicca syndrome, diabetes type 2, thyroiditis.

At CNS level it has been observed that HCV infection is an independent factor of atheromatous plaque formation contributing to cerebrovascular disease in subjects with high viral load. Most often symptoms described as “brain fog” are found which are related to depression, weakness and fatigue.

Cognitive impairments

The first evidence of HCV related brain dysfunction was reported by Forton and Coll [4, 5]. They found that the ratio of choline : creatine was increased in the frontal white matter and in the basal ganglia of HCV patients. This study, performed through the proton magnetic resonance spectroscopy (H-MRS) was followed by others demonstrating in HCV patients with acute viral replication and compared to controls, a clear relationship between the viral load and the cognitive damage. C virus was also shown to have the specific effect while the same aspects were not found in HBV patients. Since these first observations, ten studies have been published on the topic, all showing poor cognitive performances in HCV patients. However, as most had also included cirrhotic patients, who potentially have an associated hepatic encephalopathy or were treated with interferon, results were inconclusive. In a similar way the study of Hilsabeck et al [6] has been criticized as their sample included patients with chronic alcohol intake, and also having HIV infection.

A more recent work of Wissenborn and Coll (2004) has evaluated the cognitive performances of 30 HCV patients with normal liver function and has compared their results with those of healthy controls [7]. It was found that HCV patients had a significant impairment of the executive functions, that is, those brain functions which are related to mental activities such as planning and decision making, correcting errors or managing difficult situations. In general, the ability to cope with non habitual conditions. For carrying out these functions the prefrontal brain areas are necessary but not sufficient, as other brain networks are also required. Same results are reported in a study by McAndrews [8] in a cohort of 300 patients of a tertiary care liver clinic: all those having histological evidence of mild HCV disease showed an impairment of the ability to perform a verbal learning task. Recently it has also been found that HCV patients have a lower score in memory, recognition and attention tests than those without the infection.

In summary, most studies report the presence of cognitive impairments in HCV patients with two exceptions only: studies by Cordoba [9] and Soogoor M [10], both reporting no correlation between HCV and cognition. It has to be underlined, however, that the patients evaluated in the study by Soogoor were very young subjects, while in the study by Cordoba all subjects had been selected from people screened for blood donation.

3. Possible etiology of brain dysfunction

Even if the etiology of the cognitive dysfunctions in HCV subjects is unknown, some hypothesis have been suggested to explain it, the main being a direct neurotoxic effect of HCV on the brain cells, an indirect toxicity [toxicity mediated by vascular damage].

Direct neurotoxic effect of HCV on brain cells

This hypothesis is based on very recent data demonstrating that the virus can replicate in the brain endothelial cells [11]. It has been suggested that the HC virus penetrates the brain tissue through the infected monocytes, and directly damages the brain cells. No evidence, however, exists of a correlation between the viral load and the cognitive impairment, as the HCV RNA is almost undetectable in the cerebrospinal fluid.

HCV infection may also lead to changes in brain metabolism with impairment in the neurotransmitter system. These disturbances may contribute to the mechanism by which HCV produces the cognitive impairment.

Indirect toxicity

The indirect hypothesis suggests that HCV can induce an immune system response through the activation of cyto-
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kines 6 and 1, and their active transport through the blood - brain barrier. In fact an increased level of these cytokines has been found in the HCV subjects showing memory damage and the inability to perform spatial learning. The hypothesis predicts that HCV patients may have a chronic increase of proinflammatory cytokines, which would continue for decades. The possibility to prevent this effect through the administration of cytokine antagonists lends further support to this hypothesis [12].

Toxicity mediated by vascular damage:
The third hypothesis relates the cognitive impairment to a vascular damage, which is a known complicating factor of HCV infection. Ischemic stroke, transitory ischemic attacks, lacunar syndromes, small hemorrhages and brain vasculitis as well as the presence of Ab antiphospholipids are often described in HCV subjects. Cognitive damages are also related to white matter lesions in the subcortical and periventricular areas shown by the MRI in T2 sequences, which usually indicates the effect of hypoperfusion due to small vessel disease [12].

Several other studies on the role of microglia and subsequent neuroinflammatory activity have also been conducted. Grover [13] employed two independent in vivo imaging techniques to determine evidence of neuroinflammation in patients with histologically mild chronic hepatitis C. Using positron emission tomography (PET) with a ligand for microglial/brain macrophage activation (11) C-®-PK11195 (PK11195) and cerebral proton magnetic resonance spectroscopy, it has been determined whether there was any evidence of neuroinflammation, in a pilot study of 11 patients with biopsy-proven mild chronic hepatitis C, compared to healthy volunteers. Patients were characterized by cognitive testing and the fatigue impact scale to assess for CNS impairment. PK11195 binding potential was significantly increased in the caudate nucleus of patients, compared to normal controls (P = 0.03). The caudate and thalamic binding potentials were more significantly increased in six patients with genotype 1 infection (P = 0.007) and positively correlated with viraemia (r = 0.77, P = 0.005). Basal ganglia myo-inositol/creatine and choline/creatine ratios were also significantly elevated in patients with chronic hepatitis C compared to normal controls (P = 0.0004 and P = 0.01, respectively). Using PET, a microglial activation has been demonstrated, which positively correlated with HCV viraemia and altered cerebral metabolism in the brains of patients with mild hepatitis C. These aspects provide further in vivo evidence for a neurotropic role of HCV.

Discussion

The “brain fog”, a symptom often mentioned by HCV patients, usually receives poor attention. Physicians who are generally more prone to attribute the symptom to a slight depression than to the disease itself, should instead suggest an accurate evaluation of these patients. Specific neuropsychological tests are aimed at this purpose, as they allow to measure the difficulties reported by subjects, and to inscribe them in the context of a possible underlying impairment. The observation that HCV can replicate in brain cells, and that neuroinflammation is a constant feature of HCV may explain the development of such cognitive symptoms that have been confirmed by a relevant number of studies. Other aspects related to HCV infection may also have a role in cognitive symptoms. As the brain metabolism changes, an imbalance in neurotransmitters is created which leads to vascular damage. All these changes might cause, directly or indirectly, the cognitive impairments seen in HCV subjects, which often affect a significant number of daily life activities, including the ability to plan actions, accomplish duties, and to control behaviours. Memory, being related to the executive functions, may be impaired too. As HCV infection is epidemiologically very relevant, and it tends to chronicity in a large number of the cases, these results underline the necessity to investigate early and in detail these aspects, to evaluate if some therapeutic measures may be beneficial and to involve the family members of the ill person in coping with them.

References


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