

Neuropsychological alterations in hepatitis C infection: The role of inflammation

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Abstract

About 50% of patients with hepatitis C virus (HCV) infection complain of neuropsychiatric symptoms, "brain fog", weakness, fatigue, and exhibit some degree of quality of life impairment, irrespective of the severity of liver disease. Since the first observation of HCV-related cognitive deficits, 10 studies have been published that have evaluated neuropsychiatric performance in patients with HCV infection and different degrees of hepatic impairment. Unfortunately, these have often included patients with cirrhosis, patients who had acquired the infection through previous intravenous drug misuse, who had a history of relatively recent treatment with interferon, or were on psychoactive medication. In addition, different neuropsychological batteries and tests that explored different cognitive domains were

used, which makes the results of the studies difficult to compare. Finally, limited information is available on the pathogenesis of HCV-related cognitive impairment. Cerebral and/or systemic inflammation may be important players but their potential role has not been substantiated by experimental data. The present review outlines the available evidence of the presence of cognitive impairment in patients with HCV infection, with a focus on the potential relationship with cerebral and/or systemic inflammation.

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INTRODUCTION

Hepatitis C virus (HCV) infection affects up to 2% of the world population and almost 4 million people in America. Although evolution to chronic HCV infection is extremely common, only 30% of chronically infected patients go on to develop end-stage liver disease and hepatocellular carcinoma.

The occurrence of hepatic encephalopathy is well

documented in patients with viral cirrhosis, as in patients with cirrhosis of other etiologies^[1]. However, in recent years, there has been growing evidence that alterations in cerebral function in patients with chronic HCV infection may appear long before the development of severe liver fibrosis/cirrhosis. These alterations cannot be ascribed to hepatic encephalopathy. About 50% of patients with HCV infection complain of neuropsychiatric symptoms, “brain fog”, weakness, fatigue, and exhibit some degree of quality of life impairment, irrespective of the severity of liver disease^[2]. These alterations do not seem to relate to HCV genotype or replication^[3]. Their etiology is unclear but it has been hypothesized that it is related to: (1) a direct effect of HCV on the brain; or (2) the neurotoxic effect of HCV-related systemic inflammation.

In the present review, we outline the available evidence of cognitive impairment in patients with HCV infection, and the possible role of cerebral and systemic inflammation.

COGNITIVE ALTERATIONS IN PATIENTS WITH HCV LIVER DISEASE

Early in the course of infection, patients with HCV infection report symptoms like fatigue, malaise, weakness and problems in maintaining attention and recalling information. These alterations can interfere with their ability to perform their activities, thus leading to impairment in health-related quality of life, which is well documented^[4-12]. In addition, although treatment of chronic HCV infection can temporarily worsen health-related quality of life, the relationship between sustained viral response and improvement in quality of life is also well accepted^[13].

The first significant evidence for a specific role of HCV in causing cerebral function abnormalities was produced in 2001 by Forton and colleagues, who detected cerebral metabolic abnormalities (elevated choline/creatine ratio) in the frontal white matter and basal ganglia of HCV-infected patients, using proton magnetic resonance spectroscopy (¹H MRS); these alterations were not present in either controls or patients with HBV infection^[14]. In the following year, the same group showed significant impairment in concentration and working memory in 27 HCV-infected patients with active viral replication, compared to 20 controls and 16 anti-HCV-positive but HCV-RNA-negative patients^[15].

Since these original observations, 10 studies have been published that have evaluated neuropsychiatric performance in patients with HCV infection and different degrees of hepatic impairment. Unfortunately, these have often included patients with cirrhosis (potentially, also those with minimal hepatic encephalopathy); patients who had acquired the infection by previous intravenous drug misuse; patients who had a history of relatively recent treatment with interferon; patients on psychoactive medication; or those who complained of significant fatigue; all of which could impinge on cognitive perfor-

mance, in terms of motivation and psychomotor speed. In addition, different neuropsychological batteries and tests that explore different cognitive domains have been utilized, which makes it difficult to compare the results of the studies.

Hilsabeck and colleagues have documented a prevalence of cognitive dysfunction which ranged from 0% on a design copy task to 49% on a measure of sustained attention in a group of 66 HCV-infected patients; 44 (66%) of whom had cirrhosis^[16]. The HCV-infected patients were compared to a cohort of 14 patients with liver disease of other etiology, who had normal cognitive performance. However, within the study group, there were factors that could have contributed to cognitive impairment, such as previous alcohol intake and HIV co-infection; the control group also included patients with previous alcohol misuse and those with cirrhosis, and possibly minimal hepatic encephalopathy. The authors were able to correlate the degree of fibrosis with that of cognitive impairment, and suggested that the latter might parallel progressive liver injury in HCV-infected patients. However, the inclusion of even a small number of patients with cirrhosis and hepatic encephalopathy might well be responsible for the correlations observed. In addition, sustained attention, which was found to be abnormal in almost half of the study group, is known to be impaired in patients with hepatic encephalopathy^[17,18].

When the same authors administered a similar test battery to an independent group of HCV-infected patients, 33% of whom had cirrhosis, there was no correlation between perceived cognitive impairment, fatigue or depression and neuropsychological performance, which suggests that the latter might not be clinically relevant^[19]. Similarly to the previous study, a correlation was observed between neuropsychological performance and the degree of fibrosis, which led the authors to suggest that progressive liver injury might result in worsening neuropsychiatric function in HCV-infected patients. Within this setting, it would be difficult to explain how a significant proportion of patients with HCV-related cirrhosis, just like those with cirrhosis of other etiology, would show completely normal neuropsychiatric function on extensive screening for hepatic encephalopathy.

The issue of the relationship between cognitive impairment and perceived fatigue in HCV-infected patients was subsequently addressed by Weissenborn and colleagues, who compared neuropsychological performance in 30 PCR-positive HCV-infected patients with normal liver function, 15 of whom reported moderate to severe fatigue^[20]; patients with previous drug misuse, interferon treatment, psychiatric disease and patients on psychoactive drugs were excluded. The authors found a significant deficit in attention and higher executive function in patients compared to controls, in parallel with an increase in depression and anxiety. Patients with self-reported fatigue performed worse on the neuropsychological battery, whereas there was no correlation between anxiety/depression and cognitive performance. In the same

study, patients with HCV infection showed a significant decrease of the N-acetyl-aspartate/creatinine ratio in the cerebral cortex on ^1H MRS, while the electroencephalogram was slowed in 25%^[20]. In contrast, in a published abstract, Montagnese and colleagues have reported on an unexpectedly high prevalence of fast (β -dominated) electroencephalograms in a similarly well-selected population of HCV-infected patients. Similar features had been previously reported in HIV-infected individuals^[21] and could be related to some degree of desynchronization of the cerebral electrical activity.

McAndrews and co-workers have confirmed the presence of minor attention deficits and impairment in verbal learning ability in their study of 37 well-selected HCV patients without disease-associated risk factors, such as substance misuse, cirrhosis or depression^[22]. When compared with 46 age-matched controls, 13% of patients with HCV infection showed impairment in verbal learning ability; however, the chosen threshold for a pathological performance was 1.5 SDs below the norm, which is stricter than the usual 2 SDs. The authors themselves qualify the detected abnormalities as having limited clinical relevance. As in previous studies, McAndrews and colleagues also detected an increase in choline and a reduction in N-acetyl aspartate by MRS in the central white matter of patients compared to controls.

In contrast, Fontana and co-workers have found that 33% of 177 patients with HCV infection and advanced fibrosis who were enrolled in the HALT-C trial could be considered to have cognitive impairment (before interferon and ribavirin treatment), based on a composite score of 10 neuropsychological tests^[23]. The most affected domains were verbal recall and working memory. However, 38% of patients had cirrhosis, and working memory is known to be impaired in patients with cirrhosis and hepatic encephalopathy^[24], which was probably a significant confounder in this study. In addition, 50% of patients had been alcohol misusers and 46% had a history of intravenous drug abuse. In contrast with the findings by Hilsabeck and colleagues, Fontana and co-workers observed no relationship between cognitive alterations and the degree of fibrosis or mood disturbances^[23].

More recently, Lowry and colleagues studied neuropsychiatric function in a well-selected, homogeneous cohort of 20 female, iatrogenically-infected patients; of whom, 11 were positive for HCV RNA and nine had spontaneously cleared the virus^[25]. The authors showed that PCR-positive women had significantly poorer scores in the areas of memory, auditory recognition and sustained attention compared to a small group of nine healthy controls; these abnormalities were not present in the PCR-negative women.

To date, two studies that explored cognitive function in chronically HCV-infected patients were completely negative. The first was published by Cordoba and colleagues^[26], who showed normal neuropsychiatric performance in 40 HCV patients with normal hepatic function; however, these individuals still exhibited some degree of

quality of life impairment. In the same study, significant alterations in attention, executive function and motor performance were detected in a control group of patients with HCV-related cirrhosis. In contrast to most previous studies, Cordoba and co-workers selected their HCV-positive patients amongst healthy individuals screened for blood donation^[26]; this is a fairly different population compared to patients with known chronic HCV infection.

The second negative study included 103 HCV-PCR-positive young patients (aged 6-19 years) who were studied with the Adaptive Behavioural and WAIS scales. In this group, the time lag between infection and cognitive assessment might have been significantly lower compared to the other, adult cohorts, thus possibly explaining, at least to some extent, the negative results^[27].

One study that compared cognitive performance in 32 patients with chronic hepatitis C against 29 chronic hepatitis B showed that HCV patients had worse performance in verbal learning and memory compared to controls, but they did not differ from patients with hepatitis B virus liver disease^[28]. However, about 20% of patients had liver cirrhosis in both groups. Moreover, only 50% of the study group had histological assessment and no clinical exclusion of cirrhosis was described by the authors.

INFLAMMATION AND HCV

The etiology of cognitive dysfunction in patients with chronic HCV infection remains unclear but two hypotheses have been put forward: (1) the virus infects the brain and has a direct neurotoxic effect; and (2) the virus is indirectly neurotoxic *via* cerebral and/or systemic inflammation.

A direct neurotoxic role for HCV is supported by reports of HCV replication within the central nervous system^[29-31]. It has been suggested that the virus enters the brain by infecting peripheral blood mononuclear cells, which are precursors of the microglia and could act as a "Trojan horse"^[32]. However, data on the association between the virus in the brain and impaired cognitive function are still lacking. Indeed, replication of quasispecies is very low within the brain; HCV RNA is almost undetectable in the cerebrospinal fluid^[33,34] and there is no correlation between viral load and cognitive impairment in patients with HCV infection^[20]. However, this is sometimes also the case for other HCV-related complications, such as cryoglobulinemia or vasculitis^[35].

It is well known that the cytolytic effect of HCV within the liver relates to the activation of the immune system. Thus, chronic activation of the immune system could account, at least in part, for the observed cerebral alterations, due to increased systemic and/or local inflammation. A growing body of evidence supports immune system-to-brain communication, with peripheral immune activation being associated with behavioral, affective and cognitive disturbances. Peripheral proinflammatory

cytokines such as interleukin (IL)-1, and IL-6 are likely mediators of these effects, and penetrate the blood-brain barrier directly through active transport mechanisms, activation of the vagus nerve, stimulation of neurotransmitter systems, and therefore, modulation of brain activity. Most of the evidence that directly links peripheral proinflammatory cytokines with neurocognitive function is derived from animal models, in which increased peripheral IL-1 and IL-6 are associated with increased levels of these cytokines in the prefrontal cortex and hippocampus^[36].

Increased levels of IL-6 have been associated with impairment in spatial learning and memory, which are prevented by the administration of specific antagonists. This suggests a primary role for inflammatory cytokines in mediating cognitive decline and deficits in chronic inflammation^[37,38]. Likewise, peripheral markers of inflammation have been associated with cognitive decline in elderly patients. In a recent study that evaluated the correlation between IL-6 and cognitive performance in middle-aged volunteers, an inverse relationship was observed between circulating levels of IL-6 and auditory recognition memory, attention, working memory and executive function^[39].

Once a patient has chronic HCV infection, proinflammatory cytokines such as IL-6, IL-4 and tumor necrosis factor (TNF)- α are produced and may be elevated for several decades. During this period, proinflammatory cytokines can cross the blood-brain barrier and therefore contribute to cognitive impairment.

Moreover, another possible contribution of inflammation to cognitive degeneration in HCV patients is local cerebral inflammation^[34,40,41]. It has been shown that small amounts of HCV within the brain evoke a local inflammatory response, because macrophages infected with HCV *in vitro* can induce TNF- α and IL-8^[32]. In addition, a recent study has shown activation of brain macrophages/microglia in autopsy brain tissue from HCV-positive patients^[42]. Peripheral markers of the activation of cellular immunity have recently been assessed by Gess and colleagues in a group of 53 HCV-infected patients with mild liver disease. No association was observed between activated cellular immunity and subjectively perceived or objectively measured cognitive impairment^[43].

FUTURE PERSPECTIVES

The studies that have explored cognitive function in patients with chronic HCV were extremely heterogeneous in terms of patient characteristics, confounding factors (e.g. intravenous drug misuse and previous alcohol intake), control groups, methodology and tests used to assess cognitive performance. An additional issue might be the fact that the study subjects ranged from patients who had cleared HCV to those with HCV-related cirrhosis, even within the same study group. Furthermore, the role of systemic inflammation in the pathogenesis of cogni-

tive alterations in patients with HCV infection has never been directly explored.

It is possible that patients with chronic HCV infection and persistently normal transaminases for 6 mo (PNALT) could represent an extremely useful study group to provide additional information, particularly in relation to the role of HCV *per se* in causing neurocognitive dysfunction. When we evaluated systemic inflammation in this group of patients, no activation of systemic inflammation was observed^[44]. This finding suggests that patients with normal transaminases have a different immunological response profile, compared to those whose transaminases remain elevated. In line with this hypothesis, previous studies have demonstrated an increase in HCV-specific CD4⁺CD25⁺ regulatory T cells and a decrease in CD4⁺ response in patients with normal transaminases compared to patients with high transaminases^[45].

Whether the absence of an activated systemic inflammatory response in PNALT patients also reflects better cognitive performance needs to be explored. In a preliminary study, we found that PNALT patients with normal serum levels of proinflammatory cytokines performed similarly to controls as far as memory, attention and cognitive evoked potential N400, which relates to semantic memory and verbal working memory. Patients with chronic hepatitis due to HCV had impairment in memory in 60% of cases, with concomitant increased amplitude of N400, which indicated the need for increased neuronal recruitment to perform the task^[44].

In the two studies that did not demonstrate cognitive alterations in patients with HCV, HCV-positive individuals were selected from healthy volunteers screened for blood donation and young patients with hemophilia, respectively. These subjects were classified as HCV-positive individuals with normal transaminases but were not further characterized, and some might well have qualified as PNALT.

Future, prospective cohort studies should probably include patients with chronic HCV infection with minimal or no fibrosis, PNALT, hepatitis B surface antigen-positive patients with/without transaminitis and a control group with chronic systemic inflammation (i.e. inflammatory bowel disease). In addition, the neuropsychological evaluation should probably be conducted in a structured, comprehensive way, by cognitive domain, and test results scored against adequate, large and local normative databases, rather than simply compared to small internal control groups. Mood, fatigue and quality of life should also be assessed. This approach might provide more solid information on whether HCV-related cognitive impairment exists and, if so, on its clinical relevance.

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