

REVIEW

Cerebral dysfunction in chronic hepatitis C infection

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SUMMARY. A number of studies have reported an association between chronic hepatitis C (HCV) infection and significant impairments in health-related quality of life (QOL), which are independent of the severity of liver disease. There are numerous reports documenting the prevalence of symptoms such as fatigue and depression in chronic HCV infection, which may in part account for the reductions in quality of life. Although there are a large number of potential explanations for these symptoms, including depression and anxiety associated with the diagnosis of HCV infection or substance abuse, there has been recent interest in the possibility of a biological effect of HCV infection on cerebral function. There is emerging evidence of mild, but significant

neurocognitive impairment in HCV infection, which cannot be attributed to substance abuse, coexistent depression or hepatic encephalopathy. *In vivo* magnetic resonance spectroscopy and neurophysiological studies have suggested that a biological mechanism may underlie these cognitive findings. The recent detection of HCV genetic sequences in post mortem brain tissue raises the intriguing possibility that HCV infection of the central nervous system may be related to the reported neuropsychological symptoms and cognitive impairment.

Keywords: brain, cognitive impairment, fatigue, Hepatitis C.

There has been recent interest in the possibility of a link between chronic hepatitis C (HCV) infection and cerebral dysfunction. There are only a few studies that have addressed this issue directly, although there are many more that have documented the prevalence of associated phenomena, such as depression, fatigue and impairments in quality of life [1–8]. The suggestion that chronic HCV infection might cause cerebral dysfunction resulted from initial, anecdotal observations that HCV-infected patients complain of a variety of nonspecific symptoms, often in the absence of histologically advanced liver disease [9]. Complaints of fatigue, musculoskeletal and right upper abdominal discomfort, depression, mental clouding (brain fog) and a perceived inability to function effectively led to a number of published reports documenting the prevalence of such symptoms and their impact on quality of life scales in cohorts of patients with HCV infection [1–8]. However, the presence of these symptoms in the context of HCV infection does not

necessarily imply causality, as there are many associated factors which may independently affect patients' perceptions of well-being e.g. anxiety regarding diagnosis, prognosis and treatment, previous or ongoing substance abuse and associated emotional problems or personality traits. Although some of the published surveys have attempted to control for these factors, they may still have been prone to selection bias. It is therefore apparent that objective measures of cerebral function are required to determine the nature and degree of cerebral dysfunction in chronic HCV infection.

QUALITY OF LIFE

Quality of life (QOL) questionnaires have been used extensively to study both the effect of HCV infection on patients' well-being and the effect of antiviral therapy. The SF-36 questionnaire, a generic health instrument, has been used most widely in this context and generates a health profile, divided into eight separate categories, reflecting physical and emotional performance. The results from several large studies challenge the perception that HCV infection is an 'asymptomatic' disease, with general agreement that QOL is significantly reduced in HCV-infected patients, independent of the severity of the liver disease [1, 5, 6, 10]. Furthermore, in one study, SF-36 scores were lower in patients with HCV infection compared with those with chronic hepatitis B infection and were unrelated to the mode of acquisition, i.e. the presence of previous intravenous drug usage [3]. These

Abbreviations: ¹H MRS, proton magnetic resonance spectroscopy; CNS, central nervous system; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IL, interleukin; PBMC, peripheral blood mononuclear cells; PCR, polymerase chain reaction; QOL, quality of life; SCID, severe combined immunodeficiency; TNF, tumour necrosis factor.

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findings, together with large studies, which have shown significant improvements in QOL in combined cohorts of many thousands of patients after successful antiviral therapy, suggests that the viral infection itself is an important determinant of reduced QOL [5,6,11]. There are, however, other relevant determinants of QOL, which have been described in the literature [12–14]. For clear practical reasons most of the above studies did not blind their subjects to HCV polymerase chain reaction (PCR) status. The impact of diagnosis and subsequent anxiety is likely to impair QOL, as has been shown in a small study where patients who were unaware of their diagnosis reported less impaired QOL than patients who knew their HCV status [12]. Despite this, the patients who did not know their diagnosis were still impaired on three scales of the SF-36 questionnaire. It is also possible that some of the improvement in QOL, seen after successful antiviral therapy, is because of the patients' knowledge of their response. Other studies have demonstrated an association between depression and reduced QOL [13,14]. QOL studies have been useful in quantifying the impact of chronic HCV infection on patient well-being and in monitoring a response to treatment. However, these studies tell us little about the nature of symptoms or the underlying cause of perceived disability, and are influenced by a large number of factors, many of which are difficult to control for in clinical studies.

FATIGUE

Fatigue is the commonest symptom in patients with chronic HCV infection. Numerous surveys have reported the prevalence of fatigue to be between 20 and 80% in HCV infected patients [2,4,7,8,15–18] and have found no association between the severity of fatigue and the degree of hepatitis [3,4,8,13]. Furthermore, a number of studies have reported improvements in fatigue after treatment [16–18], although it appears to persist in some individuals despite a virological response. These studies are subject to the same shortcomings as described earlier, as fatigue is a multidimensional symptom and is influenced by multiple interrelating social, behavioural, psychological and personality factors [13,19,20]. Indeed, in a recent comprehensive review, Wessely stated controversially that there is no evidence that HCV infection *per se* is associated with fatigue and depression [21]. This conclusion was based on three main arguments: (1) the majority, if not all the studies in this field, are methodologically flawed and fail to take account of confounding factors, (2) there is no relationship between fatigue and markers of liver inflammation, (3) in selected retrospective studies, there was no excess of fatigue in HCV-infected patients compared with noninfected blood donors [22] and there was no excess of HCV-infection in patients presenting with the chronic fatigue syndrome [23]. In the first unpublished study [22], the prevalence of fatigue in apparently healthy blood donors was surprisingly high at 70%, suggesting that simply asking

patients to rate fatigue on a scale of 1–4 may not be an appropriate assessment tool. With regard to the chronic fatigue syndrome, patients with HCV are unlikely to be seen in chronic fatigue clinics, as an abnormality in liver function tests is likely to be detected before this stage. In the cited study [23], all patients had had an internal medicine evaluation prior to enrolment in the study and remained undiagnosed. The absence of an association between markers of liver disease and fatigue does not exclude an association between HCV infection and fatigue. Rather, the mechanism is likely to be independent of the degree of liver inflammation. It is, however, quite correct that the fatigue reported by HCV-infected patients is likely to be the result of multiple, coexistent causes. The relative contribution of a biological mechanism remains unclear. Thus, in the context of investigating the presence of a cerebral effect of HCV infection, measured fatigue is likely to be a poor marker.

DEPRESSION

The published literature and routine clinical practice inform us that depression is a common finding in HCV-infected patients [2,13,14,24–26]. It is of considerable clinical importance as depression may limit the tolerability of treatment with α -interferon [27] and reduce compliance [28]. The relationship between HCV and depression is complex. Patients with depression may have a higher incidence of HCV infection. The greatest reservoir of HCV infection is in intravenous drug users, many of whom have clinical depression [29]. Conversely, depression may exist as a secondary phenomenon to HCV infection. This may take the form of a reactive depression related to the diagnosis and concerns over long-term health or may be secondary to symptoms such as fatigue and cognitive impairment [19,26]. Finally, a biological effect of HCV infection itself may underlie depression. There is currently little evidence for this theory, although in one blinded study of intravenous drug users, HCV positive individuals had significantly lower positive affect scores than HCV negative drug users [29]. In another study there was no difference in psychological morbidity between HCV-positive and HCV-negative drug users [30], although in both these studies, the effect of HCV may have been masked by the high background prevalence of depression in active drug users. Although depression is an important variable in the context of HCV infection, it is unlikely to be useful in determining whether HCV has a biological effect on cerebral function.

COGNITIVE IMPAIRMENT

Three studies to date have evaluated whether HCV infection has an impact on cognitive function [26,31,32]. It is well-established that cognitive impairment is frequently detectable in patients with cirrhosis, even in the absence of clinical encephalopathy and is termed minimal encephalopathy [33]. It is therefore imperative to either exclude patients with

advanced liver disease or to study sufficiently large numbers to allow subgroup analyses, in any study that tests for a direct effect of HCV infection on cognitive function.

Using a computer-based cognitive battery, we reported selective impairments of attention, concentration and psychomotor speed in patients with histologically proven minimal HCV hepatitis [26]. These impairments were not seen in patients who had recovered from HCV infection, either spontaneously or after successful therapy. Furthermore, the presence of fatigue, depression or a history of substance abuse did not explain these findings. In a study by Hilsabeck *et al.*, impairment on various neuropsychological tasks was seen in up to 49% of HCV-infected patients without cirrhosis [32]. The authors found no excess of neuropsychological impairment in HCV-infected patients compared with patients with liver disease of other causes. However, the comparison group included patients with alcoholic liver disease and was small, with only six patients without cirrhosis. The pattern of cognitive dysfunction in these studies is the same, with impairment in the domains of attention and working memory. Such findings have also been reported in the medically asymptomatic stages of HIV infection [34] and are consistent with the involvement of subcortical brain systems [35].

BRAIN METABOLISM AND NEUROPHYSIOLOGY

Although strict entry criteria were observed and appropriate controls were employed in the cognitive studies, it may still be argued that cognitive impairment in HCV infection results somehow from the large number of confounding factors already described, rather than the virus itself, and that an objective physical or physiological measure of cerebral function is required.

Using *in vivo* proton magnetic resonance spectroscopy (^1H MRS), a technique which gives information on brain metabolism, we have shown cerebral metabolite abnormalities in HCV-infected patients with histologically proven mild disease [26,36]. The cerebral choline to creatine ratio was elevated in the basal ganglia and white matter, a finding which was again unrelated to previous substance abuse. Furthermore, patients with cognitive impairment had more abnormal ^1H MRS. These findings suggest that chronic HCV infection can cause both cognitive impairment and altered brain metabolism by an, as yet, unknown mechanism.

Kramer *et al.* used P300 event-related potentials, a neurophysiological test of cognitive processing, in a large cohort of patients with chronic HCV infection [37]. Although cirrhotic patients were not excluded, subgroup analyses were made. HCV-infected patients had delayed P300 peak latencies and reduced amplitudes compared with age-matched healthy subjects. Seventeen per cent of HCV infected patients had P300 latencies outside the age-adjusted normal range, suggesting slight but significant neurocognitive impairment. Subgroup analyses indicated that the findings were not accounted for by a history of substance abuse, cirrhosis or alcohol.

POSSIBLE MECHANISMS

Similar ^1H MRS changes, in a spatial distribution to those described, have been widely reported in human immunodeficiency virus (HIV)-infected patients, where central nervous system (CNS) infection by HIV is well-established [38,39]. Furthermore, prolonged P300 latencies have also been reported in HIV infection [40]. This raises the intriguing possibility that HCV may also infect the CNS [9]. Although the literature on extrahepatic HCV replication has inconsistencies (reviewed by Gowans) [41], a consensus seems to be emerging that HCV infects peripheral blood mononuclear cells (PBMCs) and bone marrow and probably replicates at a low level. The negative strand of the HCV RNA genome, considered to be a replicative intermediate, has been demonstrated in PBMCs by several research groups, using strand-specific techniques [42,43]. HCV RNA has also been detected in PBMC and haematopoietic progenitor cells from HCV-infected patients by *in situ* hybridization [44] *in vivo* and after inoculation of incubated cells from healthy donors with HCV positive sera [45]. Different HCV quasi-species have been demonstrated in liver and PBMC samples including monocytes, supporting the concept of independent viral replication in these compartments [46–48]. Finally, injection of PBMC from HCV-infected patients into severe combined immunodeficiency (SCID) mice resulted in the detection of positive and negative strand HCV RNA in mouse serum and cell fractions up to 8 weeks after injection [49]. There is good evidence that microglial cells and resident perivascular macrophages within the brain turn over continuously and originate from bone marrow derived precursors [50]. It is therefore conceivable that HCV-infected monocytes or progenitor cells may introduce the virus into the CNS by a ‘Trojan horse’ mechanism, triggering a number of pathways that may result in neuronal dysfunction. In support of this hypothesis, we have isolated unique HCV hypervariable region genomic sequences from postmortem brain tissue, suggesting that brain-specific HCV variants may replicate within the central nervous system [51]. Furthermore, Radkowski *et al.* recently reported the detection of negative strand HCV RNA in postmortem brain tissue [52].

It is clear that the neuropsychological manifestations of HCV infection are nonprogressive; a neuro-AIDS type dementia is not seen. HCV infection of the CNS would be unlikely to result in significant neuronal cell loss. However, the immune response to viral proteins within the CNS, may underlie the cerebral dysfunction, as is the case in early HIV infection. Activated microglia are thought to liberate neurosteroids such as pregnenolone [53], which may have an upregulatory role on neuroinhibitory pathways in the brain. Activated microglia also release excitatory amino acids, which can induce neuronal apoptosis through a process known as excitotoxicity [54], and are potent producers of neurotoxins such as nitric oxide. These processes may be amplified by the release of cytokines and chemokines [55,56] within the CNS.

Peripherally derived cytokines may also be implicated, either in the facilitation of viral transfer across the blood barrier [57] or independently, in the absence of HCV infection of the CNS. Although cytokines are large peptides, animal studies have demonstrated passage of cytokines across the blood–brain and blood–spinal cord barriers [58]. Peripherally derived cytokines may also be passively transported into the brain at circumventricular sites which lack a blood–brain barrier. Intracerebral cytokines have been associated with immunological, neurochemical, neuroendocrine and behavioural activities [59], probably through the pathways described above. It is clear that treatment with α -interferon is associated with depression and complaints of memory impairment and cognitive slowing [60], but whether elevated endogenous cytokines in chronic inflammatory and infective conditions exert a significant cognitive effect is unclear. A study found no correlation between levels of circulating IL-1, IL-6, tumour necrosis factor (TNF) and patients' fatigue in chronic HCV infection [61], although no study exists to date on circulating cytokine levels and cognitive function in chronic HCV infection.

There are a few case reports of CNS involvement in patients with HCV-related cryoglobulinaemia [62–64]. The clinical picture is of a cerebral vasculitis with hard neurological signs. It is unlikely that a vasculitis underlies the cerebral dysfunction described. Indeed, cryoglobulinaemia was an exclusion criterion for the ^1H MRS and P300 studies.

The above mechanisms remain hypothetical. However, current evidence suggests that mild but significant cognitive impairment does exist in some patients with HCV infection. Recent studies indicate that there is a biological, rather than functional basis to this. An effect of HCV on cognitive abilities may in part explain the high prevalence of depression, fatigue and reduced QOL in chronic HCV infection but there are many other causes for these symptoms. Studies are required to further define the cognitive dysfunction and the effect of successful antiviral treatment. The possibility that immune activation within the CNS exists as a result of HCV infection remains an attractive but unproven theory. Clinical imaging and further virological and histopathological studies will ultimately answer this question.

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