

# Hepatitis C and Cognitive Impairment in a Cohort of Patients With Mild Liver Disease

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**Patients with chronic hepatitis C virus (HCV) infection frequently report fatigue, lassitude, depression, and a perceived inability to function effectively. Several studies have shown that patients exhibit low quality-of-life scores that are independent of disease severity. We therefore considered whether HCV infection has a direct effect on the central nervous system, resulting in cognitive and cerebral metabolite abnormalities. Twenty-seven viremic patients with biopsy-proven mild hepatitis due to HCV and 16 patients with cleared HCV were tested with a computer-based cognitive assessment battery and also completed depression, fatigue, and quality-of-life questionnaires. The HCV-infected patients were impaired on more cognitive tasks than the HCV-cleared group (mean [SD]: HCV-infected, 2.15 [1.56]; HCV-cleared, 1.06 [1.24];  $P = .02$ ). A factor analysis showed impairments in power of concentration and speed of working memory, independent of a history of intravenous drug usage (IVDU), depression, fatigue, or symptom severity. A subgroup of 17 HCV-infected patients also underwent cerebral proton magnetic resonance spectroscopy (<sup>1</sup>H MRS). The choline/creatine ratio was elevated in the basal ganglia and white matter in this group. Patients who were impaired on 2 or more tasks in the battery had a higher mean choline/creatine ratio compared with the unimpaired patients. In conclusion, these preliminary results demonstrate cognitive impairment that is unaccounted for by depression, fatigue, or a history of IVDU in patients with histologically mild HCV infection. The findings on MRS suggest that a biological cause underlies this abnormality. (HEPATOLOGY 2002;35:433-439.)**

Chronic hepatitis C (HCV) infection is estimated to affect 170 million people worldwide<sup>1</sup> and constitutes a major public health problem. It causes a fluctuating chronic hepatitis that may progress to cirrhosis and hepatocellular carcinoma. Attempts to understand the natural history of this infection have largely focused on the viral and host factors that predict progression of liver pathology from necroinflammation and fibrosis to cirrhosis and hepatocellular carcinoma. Consequently, the decision to treat patients is normally based on an assessment of these factors, including staging of disease with a liver biopsy,<sup>2</sup> rather than

on particular symptoms. There is, however, emerging literature suggesting that, even in the absence of clinically significant liver disease, chronic HCV infection causes a substantial reduction in quality of life<sup>3</sup> that improves following successful antiviral treatment.<sup>4</sup> These findings are in agreement with the clinical observation that patients with chronic HCV infection frequently report fatigue, lassitude, depression, and a perceived inability to function effectively.<sup>5,6</sup> The etiology of these symptoms is unknown. The symptoms do not appear to be associated with the degree of hepatitis, the presence of autoimmune disorders<sup>5</sup> or cirrhosis,<sup>3</sup> a history of intravenous drug usage (IVDU),<sup>3</sup> or the level of circulating cytokines.<sup>7</sup>

We have previously reported cerebral metabolite abnormalities in patients with histologically proven mild HCV infection using proton magnetic resonance spectroscopy (<sup>1</sup>H MRS).<sup>8</sup> These abnormalities are similar to the <sup>1</sup>H MRS changes reported in cerebral human immunodeficiency virus (HIV) infection in both cognitively impaired<sup>9,10</sup> and asymptomatic individuals.<sup>11</sup>

In this study, we address the hypothesis that HCV infection can result in cerebral dysfunction, which may underlie both the neuropsychological symptoms and the <sup>1</sup>H MRS abnormalities described. We used a cognitive assessment battery to determine whether cognitive impairment exists in patients with histologically defined mild chronic HCV infection and <sup>1</sup>H MRS to determine whether cerebral metabolite abnormalities are associated with impaired cognitive function.

*Abbreviations: HCV, hepatitis C virus; IVDU, intravenous drug usage; <sup>1</sup>H MRS, proton magnetic resonance spectroscopy; HIV, human immunodeficiency virus; ALT, alanine aminotransferase; PCR, polymerase chain reaction; IL, interleukin.*

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## Patients and Methods

**Patient Groups.** Thirty-five patients with histologically defined mild chronic HCV infection were randomly selected from the St. Mary's hepatology clinic for the study. The patients had been referred for assessment of their liver disease. Of these, 8 patients were excluded from the study because they were taking central nervous system-altering medication, most commonly an antidepressant. Therefore, 27 patients underwent cognitive testing. The mean age (range) was 44.5 (28-69) years, and 59% of the subjects were men. Liver biopsies had been performed within 18 months of the study. All individuals had mild inflammation only, in the absence of cirrhosis or significant fibrosis. The median Ishak necroinflammatory score was 3, and the median Ishak fibrosis score was 1.<sup>12</sup> The median alanine aminotransferase (ALT) level was 44 IU/L (normal range, <40 IU/L). All patients were viremic at the time of the study, as defined by a positive polymerase chain reaction (PCR) for HCV RNA (Roche Amplicor version 2). The method of viral transmission was related to IVDU in 48% of cases and to infected blood products or undefined sources in 52% of cases. All patients were carefully questioned for a history of major drug usage. Individuals were asked whether they had ever used any of 5 substances (heroin, methadone, LSD, cocaine, ecstasy) after reassurance that there would be no clinical record of their answers. The clinical notes were then cross-checked, and individuals were only classified as nonusers if a history of major drug usage was unequivocally absent. A subgroup of 17 HCV-PCR-positive patients also underwent <sup>1</sup>H MRS of the brain. The mean age (range) was 42.1 (28-57) years, and 47% of the subjects were men.

Sixteen individuals with immunoglobulin G antibodies to HCV, confirmed by recombinant immunoblock assay, normal liver function test results, and negative HCV-PCR (on at least 2 occasions 6 months apart), also underwent cognitive testing. This group had been exposed to HCV and had cleared HCV, either spontaneously (31%) or after successful treatment (69%). The mean age (range) was 42.3 (32-60) years, and 38% of the subjects were men. There was a history of IVDU in 50%. The median ALT level was 13 IU/L, and all treated patients had a pretreatment liver biopsy that had been graded as histologically mild or moderate HCV hepatitis. None of the patients regularly exceeded the UK National safe drinking limits (30 g and 20 g of alcohol per day for men and women, respectively), and there were no features of alcoholic liver disease in any of the liver biopsy specimens. The 2 patient groups were matched for occupational status, with 63% of HCV-infected and 56% of HCV-cleared individuals working in professional or skilled nonmanual positions.

The reference population for the <sup>1</sup>H MRS included 29 healthy controls recruited from available hospital staff. The mean (range) age was 42 (30-54) years, 52% of the subjects were men, and there was no history of IVDU in any of the controls. There were no statistical differences in age or sex distribution between the healthy controls and the HCV group that underwent <sup>1</sup>H MRS.

**Cognitive Assessment.** Computer-based and paper-based cognitive<sup>13,14</sup> batteries were administered to all the subjects, under standardized conditions, by 1 of 2 trained individuals following a protocol. The Cognitive Drug Research<sup>15</sup> computerized assessment system comprises tests of attention, working memory, and

episodic secondary memory, the components of which are shown in Table 1. The results were compared with age-matched normal data from between 85 and 420 healthy subjects (provided by CDR Ltd., Reading, Berkshire, England) to generate *z* scores. Performance on an individual task was judged to be impaired if either the reaction time or sensitivity index for that task fell below the normative mean by 1 SD or more (*i.e.*, *z* score >1). All the patients tested had a good command of working English and fully understood their instructions. However, the mother tongue of 8 of the PCR-positive patients and 1 of the PCR-negative patients was not English. In these cases, if there was impaired performance in the delayed word recall task, it was discounted because it was the only task that required language skills. The results were also used to generate 4 factor scores that have previously been shown to reflect the following processes: power of concentration, quality of working memory, speed of memory processes, and ability to sustain attention.<sup>16</sup>

In addition, 19 patients in the HCV-infected group and the entire HCV-cleared group completed self-report questionnaires to assess mood (Beck Depression Inventory,<sup>17</sup> Hospital Anxiety and Depression Scales<sup>18</sup>) and fatigue.<sup>19</sup> These patients also completed the SF-36 questionnaire, a well-validated tool that has been used extensively in studies of health perception in patients with chronic HCV infection.<sup>3,4</sup> It generates an 8-scale profile of health perception that can be summarized into 2 mental and physical health measures.<sup>20</sup> The National Adult Reading Test<sup>21</sup> was administered to individuals whose first language was English. This test allows a reliable estimate of premorbid full-scale intelligence quotient. The total testing time was 90 minutes.

**Cerebral MRS.** A subset of 17 HCV-infected patients and a group of healthy volunteers underwent cerebral MRS using a 1.5T Eclipse<sup>TM</sup> spectroscopy system (Marconi Medical Systems, Cleveland, OH). T<sub>1</sub>-weighted magnetic resonance images were acquired in the transverse plane to exclude organic brain disease and position the voxels of interest (repetition time, 21 milliseconds; echo time, 6 milliseconds). Two 8-cm<sup>3</sup>-sized voxels were positioned in the basal ganglia and in the white matter at the level of the centrum semiovale. Single-voxel <sup>1</sup>H MRS examinations were performed using an automated PRESS sequence (repetition time, 1,500 milliseconds; echo time, 135 milliseconds; 128 acquisitions).<sup>8</sup> The

**Table 1. Components of the Computer-Based and Paper-Based Batteries**

Battery	Test	Measures
Computer	Simple reaction time	Reaction time
	Choice reaction time	Reaction time Accuracy
	Digit vigilance	Reaction time Accuracy
	Numerical working memory	Reaction time Sensitivity index
	Spatial memory	Reaction time Sensitivity index
	Delayed word recognition	Reaction time Sensitivity index
	Paper	Number connection test A
Number connection test B		Time
Digit symbol substitution test		Number correct

total examination time was 50 minutes. Magnetic resonance spectra were analyzed by a single observer in each case who was blinded to the clinical status of the patients. Peak areas were measured for choline, creatine, and *N*-acetylaspartate<sup>22</sup> using Marconi proprietary software. Peak area ratios for choline/creatine were then calculated. The magnetic resonance images were reviewed by a neuroradiologist.

**Statistical Methods.** Data were tested for normality using the Shapiro-Wilk test. Between-group comparisons were made with the Student's *t* test or the Mann-Whitney U test as appropriate. Correlations were tested with the Spearman rank test. All tests were 2-tailed. Statistical analyses were performed using SPSS version 9 (SPSS Inc., Chicago, IL).

**Ethics.** Ethical approval was obtained from the ethics committees of the Imperial College School of Medicine (Rec 4047/93) and St. Mary's Hospital, London (98/BG/303), and was in accordance with the 1975 Helsinki Declaration. All subjects provided written informed consent.

## Results

**Neuropsychometry.** There was no statistical difference between the estimates of premorbid full-scale intelligence quotient in the HCV-infected and the HCV-cleared (PCR-negative) groups (median intelligence quotient, 117 and 115, respectively). To determine if there were any differences between the HCV-infected and HCV-cleared patients on the computer-based battery, we compared the mean number of impaired tasks, as previously defined, in each group. The HCV-infected patients were impaired on more computer-based tasks than the HCV-cleared group (mean [SD]: HCV-infected, 2.15 [1.56]; HCV-cleared, 1.06 [1.24];  $P = .02$ ). There were no statistically significant differences between individuals with and without a history of IVDU, regardless of HCV status (IVDU-positive, 1.95 [1.83]; IVDU-negative, 1.55 [1.18];  $P = .62$ ) or sex (male, 1.90 [1.63]; female, 1.57 [1.43];  $P = .50$ ). There were no statistically significant correlations between the estimates of premorbid full-scale intelligence quotient and the number of tasks for which an individual was impaired in either the HCV-infected group ( $r = -0.01$ ;  $P = .97$ ) or the patient group as a whole ( $r = -0.07$ ;  $P = .74$ ).

To determine which cognitive functions were impaired, the factor scores were analyzed. The scores were compared between the 2 study groups and a third group of 362 age-matched healthy controls using a one-way ANOVA (Table 2). The HCV-infected group scored significantly worse on the power of concentration ( $P = .001$ ) and on the speed of memory processes ( $P = .001$ ) factor scores than the healthy controls. The performance of the HCV-cleared group on these scores was equivalent to the healthy controls. There were no differences in the quality of working memory and attention factor scores. There were no statistically significant differences between the study groups on any of the paper-based tasks.

With respect to the affective scores, the HCV-infected group scored worse on the Hospital Anxiety and Depression Scales (median [SD]: HCV-infected, 5 [4.7]; HCV-cleared, 1.0 [3.9];  $P = .02$ ) and the Beck Depression Inventory (HCV-infected, 8.0 [10.7]; HCV-cleared, 3.0 [9.1];  $P = .03$ ). The Hospital Anxiety and Depression anxiety score did not differ between the 2 groups.

**Table 2. Computer Battery Factor Scores for Each Study Group**

	Healthy Controls (n = 362)	HCV Infected (n = 27)	HCV Cleared (n = 16)
Power of concentration/ms*	1,099 (105)	1,174 (105) [-116, -34]‡	1,125 (107) [-79, 26]
Speed of memory processes/ms*	1,610 (478)	1,915 (394) [-472, -136]‡	1,690 (257) [-280, 120]
Quality of working memory†	1.68 (0.40)	1.60 (0.42) [-0.06, 0.22]	1.73 (0.24) [-0.22, 0.11]
Ability to sustain attention†	96.0 (3.6)	95.9 (3.0) [-1.3, 1.5]	97.5 (1.7) [-3.3, 0.3]

NOTE. Mean values and SDs are shown for each factor score. The 95% confidence intervals for the difference between means when compared with the healthy controls are shown in brackets. Power of concentration = simple reaction time + digit vigilance reaction time + choice reaction time; quality of working memory = spatial memory sensitivity + numerical working memory sensitivity; speed of memory processes = spatial memory reaction time + numerical working memory reaction time; ability to sustain attention = digit vigilance accuracy + choice reaction accuracy.

\*Increase indicates worse performance.

†Decrease indicates worse performance.

‡ $P = .001$ .

There were no differences on the affective scales between subjects with and without a history of IVDU.

There were no statistically significant differences in the subjects' assessment of fatigue in either the physical or mental domains, although there was a trend toward increased fatigue in the HCV-infected group. Similarly, with respect to the SF-36 quality-of-life scale, there were no differences between the 2 groups in the mental summary score. However, there was a significant difference in the physical summary score ( $P = .006$ ), with lower ratings in the HCV-infected group.

We then considered whether performance on the computer-based battery was related to depression, the patients' symptoms, or the degree of hepatic inflammation. Correlations between each of the 4 cognitive factor scores and the Beck Depression Inventory score, the SF-36 physical summary score, the physical fatigue score, and the serum ALT level were tested. A correction factor of 4 was used because multiple comparisons were made. There were no correlations between the serum ALT level and any of the factor scores. For the 2 factor scores, which were abnormal in the HCV-infected group, there were no significant associations with the Beck Depression Inventory score, the SF-36 physical summary score, or the physical fatigue score. There was also no association between any of these measures and the number of tasks for which an individual was impaired. The only significant correlation was between the Beck Depression Inventory score and the ability to sustain attention score ( $r = -0.43$ ;  $P = .04$ ).

**MRS.** Magnetic resonance imaging was normal in all cases. There was no evidence of cerebral vasculitis or any white matter abnormality. Typical <sup>1</sup>H magnetic resonance spectra contained 3 main resonances; they were assigned to choline at 3.22 ppm, creatine at 3.02 ppm, and *N*-acetylaspartate at 2.02 ppm. The metabolite ratios were normally distributed. As we have previously reported,<sup>8</sup> the choline/creatine ratio was significantly elevated in the HCV-infected group compared with the healthy volunteers in

both the basal ganglia (mean [SD]: HCV, 1.15 [0.14]; controls, 1.06 [0.13];  $P = .04$ ) and white matter (HCV, 1.32 [0.19]; controls, 1.18 [0.14];  $P = .008$ ).

There were no statistically significant correlations between the MRS ratios and the cognitive factor scores. However, the HCV-infected patients who were impaired on 2 or more computer-based tasks had a higher mean basal ganglia choline/creatine ratio (1.20 [0.13]) as a group compared with both those who were unimpaired (1.04 [0.08];  $P = .036$ ) and the healthy volunteers (1.06 [0.13];  $P = .007$ ) (Fig. 1). There were no differences between the impaired and unimpaired HCV-infected patients (1.34 [0.21] and 1.25 [0.17], respectively;  $P = .82$ ) in the white matter, but the impaired patients had a significantly higher choline/creatine ratio compared with healthy controls (1.18 [0.14];  $P = .02$ ). There were no associations between the MRS ratios and the affective, fatigue, or SF-36 scores.

## Discussion

These preliminary findings are consistent with cognitive and cerebral  $^1\text{H}$  MRS metabolite abnormalities in patients with histologically defined mild hepatitis due to HCV infection. The data support the clinical impression and assertions of many HCV-infected patients that they are cognitively impaired ("brain fog"). However, the mechanism underlying these findings remains to be defined.

A number of explanations may account for or contribute to the cognitive dysfunction observed in HCV-infected patients, including (1) a biological effect of HCV infection on the central nervous system, (2) the effect of personality or HCV acquisition-associated factors such as a history of IVDU, (3) the effect of affective disorders such as depression, or (4) the effect of subjectively experienced symptoms such as fatigue. It should be noted that these explanations are not necessarily mutually exclusive and might interact.

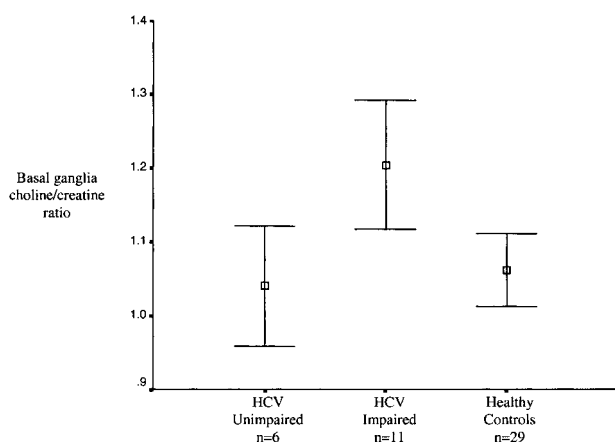


Fig. 1. Basal ganglia choline/creatine ratios in the HCV-infected groups and healthy controls. Mean and 95% CIs are shown. HCV-infected patients were classified as impaired on the computer-based battery if their performance on 2 tasks or more differed from normative data by 1 SD or more. The groups were compared with a 1-way ANOVA with a Bonferroni correction. The HCV-impaired group had a higher mean basal ganglia choline/creatine ratio than the HCV-unimpaired group ( $P = .036$ ) and the healthy controls ( $P = .007$ ).

Patients with significant fibrosis or cirrhosis were excluded from the study, thereby excluding minimal hepatic encephalopathy as the cause of the abnormalities. Indeed, the spectroscopic abnormalities associated with hepatic encephalopathy are qualitatively different with a globally reduced choline/creatine ratio.<sup>23,24</sup> Furthermore, there were no differences between the groups in the number connection or digit substitution tests, tools that have traditionally been used to establish the presence of minimal hepatic encephalopathy.

A history of serious drug usage that had stopped at least 2 years before participation in the study (and in most cases much earlier) did not have an impact on cognitive performance, regardless of HCV status. Individuals who had cleared HCV were chosen as the second study group to control for confounding factors, such as a history of major drug usage or lifestyle and personality factors, that may have been associated with HCV acquisition. The proportion of individuals in the 2 study groups with a history of IVDU was equivalent; when we analyzed our data with respect to a history of IVDU, it was not found to account for impaired cognitive performance. Similarly, consumption of alcohol is unlikely to explain these results because none of the subjects were alcoholic or heavy social drinkers. We have previously reported no statistical differences in  $^1\text{H}$  MRS ratios between HCV-infected patients with a history of IVDU and those without.<sup>8</sup> Furthermore, a number of cerebral MRS studies have investigated the effect of illicit drug use, but chronic cocaine, heroin, or alcohol abuse have not been found to increase cerebral choline-containing compounds.<sup>25-27</sup> It is therefore unlikely that a history of substance abuse underlies either the excess of cognitive impairment or the magnetic resonance abnormalities in the HCV-infected group.

The factor score analysis suggests that concentration and working memory processes may be preferentially impaired. These scores are derived from the summation of the reaction times on various tasks. We considered that the abnormalities might simply be a reflection of pure motor slowing as a result of a peripheral neuromuscular abnormality, but there were no differences in the simple reaction time between the 2 groups indicating impairment of central cognitive processes. Similar findings of slowed processing speed and impaired working memory are the most prominent features of cognitive dysfunction in patients with chronic fatigue syndrome.<sup>28</sup> Such findings have also been reported in the medically asymptomatic stages of HIV infection<sup>29</sup> and are consistent with the involvement of subcortical or frontostriatal brain systems.<sup>30</sup>

Although every attempt was made to prevent selection bias in this study, we accept that the study populations may not be wholly representative of the HCV-infected population because they were drawn from a tertiary referral HCV clinic. In particular, it is possible that patients with worse symptoms, both physical and psychological, are more likely to attend the clinic. Conversely, the exclusion of patients who were taking antidepressants, comprising 20% of the initial recruits and possibly those HCV-infected patients who were most likely to have cognitive dysfunction, may have led to an underestimation of the level of cognitive impairment. The purpose of this study was to investigate whether cognitive dysfunction is a feature of HCV infection, whereas larger studies will be required to estimate the prevalence.

The HCV-infected patients were found to be more depressed than the HCV-cleared group, as has been previously reported.<sup>31</sup> This result is not unexpected because the patients were not blind to their viral status. The median scores for both scales did not reach the range for mild mood disturbance. There were no statistically significant correlations between the cognitive factor scores that were abnormal in the HCV-infected group and the depression scores, indicating that impairment on these tasks is unlikely to be secondary to depression. Furthermore, if depression was the sole explanation for cognitive impairment in the HCV-infected patients, it is unlikely that it would cause the selective cognitive impairments that we report. In addition, the cerebral <sup>1</sup>H MRS abnormality we describe is not associated with unipolar depression, in which the choline/creatine ratio is reduced or normal and can increase following pharmacological treatment or electroconvulsive therapy.<sup>32,33</sup> It is therefore likely that the mild mood disturbance we report here is a component of a neuropsychological syndrome associated with HCV infection and may itself be secondary to physical or cognitive symptoms or indeed the impact of diagnosis and perception of illness.

The SF-36 quality-of-life questionnaire has been used to measure perception of health in patients with HCV infection<sup>3,4</sup> and serves as a robust assessment of the patients' perception of the impact of HCV on activities of daily living. It is important to note that it is not designed as a cognitive assessment tool. We were interested in whether patients with worse symptoms exhibited greater cognitive impairment, but we found no associations between performance on the battery and the SF-36 factor scores. These analyses were performed with a conservative correction factor to reduce the chance of a type I error, thereby also increasing the chance of a type II error (*i.e.*, the chance of not detecting a significant association). Although such a correction may be too stringent, we found no strong associations, even when it was not used. This strongly indicates that impaired cognitive performance is unlikely to be accounted for solely by the severity of symptoms. Indeed, there may be other factors that affect both cognitive performance and symptom severity.

Using <sup>1</sup>H MRS, we found an increase in the basal ganglia and whitematter choline/creatine ratio in patients with chronic HCV infection. The choline resonance mainly reflects intracerebral phospholipid cell membrane precursor and degradation products<sup>22</sup> and is increased in conditions in which there is cellular proliferation or altered membrane fluidity, most notably in inflammatory or infective conditions such as multiple sclerosis<sup>34</sup> or HIV infection.<sup>11</sup> The creatine resonance reflects cellular energy status and is a largely stable entity.<sup>22</sup> We found no evidence of abnormal *N*-acetylaspartate levels, which is considered to be a neuronal cell marker and is reduced in conditions of neuronal cell loss, such as stroke and dementia.<sup>22</sup> There were no statistically significant correlations between the cognitive factor scores, reflecting particular cognitive functions, and the MRS ratios. However, HCV-infected patients who had *z* scores greater than 1 on 2 tasks or more tended to have higher basal ganglia choline/creatine ratios than those who performed better on the computer-based battery. This comparison is based on an arbitrary cutoff point, which was set low to increase sensitivity, and the patient numbers are small. A larger study may

in time show statistical associations between specific cognitive functions and MRS ratios.

Similar metabolite abnormalities in the same spatial distribution as those reported here have been extensively documented in cerebral HIV infection, both in neurosymptomatic and neuroasymptomatic individuals.<sup>11</sup> In the case of HIV, infection of cerebral microglia,<sup>35</sup> possibly via infected monocytes entering the brain, and subsequent microglial activation are believed to underlie the MRS changes. This raises the prospect that the metabolite abnormalities reported in this study are due to direct infection of the brain by HCV. The concept of extrahepatic replication of HCV is not novel, with several lines of evidence suggesting that peripheral blood mononuclear cells are infected.<sup>36-39</sup> Microglia comprise up to 20% of all glial cells and are developmentally derived from bone marrow precursors of monocytic lineage.<sup>40</sup> It is believed that resident microglia turn over slowly and are replaced by circulating monocytes.<sup>41</sup> It is therefore possible that HCV may be introduced to the central nervous system via infected monocytes, through a "trojan horse" mechanism.

An alternative explanation for our findings is a centrally mediated effect of peripherally derived cytokines that may cross the blood-brain barrier. Although cytokines are large peptides, animal studies have demonstrated passage of cytokines including tumor necrosis factor  $\alpha$ , interferons alfa and gamma, and interleukins (IL) 1 $\alpha$  and 1 $\beta$  across the blood-brain and blood-spinal cord barriers.<sup>42</sup> Alternatively, peripherally derived cytokines may bind to the cerebral vascular endothelium, inducing the generation of secondary messengers. Intracerebral cytokines have been associated with immunologic, neurochemical, neuroendocrine, and behavioral activities.<sup>43</sup> Indeed, treatment with interferon alfa is associated with a constellation of symptoms, including depression and reports of memory impairment and cognitive slowing. Whether elevated endogenous cytokines in chronic inflammatory and infective conditions exert a significant cognitive effect is unclear. Several studies have reported elevated levels of circulating cytokines, including IL-1 $\beta$ , IL-2, IL-4, IL-6, IL-10, and tumor necrosis factor, in chronic HCV infection<sup>44</sup>; however, a recent study found no correlation between levels of circulating IL-1, IL-6, tumor necrosis factor, and fatigue in chronic HCV infection.<sup>7</sup>

Our findings will require verification in larger studies. In addition, longitudinal cerebral <sup>1</sup>H MRS and detailed neuropsychometry in patients with chronic HCV infection before and after antiviral treatment may allow further definition of the associated neuropsychological symptoms. The use of a cognitive assessment battery in clinical trials of antiviral therapy may be a useful adjunct to quality-of-life questionnaires, which are not designed to detect cognitive abnormalities. A demonstrated central nervous system response to treatment would have major implications in terms of the criteria for patient selection for antiviral therapy and the development of future therapeutic regimens.

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