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EDITORIAL

Cognitive dysfunction and hepatitis C virus infection

Antonio Solinas, Maria Rita Piras, Angelo Deplano

Antonio Solinas, Department of Biomedical Sciences, University of Sassari, 07100 Sassari, Italy
Maria Rita Piras, Department of Clinical and Experimental Medicine, University of Sassari, 07100 Sassari, Italy
Angelo Deplano, Department of Surgical Sciences, University of Sassari, 07100 Sassari, Italy
Angelo Deplano, Unit of Internal Medicine, Lanusei Hospital, 08045 Lanusei, Italy
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Correspondence to: Antonio Solinas, Professor, Department of Biomedical Sciences, University of Sassari, Viale San Pietro 8, 07100 Sassari, Italy. soltoc@uniss.it
Telephone: +39-79-228443
Fax: +39-79-216282
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Abstract

Cognitive dysfunction in patients with chronic hepatitis C virus (HCV) infection is a distinct form of minimal hepatic encephalopathy (MHE). In fact, the majority of HCV-positive patients, irrespective of the grading of liver fibrosis, display alterations of verbal learning, attention, executive function, and memory when they are evaluated by suitable neuropsychological tests. Similarities between the cognitive dysfunction of HCV patients and MHE of patients with different etiologies are unclear. It is also unknown how the metabolic alterations of advanced liver diseases interact with the HCV-induced cognitive dysfunction, and whether these alterations are reversed by antiviral therapies. HCV replication in the brain may play a role in the pathogenesis of neuroinflammation. HCV-related brain dysfunction may be associated with white matter neuronal loss, alterations of association tracts and perfusion. It is unclear to what extent, in patients with cirrhosis, HCV triggers an irreversible neurodegenerative brain damage. New insights on this issue will be provided by longitudinal studies using the protocols established by the diagnostic and statistical manual of mental disorders fifth edition for cognitive disorders. The domains to be evaluated are complex attention; executive functions; learning and memory; perceptual motor functions; social cognition. These evaluations should be associated with fluorodeoxyglucose positron emission tomography and magnetic resonance imaging (MRI) protocols for major cognitive disorders including magnetic resonance spectroscopy, diffusion tensor imaging, magnetic resonance perfusion, and functional MRI. Also, the characteristics of portal hypertension, including the extent of liver blood flow and the type of portal shunts, should be evaluated.

Key words: Cognitive impairment; Neuropsychological tests; Magnetic resonance imaging spectroscopy; Magnetic resonance imaging spectroscopy; Hepatitis C virus infection

Core tip: Cognitive dysfunction in patients with chronic hepatitis C virus (HCV) infection is a distinct form of minimal hepatic encephalopathy. It is unclear to what extent HCV triggers an irreversible neurodegenerative brain damage. New insights on this issue will be provided by longitudinal studies using the protocols established by the DSM-5 for cognitive disorders associated with FDG-PET and magnetic resonance imaging protocols for major cognitive disorders. Also, the characteristics

of portal hypertension, including the extent of the liver blood flow and the type of portal shunts, should be evaluated.

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INTRODUCTION

Minimal hepatic encephalopathy (MHE) is defined as the presence of test-dependent brain dysfunction in patients with chronic liver disease who are not disoriented and do not display asterixis[1,2]. MHE is clinically relevant, as it affects the quality of life and the job performance of patients with chronic liver disease, and because it is a recognized risk factor of overt hepatic encephalopathy[3-5]. Cognitive dysfunction in patients with chronic hepatitis C virus (HCV) infection is a distinct form of MHE. In fact, the majority of HCV-positive patients, irrespective of the grading of liver fibrosis, display alterations of verbal learning, attention, executive function, and memory when they are evaluated by suitable neuropsychological tests[6-8].

WHAT WE KNOW

Recent years have witnessed significant insights into the pathogenesis and management of this disorder. However, several questions remain unanswered. In particular, commonalities between the cognitive dysfunction of HCV patients and MHE of patients with different etiologies are unclear. It is also unknown how the metabolic alterations of advanced liver diseases interact with the HCV-induced cognitive dysfunction, and whether these alterations are reversed by antiviral therapies.

HCV sequences were detected in the cerebrospinal fluid of 8 of 13 patients in whom a lumbar puncture had been performed for diagnostic purposes[9]. Ten of these patients were co-infected with human immunodeficiency virus, and were affected by aseptic meningitis (5 cases), reactive meningitis (1 case), neurotoxoplasmosis (3 cases), tuberculosis (2 cases), neurosyphilis (1 case) and multiphocal leukoencephalopathy (1 case). In 4 patients different virus strains were found in serum and in peripheral mononuclear blood cells (PBMC). Of note, virus strains detected in cerebrospinal fluid were similar to those detected in PBMC. This finding led to the hypothesis that infected PBMC cross the blood brain barrier and, by this mechanism, HCV infects the brain. Subsequent studies[10,11] confirmed the tissue compartmentalization of HCV quasispecies, and showed that microglial cells and, to a lesser extent, astrocytes harbored HCV-RNA sequences and HCV specific proteins. Recently, it has been shown that brain microvascular endothelium expresses HCV receptors, and HCV replicates within endothelial cell lines[12]. These findings support the hypothesis that HCV distinct viral strains replicate in the brain. Although the level of viral replication is generally low (apart from the cases with alterations of the blood-brain barrier), it may play a significant role in the pathogenesis of the neuroinflammation. Compared with HCV-negative controls, HCV-positive patients demonstrated significantly higher levels of proinflammatory cytokines within the brain[13,14]. Additional evidence of neuroinflammation in HCV positive patients is suggested by magnetic resonance spectroscopy studies[15,16]. In fact, choline/creatine ratios (a putative indicator of inflammation) were significantly higher in the basal ganglia and white matter of HCV positive patients compared to HBV positive patients and normal controls[17]. This finding was associated with elevated myo-inositol/creatine ratios (a putative marker of glial density)[18]. Subsequent quantitative analysis of brain metabolites[19] showed that the spectra related to choline and myo-inositol were significantly higher in the basal ganglia of patients with HCV chronic hepatitis. Compared to controls, the spectrum of N-acetyl aspartate (NNA) and NNA-glutamate, which is related to the neuronal density and nitrogen removal, was also significantly higher in basal ganglia of HCV patients. When the same metabolites were evaluated according to the Fatigue Impact Scale Score, it was found that both markers of inflammation and neuronal density were inversely related to the grade of fatigue. Similar to the elevated NNA/creatine ratio observed in the contra-lesional pre-frontal regions of stroke patients[20], a possible explanation of this finding is a compensatory mechanism of HCV-related brain inflammation. When compensatory mechanisms fail, fatigue, and possibly other signs of neurocognitive impairment, take place. HCV-related brain dysfunction does not seem limited to functional alterations. Evidence of white matter neuronal loss, alterations of several commissural and association tracts, cortical hypoperfusion, and basal ganglia hyperperfusion was recently provided by magnetic resonance (MR) spectroscopy associated with perfusion weighted imaging and diffusion tensor imaging[21]. Of note, this study was conducted in patients without cirrhosis. Scanty data are available on the natural history of neurocognitive dysfunction when chronic hepatitis progresses to cirrhosis. In patients with cirrhosis unrelated to HCV, MHE was associated with widespread microstructural disintegration of the white matter, and with focal cortical damage. These findings have been related to hyperammonaemia-induced neuroinflammation[22-24]. It is unclear to what extent HCV infection exacerbates this condition, and whether it triggers an irreversible neurodegenerative brain damage.

FUTURE DIRECTIONS

In order to get insights on these issues, longitudinal studies of well characterized cohorts of patients are

needed. Such studies should be based on extended neuropsychological evaluation, standard and advanced MR imaging (MRI) protocols, and accurate characterization of portal hypertension. In the current clinical practice the diagnosis of MHE is not uniform. Current guidelines[1,2] recommend that this diagnosis should be based on at least two of the following tests: the portosystemic encephalopathy syndrome test[25], the critical flicker test[26], the continous reaction time test[27], the inhibitory control test[28], the the Stroop test[29], the SCAN test[30]. These tests are mostly aimed at evaluating attention, working memory, and visuospatial ability. However, if we assume that HCV-related brain impairment could also represent the harbinger of a slowly progressing neurodegenerative alteration[31], when evaluating these patients we should apply the protocols established by the DSM-5 for cognitive disorders[32]. Accordingly, cognitive domains to be evaluated are the following: complex attention (including sustained attention, divided attention, selective attention and processing speed); executive functions (including planning, decision making, working memory, mental flexibility, abstract reasoning skills, and judgment); learning and memory; perceptual motor functions; social cognition. In addition, further study should be performed, using FDG-PET and MRI protocols for major cognitive disorders including magnetic resonance spectroscopy, diffusion tensor imaging, magnetic resonance perfusion, and functional MRI[33]. Finally, the characteristics of portal hypertension should also be evaluated. In this regard, it is worth to mention that not only the amount of blood diverted from the liver, but also the type of shunting is of relevance in the pathogenesis of hepatic encephalopathy[34,35]. In conclusion, the mechanisms of neurocognitive disorders in patients with chronic HCV infection have been partially elucidated. The impact of this condition on the long-term outcome of these patients should be further clarified.

REFERENCES

1 **Vilstrup H**, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, Weissenborn K, Wong P. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology* 2014; **60**: 715-735 [PMID: 25042402 DOI: 10.1002/hep.27210]

2 **American Association for the Study of Liver Diseases**; European Association for the Study of the Liver. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. *J Hepatol* 2014; **61**: 642-659 [PMID: 25015420 DOI: 10.1016/j.jhep.2014.05.042]

3 **Groeneweg M**, Moerland W, Quero JC, Hop WC, Krabbe PF, Schalm SW. Screening of subclinical hepatic encephalopathy. *J Hepatol* 2000; **32**: 748-753 [PMID: 10845661 DOI: 10.1016/S0168-8278(00)80243-3]

4 **Zamora Nava LE**, Torre Delgadillo A. Minimal hepatic encephalopathy. *Ann Hepatol* 2011; **10** Suppl 2: S50-S54 [PMID: 22228882]

5 **Stinton LM**, Jayakumar S. Minimal hepatic encephalopathy. *Can J Gastroenterol* 2013; **27**: 572-574 [PMID: 24106728]

6 **Kramer L**, Bauer E, Funk G, Hofer H, Jessner W, Steindl-Munda P, Wrba F, Madl C, Gangl A, Ferenci P. Subclinical impairment of brain function in chronic hepatitis C infection. *J Hepatol* 2002; **37**: 349-354 [PMID: 12175630 DOI: 10.1016/S0168-8278(02)00172-1]

7 **Kramer L**, Hofer H, Bauer E, Funk G, Formann E, Steindl-Munda P, Ferenci P. Relative impact of fatigue and subclinical cognitive brain dysfunction on health-related quality of life in chronic hepatitis C infection. *AIDS* 2005; **19** Suppl 3: S85-S92 [PMID: 16251834 DOI: 10.1097/01.aids.0000192075.26314.87]

8 **Forton DM**, Taylor-Robinson SD, Thomas HC. Cerebral dysfunction in chronic hepatitis C infection. *J Viral Hepat* 2003; **10**: 81-86 [PMID: 12614463]

9 **Laskus T**, Radkowski M, Bednarska A, Wilkinson J, Adair D, Nowicki M, Nikolopoulou GB, Vargas H, Rakela J. Detection and analysis of hepatitis C virus sequences in cerebrospinal fluid. *J Virol* 2002; **76**: 10064-10068 [PMID: 12208987 DOI: 10.1128/JVI.76.19.10064-10068.2002]

10 **Forton DM**, Karayiannis P, Mahmud N, Taylor-Robinson SD, Thomas HC. Identification of unique hepatitis C virus quasispecies in the central nervous system and comparative analysis of internal translational efficiency of brain, liver, and serum variants. *J Virol* 2004; **78**: 5170-5183 [PMID: 15113899 DOI: 10.1128/JVI.78.10.5170-5183.2004]

11 **Wilkinson J**, Radkowski M, Laskus T. Hepatitis C virus neuroinvasion: identification of infected cells. *J Virol* 2009; **83**: 1312-1319 [PMID: 19019968 DOI: 10.1128/JVI.01890-08]

12 **Fletcher NF**, Wilson GK, Murray J, Hu K, Lewis A, Reynolds GM, Stamataki Z, Meredith LW, Rowe IA, Luo G, Lopez-Ramirez MA, Baumert TF, Weksler B, Couraud PO, Kim KS, Romero IA, Jopling C, Morgello S, Balfe P, McKeating JA. Hepatitis C virus infects the endothelial cells of the blood-brain barrier. *Gastroenterology* 2012; **142**: 634-643.e6 [PMID: 22138189 DOI: 10.1053/j.gastro.2011.11.028]

13 **Wilkinson J**, Radkowski M, Eschbacher JM, Laskus T. Activation of brain macrophages/microglia cells in hepatitis C infection. *Gut* 2010; **59**: 1394-1400 [PMID: 20675697 DOI: 10.1136/gut.2009.199356]

14 **Liu Z**, Zhao F, He JJ. Hepatitis C virus (HCV) interaction with astrocytes: nonproductive infection and induction of IL-18. *J Neurovirol* 2014; **20**: 278-293 [PMID: 24671718]

15 **Zahr NM**, Mayer D, Rohlfing T, Sullivan EV, Pfefferbaum A. Imaging neuroinflammation? A perspective from MR spectroscopy. *Brain Pathol* 2014; **24**: 654-664 [PMID: 25345895 DOI: 10.1111/bpa.12197]

16 **Chang L**, Munsaka SM, Kraft-Terry S, Ernst T. Magnetic resonance spectroscopy to assess neuroinflammation and neuropathic pain. *J Neuroimmune Pharmacol* 2013; **8**: 576-593 [PMID: 23666436 DOI: 10.1007/s11481-013-9460-x]

17 **Forton DM**, Allsop JM, Main J, Foster GR, Thomas HC, Taylor-Robinson SD. Evidence for a cerebral effect of the hepatitis C virus. *Lancet* 2001; **358**: 38-39 [PMID: 11454379 DOI: 10.1016/S0140-6736(00)05270-3]

18 **Forton DM**, Hamilton G, Allsop JM, Grover VP, Wesnes K, O'Sullivan C, Thomas HC, Taylor-Robinson SD. Cerebral immune activation in chronic hepatitis C infection: a magnetic resonance spectroscopy study. *J Hepatol* 2008; **49**: 316-322 [PMID: 18538439 DOI: 10.1016/j.jhep.2008.03.022]

19 **Bokemeyer M**, Ding XQ, Goldbecker A, Raab P, Heeren M, Arvanitis D, Tillmann HL, Lanfermann H, Weissenborn K. Evidence for neuroinflammation and neuroprotection in HCV infection-associated encephalopathy. *Gut* 2011; **60**: 370-377 [PMID: 20926642 DOI: 10.1136/gut.2010.217976]

20 **Glodzik-Sobanska L**, Li J, Mosconi L, Slowik A, Walecki J, Szczudlik A, Sobiecka B, de Leon MJ. Prefrontal N-acetylaspartate and poststroke recovery: a longitudinal proton spectroscopy study. *AJNR Am J Neuroradiol* 2007; **28**: 470-474 [PMID: 17353314]

21 **Bladowska J**, Zimny A, Knysz B, Małyszczak K, Kołtowska A, Szewczyk P, Gąsiorowski J, Furdal M, Sąsiadek MJ. Evaluation of early cerebral metabolic, perfusion and microstructural changes in HCV-positive patients: a pilot study. *J Hepatol* 2013; **59**: 651-657 [PMID: 23680314 DOI: 10.1016/j.jhep.2013.05.008]

22 **Felipo V**. Hepatic encephalopathy: effects of liver failure on brain

function. *Nat Rev Neurosci* 2013; **14**: 851-858 [PMID: 24149188 DOI: 10.1038/nrn3587]

23 **Montoliu C**, Urios A, Forn C, García-Panach J, Avila C, Gimenez-Garzó C, Wassel A, Serra MA, Giner-Durán R, Gonzalez O, Aliaga R, Belloch V, Felipo V. Reduced white matter microstructural integrity correlates with cognitive deficits in minimal hepatic encephalopathy. *Gut* 2014; **63**: 1028-1030 [PMID: 24218171 DOI: 10.1136/gutjnl-2013-306175]

24 **Montoliu C**, Gonzalez-Escamilla G, Atienza M, Urios A, Gonzalez O, Wassel A, Aliaga R, Giner-Duran R, Serra MA, Rodrigo JM, Belloch V, Felipo V, Cantero JL. Focal cortical damage parallels cognitive impairment in minimal hepatic encephalopathy. *Neuroimage* 2012; **61**: 1165-1175 [PMID: 22465844 DOI: 10.1016/j.neuroimage.2012.03.041]

25 **Weissenborn K**. Psychometric tests for diagnosing minimal hepatic encephalopathy. *Metab Brain Dis* 2013; **28**: 227-229 [PMID: 22993201 DOI: 10.1007/s11011-012-9336-4]

26 **Kircheis G**, Wettstein M, Timmermann L, Schnitzler A, Häussinger D. Critical flicker frequency for quantification of low-grade hepatic encephalopathy. *Hepatology* 2002; **35**: 357-366 [PMID: 11826409 DOI: 10.1053/jhep.2002.30957]

27 **Lauridsen MM**, Thiele M, Kimer N, Vilstrup H. The continuous reaction times method for diagnosing, grading, and monitoring minimal/covert hepatic encephalopathy. *Metab Brain Dis* 2013; **28**: 231-234 [PMID: 23299303 DOI: 10.1007/s11011-012-9373-z]

28 **Bajaj JS**, Hafeezullah M, Franco J, Varma RR, Hoffmann RG, Knox JF, Hischke D, Hammeke TA, Pinkerton SD, Saeian K. Inhibitory control test for the diagnosis of minimal hepatic encephalopathy. *Gastroenterology* 2008; **135**: 1591-1600.e1 [PMID: 18723018]

29 **Bajaj JS**, Thacker LR, Heuman DM, Fuchs M, Sterling RK, Sanyal AJ, Puri P, Siddiqui MS, Stravitz RT, Bouneva I, Luketic V, Noble N, White MB, Monteith P, Unser A, Wade JB. The Stroop smartphone application is a short and valid method to screen for minimal hepatic encephalopathy. *Hepatology* 2013; **58**: 1122-1132 [PMID: 23389962 DOI: 10.1002/hep.26309]

30 **Montagnese S**, Schiff S, Turco M, Bonato CA, Ridola L, Gatta A, Nousbaum JB, Riggio O, Merkel C, Amodio P. Simple tools for complex syndromes: a three-level difficulty test for hepatic encephalopathy. *Dig Liver Dis* 2012; **44**: 957-960 [PMID: 22819289 DOI: 10.1016/j.dld.2012.06.010]

31 **Cattie JE**, Letendre SL, Woods SP, Barakat F, Perry W, Cherner M, Umlauf A, Franklin D, Heaton RK, Hassanein T, Grant I. Persistent neurocognitive decline in a clinic sample of hepatitis C virus-infected persons receiving interferon and ribavirin treatment. *J Neurovirol* 2014; **20**: 561-570 [PMID: 25326107 DOI: 10.1007/s13365-014-0265-3]

32 **The American Psychiatric Association**. Neurocognitive Disorders. In Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition. American Psychiatric Publishing, 2013: 591-645

33 **Bertelson JA**, Ajtai B. Neuroimaging of dementia. *Neurol Clin* 2014; **32**: 59-93 [PMID: 24287385 DOI: 10.1016/j.ncl.2013.07.001]

34 **Deplano A**, Migaleddu V, Pischedda A, Garrucciu G, Gregu G, Multinu C, Piredda M, Tocco A, Urigo F, Cossu PA, Solinas A. Portohepatic gradient and portal hemodynamics in patients with cirrhosis due to hepatitis C virus infection. *Dig Dis Sci* 1999; **44**: 155-162 [PMID: 9952237]

35 **Watanabe K**, Kimura K, Matsutani S, Ohto M, Okuda K. Portal hemodynamics in patients with gastric varices. A study in 230 patients with esophageal and/or gastric varices using portal vein catheterization. *Gastroenterology* 1988; **95**: 434-440 [PMID: 3391371]

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