

## Liver Disease as a Risk Factor for Cognitive Decline and Dementia: an Under-Recognized Issue

### To the Editor:

We read with great interest the article by Newton and colleagues<sup>1</sup> showing the presence of cognitive deficits in patients diagnosed with primary biliary cirrhosis, with a significant decline detected over a 2-year follow-up. Notably, cognitive impairment was associated with the presence of significant structural brain lesions and abnormality in dynamic blood pressure regulation.<sup>1</sup> Although it is well established that advanced forms of liver disease are frequently accompanied by overt and global cognitive deficits (hepatic encephalopathy), the article by Newton et al. adds to the current evidence that the presence of chronic liver disease might represent an important risk factor for neuropsychological impairment. Accordingly, it has been previously demonstrated that patients with chronic hepatitis C virus infection frequently show a decline in power of concentration and speed of working memory,<sup>2</sup> and that they perform significantly worse than healthy controls on verbal learning and memory.<sup>3</sup> Other evidence suggesting a relation between liver and brain function include the observation that liver-derived circulating insulin-like growth factor-1 affects crucial aspects of mature brain function, and may exert a significant procognitive function in adults.<sup>4</sup>

Besides this evidence, we believe that another important issue that may merit further investigation in future studies is the potential association between the presence of nonalcoholic fatty liver disease (NAFLD) and the development of cognitive decline in adults. Accordingly, previous studies have shown that patients with NAFLD have an increased risk of carotid atherosclerosis as compared to controls,<sup>5</sup> and increased carotid intima media thickness has been in turn associated with cognitive impairment.<sup>6</sup> In addition, patients with NAFLD have been reported to have high prevalence rates of metabolic syndrome,<sup>7</sup> which is considered a predictor of future cognitive decline.<sup>8</sup> Finally, it is noteworthy that recent studies found that elevated gamma glutamyltransferase, a common biochemical finding in NAFLD, may be involved in the pathogenesis of Alzheimer disease by promoting oxidative stress.<sup>9</sup>

Although the association between NAFLD with cognitive decline certainly merits further investigation, we believe that the evidence presented here underlines the importance to perform a longitudinal evaluation of cognitive function in all patients suffering from chronic liver disease.

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Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.22752

Potential conflict of interest: Nothing to report.

### Reply:

We appreciate the very positive comments from Dr. Yilmaz and Dr. Ozdogan regarding our recently published article.<sup>1</sup>

We absolutely agree that further work is needed to explore the prevalence of cognitive impairment in other chronic liver diseases, particularly in the earliest (precirrhotic) stages of the disease. It is time to revisit the conventional view that cognitive problems in chronic liver disease are entirely due to hepatic encephalopathy.

The potential risk factors for cognitive decline that Yilmaz and Ozdogan describe in those with nonalcoholic fatty liver disease (NAFLD) are all certainly plausible. We would also suggest that the relationship between autonomic dysfunction and cognitive decline highlighted in our recent article<sup>1</sup> (and recognized in nonhepatic diseases) is an additional potential pathogenetic mechanism for cognitive impairment in NAFLD. We have recently presented work at the American Association for the Study of Liver Diseases confirming that autonomic dysfunction is as prevalent and severe in NAFLD as that seen in primary biliary cirrhosis.<sup>2</sup>

We therefore agree wholeheartedly that further studies are urgently needed to explore the prevalence and pathogenesis of cognitive dysfunction in those with all forms of chronic liver disease. Recognizing that symptoms related to cognitive impairment can affect not only those with end-stage liver disease is the first step to improving our understanding of this phenomenon, developing appropriate targeted treatments, and ultimately improving the quality of life of those with chronic liver disease.

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Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.22784

Potential conflict of interest: Nothing to report.