Sir,

We read with interest the article by Cash et al. reviewing the pathophysiology and management of hepatic encephalopathy (HE). We agree that this condition is understudied and sub-optimally treated, highlighting the importance of the astrocyte-swelling hypothesis and other well-described pathophysiological mechanisms. While increased intra-astrocytic glutamine accumulation, driven by ambient hyper-ammonaemia, is probably a dominant process, neuroinflammation and neurosteroid-driven GABAergic modulation are also of importance. We would no longer consider zinc depletion to be a modern pathological dogma in describing HE and manganese deposition may reflect impaired biliary excretion of this agent, rather than be pathognomonic of HE, since studies correlate with cholestasis, rather than neuropsychiatric impairment.

We would also suggest that greater emphasis should be given to minimal hepatic encephalopathy (MHE) than was given in the review by Cash et al. Epidemiological studies have demonstrated the importance of this more recently recognized entity, with up to 50% of patients who have been diagnosed with cirrhosis estimated to have MHE. A wealth of diagnostic tests have arisen that can clearly define MHE with psychometric abnormalities and difficulties with skilled daily tasks, such as driving. The definition of these cognitive changes is likely to be of profound importance in the future.

These tests include the Psychometric Hepatic Encephalopathy Score (PHES) battery (a series of ‘paper and pencil’ tests), the critical flicker frequency and the computer-based Cognitive Drug Research battery, which is available ‘on-line’, among others. We would not recommend measurement of serum ammonia in diagnosis, owing to its poor correlation with the symptoms of HE and with the levels of neuropsychiatric impairment.

Hepatologists should point out the importance of psychometric testing to non-specialists and make arrangements for this as part of a standard investigative pathway in patients with cirrhosis. However, the psychometric battery with greatest reproducibility and ease of use in clinical practice has yet to be defined in practice guidelines, since the test batteries that are used differ between countries (the PHES test being particularly popular in Germany, for example). We would caution against the late referral to specialist hepatology services suggested by Cash et al. at the stage of treatment failure by a second-line agent. We suggest that all patients with cirrhosis, irrespective of the presence of overt HE, should be managed by specialists and any decompen-sation leading to HE should be referred to hepatologists with links to liver transplant centres.

The incidence, morbidity and mortality figures in patients with cirrhosis are all rising. An integrated diagnostic pathway from MHE to overt HE,
incorporating transplant assessment, will be a requirement for any modern hepatology practice.

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