Letters to the Editor

Ammonia and cerebral water. Importance of structural analysis of the brain in hepatic encephalopathy

To the Editor:
We read with interest the article by Mardini and colleagues [1], who induced hyperammonaemia experimentally in patients with cirrhosis. They show an increase in apparent diffusion coefficient (ADC) reported on diffusion tensor MR imaging (DTI) of the brain and a decrease in frontal white matter (FWM) myo-inositol (mI) demonstrated on concurrent 1H MR spectroscopy (MRS). These imaging abnormalities were reported in the absence of a change in cognitive status of the patients longitudinally across the study. The authors conclude that this is further evidence of compensated, low grade cerebral oedema in minimal hepatic encephalopathy (MHE), but we would caution against this firm conclusion in MHE patients, because the accumulated published data are uncertain, owing to a lack of direct structural analysis of brain volumes to date.

While measurement of ADC is a valid, but indirect method of assessing shifts in brain water content in cellular compartments, there is debate about the precise contribution to structural changes and to the formation and nature of cerebral oedema itself in MHE. Mardini and her group suggest that the low mI changes and to the formation and nature of cerebral oedema there is debate about the precise contribution to structural volumetric analysis, we believe that this would assist hepatologists in their ongoing debates regarding the pathophysiological significance of brain water and low grade cerebral oedema in MHE.

Conflict of interest
The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Reply to: “Ammonia and cerebral water. Importance of structural analysis of the brain in hepatic encephalopathy”

To the Editor:
We thank McPhail et al. [1] for their comments regarding our paper [2] in which we reported that induced hyperammonaemia in patients with hepatic encephalopathy (HE) leads to a transient increase in brain water apparent diffusion coefficient (ADC) reported from diffusion tensor imaging (DTI), accompanied by a decrease in frontal white matter myo-inositol (ml) measured by proton magnetic resonance spectroscopy (MRS). McPhail et al.
suggested that assessment of regional brain volume changes using voxel-based morphometry (VBM) would provide additional evidence available from our existing MR data as to the pathophysiological significance of brain water and low grade cerebral oedema in HE. In response to these comments, we have revisited the structural scans acquired during our study and performed a post hoc volumetric analysis of the brain in our patient group by three different methods.

We compared the baseline 3D T1 weighted volumetric images (TR/TE 9.6/4.6 ms, flip angle 8°, isotropic 1 mm resolution) against the post amino acid challenge images using VBM (SPM8) [3] for all subjects in a group analysis to identify any areas of white and gray matter volume change. As an alternative measure, we also compared individual subject data using the SIENA approach (Structural Image Evaluation, using Normalisation, of Atrophy, Version 2.2) [4], which provides a measurement of the change in total brain volume between baseline and following the challenge. Finally, we directly subtracted the co-registered baseline and post challenge images for each subject. Images were then visual inspected for evidence of volume change around the brain–CSF boundary [5].

VBM analysis showed no statistically significant areas of volume change in gray or white matter following the amino acid challenge. Likewise, subtraction of co-registered images did not reveal any visual evidence of shifts in the brain size. Formal assessment of boundary shifts using SIENA showed a mean (± SD) difference in total brain volume of −0.2 (± 0.69) percent across all subjects, however the SIENA method is accurate to around 0.2% brain volume change error [4], therefore these results were deemed insignificant.

The results from this paired volumetric analysis showed no significant change in brain volume following the challenge. This is consistent with the original findings of our paper in which we concluded that ammonia can directly drive changes in brain water distribution, suggesting that glial swelling and the redistribution of extra-intracellular water during hyperammonemia are the likely mechanism of cerebral oedema development in patients with HE. Our findings do not support a vasogenic mechanism for the transient changes in brain water diffusion seen following transient, induced hyperammonemia in this subject group.

C reactive protein levels in non-alcoholic fatty liver disease

To the Editor:
Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the world. It represents a wide spectrum of conditions ranging from fatty liver, which in general follows a benign, non-progressive clinical course, to nonalcoholic steatohepatitis (NASH), a more serious form of NAFLD that may progress to cirrhosis and end-stage liver disease. Accurate evaluation of liver fibrosis in patients with NAFLD is important to identify patients who may develop complications. Over time, several biological markers have been studied for evaluating the extent of steatosis, the presence of necroinflammation, and the development of fibrosis to avoid performing liver biopsy, an invasive procedure that still represents the gold standard of diagnosis. The most important parameter to be identified through non-invasive methods is inflammation, as it plays a central role in NAFLD progression. Several biomarkers of inflammation were extensively studied in relation to fatty liver disease. The C reactive protein (CRP) is an acute-phase reactant produced by the liver and has an increased serum concentration in a variety of inflammatory conditions. The assessment of circulating levels of high sensitive CRP (hsCRP) proved to be useful in differentiating between simple steatosis and NASH. Moreover, it seems that high concentrations of hsCRP are associated with extensive liver fibrosis in NASH [1].

In a recent issue of the Journal of Hepatology, Zimmermann et al. reported the association of hsCRP with various features of NAFLD in a large obese population. The authors concluded that, based on their results, hsCRP may be a marker of steatosis, but not of severity of NAFLD in these patients [2]. The findings of this report are interesting and contribute to our understanding of this issue. However, we have some concerns about the data presented by the authors.

Firstly, circulating hsCRP levels have been reported to be elevated in subjects with diabetes mellitus (DM) and also prediabetes [3,4]. Although it was stated in the article that some of the

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References