LETTERS

Reduced white matter microstructural integrity correlates with cognitive deficits in minimal hepatic encephalopathy

We read with interest the article by Goldbecker et al., comparing the accuracy for the diagnosis of hepatic encephalopathy (HE) of the three most commonly used batteries of psychometric test and critical flicker frequency. They conclude that the Psychometric Hepatic Encephalopathy Score (PHES) battery is the most robust method for diagnosis of HE.

As mentioned by Goldbecker et al., there is a wide agreement that HE needs to be diagnosed and treated and an increasing body of evidence shows that patients benefit from early treatment of overt and minimal HE (MHE). However, the diagnosis of MHE and lower stages of overt HE strongly depends on the experience of the examiner and, as indicated by Ferenci in his commentary to the paper of Goldbecker et al., psychometric tests are not used routinely in clinical practice for diagnosis of MHE. As a consequence, most patients with MHE (around two million people in the USA and a similar number in the European Union) remain undiagnosed and untreated. This is an important clinical, social and economical problem. Reliable diagnostic procedures are necessary to generalise early diagnosis and treatment of MHE worldwide.

Psychometric tests will be useful for detailed characterisation of the neurological alterations of each patient with MHE. However, it is unlikely that the use of psychometric tests may be extended worldwide to all hepatology/gastroenterology services and they do not seem promising as a general initial tool for early diagnosis of MHE.

It is therefore important to identify biomarkers which can be objectively quantified by reproducible methods and could serve as early indicators of the presence of MHE. Although MHE is a consequence of liver failure, the neurological manifestations of MHE are a consequence of the cerebral alterations, which are also influenced by other factors. Early detection of cerebral alterations by brain imaging may be very useful for diagnosis of MHE. This is also the case in other pathological situations associated with cognitive impairment. For example, the diagnostic guidelines of Alzheimer’s disease have recently been updated to include brain imaging biomarkers.

Identification of brain imaging biomarkers for diagnosis of MHE is therefore of great interest. We have investigated whole-brain white matter (WM) microstructural abnormalities associated with MHE using diffusion tensor imaging and tract-based spatial statistics. Patients with MHE have widespread altered anatomical connectivity of WM in the brain, with increased mean diffusivity (MD) and reduced fractional anisotropy (FA) as compared with controls or patients without MHE (table 1). This would reflect reduced structural integrity. The WM tracts showing significant differences between groups in FA and MD are shown in figure 1. Patients with MHE show reduced FA in the superior longitudinal fasciculus, anterior corona radiata/inferior fronto-occipital fasciculus/anterior thalamic radiation/uncinate fasciculus, anterior thalamic radiation/anterior limb of internal capsule and right anterior corona radiata. Patients with MHE show increased MD in the body of corpus callosum and in the left superior longitudinal fasciculus, anterior corona radiata/inferior fronto-occipital fasciculus/uncinate fasciculus/anterior thalamic radiation and in the corticospinal tract (figure 1).

Patients with MHE show reduced performance in psychometric tests as compared with patients without MHE (table 1). Correlation analysis shows that reduced FA of some tracts correlates with performance in line tracing and serial dotting tests. Increased MD correlates with performance in these same tests and also in the Stroop, symbol digit and number connection A tests. These findings suggest an association between microstructural alterations and mild cognitive impairment in MHE. Analysis of WM microstructural integrity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls</th>
<th>Patients with NMHE p vs control</th>
<th>Patients with MHE p vs control</th>
<th>MHE p vs NMHE</th>
<th>Global ANOVA p Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractional anisotropy</td>
<td>0.438±0.0043</td>
<td>0.442±0.0041</td>
<td>0.433±0.0054</td>
<td>p&lt;0.05</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean diffusivity (×1000)</td>
<td>0.735±0.0074</td>
<td>0.732±0.0089</td>
<td>0.758±0.0107</td>
<td>p&lt;0.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cognitive tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHES score</td>
<td>0±0.2</td>
<td>−0.26±0.26</td>
<td>−5.1±0.4 p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Digit symbol test</td>
<td>0±0.08</td>
<td>0±0.09</td>
<td>−0.6±0.16 p&lt;0.001</td>
<td>p&lt;0.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number connection test A</td>
<td>0.06±0.1</td>
<td>−0.07±0.07</td>
<td>−1.13±0.29 p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number connection test B</td>
<td>−0.11±0.18</td>
<td>−0.13±0.21</td>
<td>−1.2±0.3 p&lt;0.05</td>
<td>p&lt;0.05</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Serial dotting test</td>
<td>0±0</td>
<td>−0.07±0.15</td>
<td>−0.6±0.2 p&lt;0.05</td>
<td>ns</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Line tracing test</td>
<td>0.06±0.06</td>
<td>0.0±0.09</td>
<td>−1.5±0.3 p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroop test scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congruent (words)</td>
<td>110±4</td>
<td>102±5</td>
<td>80±5 p&lt;0.001</td>
<td>p&lt;0.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neutral (colours)</td>
<td>79±4</td>
<td>75±4</td>
<td>59±4 p&lt;0.001</td>
<td>p&lt;0.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incongruent (colour-words)</td>
<td>45±2</td>
<td>41±3</td>
<td>33±2 p&lt;0.01</td>
<td>p&lt;0.05</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Bimanual coordination* (min)</td>
<td>1.7±0.06</td>
<td>2.07±0.06</td>
<td>2.55±0.22 p&lt;0.001</td>
<td>ns</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Visuomotor coordination* (min)</td>
<td>2.12±0.08</td>
<td>2.4±0.1</td>
<td>3.23±0.25 p&lt;0.001</td>
<td>p&lt;0.05</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are the mean±SEM of 17 control subjects, 15 patients without MHE (NMHE) and 15 patients with MHE. PHES, psychometric hepatic encephalopathy score; ns, difference no significant. Stroop Test scores: number of items completed (age-corrected). Differences between groups were analysed using one-way analysis of variance (ANOVA) followed by post hoc Bonferroni.

* For bimanual and visuomotor coordination tests, differences between groups were analysed using univariate analysis of covariance (ANCOVA) with age included as covariate, followed by post hoc Bonferroni.
by magnetic resonance may provide new, strong, in vivo neuroimaging biomarkers for early diagnosis of MHE and to follow the efficacy of treatments.

Figure 1  Tracts showing fractional anisotropy (FA) and mean diffusivity (MD) differences between patients with minimal hepatic encephalopathy (MHE) and patients without MHE (NMHE) or controls. Tract-based spatial statistics show decreased white matter FA and increased MD in MHE as compared with controls and patients with NMHE. Green colour represents mean FA or MD skeleton of all participants. Red colour represents tracts with significant reduction of FA in MHE. Blue colour represents tracts with significant increase of MD in MHE. Images are presented with left as right, according to radiological convention at statistical level of p<0.05, Z=24. Each image represents a mean of 17 control subjects, 15 NMHE and 15 patients with MHE.

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Contributors CM: study concept and design, obtaining funding, performing psychometric tests, analysis and interpretation of data, revising the manuscript. AU and CG-G: performing psychometric tests and biochemical determinations. CA, CF and JG-P: performing TBSS analysis of data, interpretation of data, critical revision of the manuscript. AW, MAS, RG-D and OG: selection of patients, providing the analytical data. RA and VB: magnetic resonance acquisition. VF: study concept and design, obtaining funding, analysis and interpretation of data and writing the article.

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REFERENCES

Postscript


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