January 29, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6680-review.doc).

**Title:** Multimodality Magnetic Resonance Imaging in Hepatic Encephalopathy: An update

**Author:** Xiao Dong Zhang, Long Jiang Zhang, Shengyong Wu, Guang Ming Lu

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 6680

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

**(1)Responses to R1**
**R1-1:** Line 5, first paragraph: "mildest minimal hepatic encephalopathy" has no sense.
**Response**
As you suggest, the phrase has been rewritten as "minimal hepatic encephalopathy".

**R1-2**
The second paragraph could be made clearer.
**Response:**
Revised as suggested.

**R1-3**
Imaging biomarkers are they "biomarkers"?
**Response:**
Yes, nowadays "imaging biomarkers" is gradually used widely in literature. Please let's do kindly explanation (and brief description) for that.As we knew, there is "The Quantitative Imaging Biomarkers Alliance (QIBA)" which was organized by Radiological Society of North America (RSNA) in 2007 (http://www.rsna.org/QIBA.aspx). It is to unite researchers, healthcare professionals and industry stakeholders in the advancement of quantitative imaging and the use of biomarkers in clinical trials and practice. QIBA is an initiative to advance quantitative imaging and the use of imaging biomarkers in clinical trials and clinical practice by engaging researchers, healthcare professionals and industry. This involves: 1. collaborating to identify needs, barriers, and solutions to develop and test consistent, reliable, valid, and achievable quantitative imaging results across imaging platforms, clinical sites, and time; 2. accelerating the development and adoption of hardware and software standards needed to achieve accurate and reproducible quantitative results from imaging methods.
Afterwards, the proper application and validation of quantitative imaging tools as biomarkers in clinical

medicine has been extensively discussed including in a recent NIH Consensus Conference on Imaging Biomarkers.

Within "FDA Draft Guidance on Medical Device Development Tools Issued Today" (http://www.fda.gov/medicaldevices/resourcesforyou/industry/ucm374789.htm, Page Last Updated: 11/13/2013), it is read -

"Today, the Food and Drug Administration (FDA) released a draft guidance, Medical Device Development Tools: Draft Guidance for Industry, Tool Developers, and Food and Drug Administration Staff. Once finalized, this policy will support the development and timely evaluation of innovative medical devices.

An MDDT is a scientifically validated tool – a clinical outcome assessment (e.g. patient-reported or clinician-reported rating scales), a test used to detect or measure a biomarker (e.g. assay for a chemical analyte or medical imaging method), or non-clinical assessment method or model (e.g. in vitro, animal or computational model) - that aids device development and regulatory evaluation."

**R1-4**

Categorization of HE is not a used term. In fact you are speaking about nomenclature and classification. You should change it.

**Response:**

Revised as suggested.

**R1-5**

The second paragraph from categorization, 4th line:"The diagnosis of MHE still be lack of standard" is not clear, should be reformulated.

**Response:**

The sentence has been rewritten. 'The diagnosis of MHE still lack of standard, although a battery of psychometric tests have been used to detect neurocognitive impairment. However, neuropsychological tests cannot provide information about the cerebral regions involved.

**R1-6**

Pathogenesis, second phrase should be rewritten, make it clearer.

**Response:**

Revised as suggested.

**(2)Responses to R2**

**R2-1**

P7.It is common utility of VBM in measurement of white matter volume change of HE patients. Please explain me the reason why you measure white matter volume in HE.

**Response:**

Revised as suggested.

**R2-2**

P8 DWI and DTI can be used in assessing the effectiveness after TIPS or manitol infusion therapy.→DWI and DTI reflect the degree of portalsystemic shunt in HE. Please explain the reason "DWI and DTI can be used in assessing the effectiveness after TIPS".

**Response:**

Revised as suggested.

**(3)Responses to R3**

**R3:**Minor comments Please add table to summarize the imaging method, diagnostic performance and so on with literatures.

**Response:**

**A**dded as suggested, see Table 1.

**(4)Responses to R4**

**R4-1**

**.....**focusing the pathogenesis of HE on astrocyte swelling and cytotoxic edema is misleading. This must be corrected along the text to provide more accurate information to the readers. Some of the above references must be also included.

**Response:**

Revised as suggested.

**R4-2**

The authors say in the Abstract and in other parts of the text that HE occurs in end-stage or advanced liver diseases. This is not correct. MHE and mild cognitive impairment may appear very early during liver disease, even before cirrhosis appears, if the levels of ammonia and inflammation are high enough.

**Response:**

Revised as suggested.

**R4-3**

Page 11. The authors properly describe that blood flow is reduced

**Response:**

Thank you for your thoughtful comment.

Additionally, references and typesetting were corrected.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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