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Flat C, 23/F., Lucky Plaza,  
315-321 Lockhart Road,  
Wan Chai, Hong Kong, China

## ESPS Peer-review Report

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

**ESPS Manuscript NO:** 6680

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

**Reviewer code:** 00159305

**Science editor:** Ma, Ya-Juan

**Date sent for review:** 2013-10-27 13:55

**Date reviewed:** 2013-12-16 02:48

| CLASSIFICATION                                     | LANGUAGE EVALUATION   | RECOMMENDATION                      | CONCLUSION   |
|--|---|-------------------------------------|--|
| <input type="checkbox"/> Grade A (Excellent)       | <input type="checkbox"/> Grade A: Priority Publishing                 | Google Search:                      | <input type="checkbox"/> Accept                        |
| <input type="checkbox"/> Grade B (Very good)       | <input checked="" type="checkbox"/> Grade B: minor language polishing | <input type="checkbox"/> Existed    | <input type="checkbox"/> High priority for publication |
| <input checked="" type="checkbox"/> Grade C (Good) | <input type="checkbox"/> Grade C: a great deal of language polishing  | <input type="checkbox"/> No records | <input type="checkbox"/> Rejection                     |
| <input type="checkbox"/> Grade D (Fair)            | <input type="checkbox"/> Grade D: rejected                            | <input type="checkbox"/> Existed    | <input checked="" type="checkbox"/> Minor revision     |
| <input type="checkbox"/> Grade E (Poor)            |   | <input type="checkbox"/> No records | <input type="checkbox"/> Major revision                |

## COMMENTS TO AUTHORS

I have read with interest your manuscript which adds to your great work published in the field. I am a gastroenterologist and it is hard for me to comment on the last part of your paper (interpretation of multimodality MR imaging, diffusion weighted imaging and diffusion tensor imaging etc). However, concerning the first part, I have some concerns listed below: Introduction: 1. Line 5, first paragraph: "mildest minimal hepatic encephalopathy" has no sense. 2. The second paragraph could be made clearer. Imaging biomarkers are they "biomarkers"? Categorization of HE is not a used term. In fact you are speaking about nomenclature and classification. You should change it. The second paragraph from categorization, 4th line: "The diagnosis of MHE still be lack of standard" is not clear, should be reformulated. Pathogenesis, second phrase should be rewritten, make it clearer. Throughout the text there are some grammatical errors that must be corrected. Overall, the English is good.



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## ESPS Peer-review Report

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

**ESPS Manuscript NO:** 6680

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

**Reviewer code:** 00182114

**Science editor:** Ma, Ya-Juan

**Date sent for review:** 2013-10-27 13:55

**Date reviewed:** 2013-12-30 17:54

| CLASSIFICATION                                     | LANGUAGE EVALUATION  | RECOMMENDATION                      | CONCLUSION   |
|--|--|-------------------------------------|--|
| <input type="checkbox"/> Grade A (Excellent)       | <input checked="" type="checkbox"/> Grade A: Priority Publishing     | Google Search:                      | <input type="checkbox"/> Accept                        |
| <input type="checkbox"/> Grade B (Very good)       | <input type="checkbox"/> Grade B: minor language polishing           | <input type="checkbox"/> Existed    | <input type="checkbox"/> High priority for publication |
| <input checked="" type="checkbox"/> Grade C (Good) | <input type="checkbox"/> Grade C: a great deal of language polishing | <input type="checkbox"/> No records | <input type="checkbox"/> Rejection                     |
| <input type="checkbox"/> Grade D (Fair)            |  | BPG Search:                         | <input type="checkbox"/> Minor revision                |
| <input type="checkbox"/> Grade E (Poor)            | <input type="checkbox"/> Grade D: rejected                           | <input type="checkbox"/> Existed    | <input type="checkbox"/> Major revision                |
|  |  | <input type="checkbox"/> No records |  |

## COMMENTS TO AUTHORS

Dear Author Authors conclude combination of fMRI and other advanced MR modality such as DTI should be widely applied in this field to deepen our understanding of the whole story of HE. Formerly, we check NH3 and amino acid imbalance to make a diagnosis of hepatic encephalopathy (HE). But authors say "multimodality MR imaging plays an important role in helping to understand pathological process of HE". This is very interesting paper for the purpose of pathophysiology of HE. I ask some questions. 1.P6. Currently, a consensus has been reached as a decreased grey matter volume in cirrhosis patients. P7 Child-Pugh score was a major factor to affect gray matter volume, while portosystemic shunt mainly affected white matter volume. →hepatic parenchymal damage reflect gray matter, portal systemic shunt reflect white matter 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. 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".



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## ESPS Peer-review Report

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

**ESPS Manuscript NO:** 6680

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

**Reviewer code:** 00053451

**Science editor:** Ma, Ya-Juan

**Date sent for review:** 2013-10-27 13:55

**Date reviewed:** 2014-01-08 14:05

| CLASSIFICATION                                     | LANGUAGE EVALUATION  | RECOMMENDATION                      | CONCLUSION   |
|--|--|-------------------------------------|--|
| <input type="checkbox"/> Grade A (Excellent)       | <input checked="" type="checkbox"/> Grade A: Priority Publishing     | Google Search:                      | <input type="checkbox"/> Accept                        |
| <input type="checkbox"/> Grade B (Very good)       | <input type="checkbox"/> Grade B: minor language polishing           | <input type="checkbox"/> Existed    | <input type="checkbox"/> High priority for publication |
| <input checked="" type="checkbox"/> Grade C (Good) | <input type="checkbox"/> Grade C: a great deal of language polishing | <input type="checkbox"/> No records | <input type="checkbox"/> Rejection                     |
| <input type="checkbox"/> Grade D (Fair)            | <input type="checkbox"/> Grade D: rejected                           | <input type="checkbox"/> Existed    | <input checked="" type="checkbox"/> Minor revision     |
| <input type="checkbox"/> Grade E (Poor)            |  | <input type="checkbox"/> No records | <input type="checkbox"/> Major revision                |

## COMMENTS TO AUTHORS

**Summary and general comments** This is a review article about the study of MR imaging for Hepatic encephalopathy. The authors overviewed many literatures, outlined the current clinical significance and discussed future perspective. Although most of the knowledge is well known, this manuscript may be attractive to the readers of WJG. **Minor comments** Please add table to summarize the imaging method, diagnostic performance and so on with literatures.



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## ESPS Peer-review Report

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

**ESPS Manuscript NO:** 6680

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

**Reviewer code:** 00053571

**Science editor:** Ma, Ya-Juan

**Date sent for review:** 2013-10-27 13:55

**Date reviewed:** 2014-01-09 00:20

| CLASSIFICATION  | LANGUAGE EVALUATION  | RECOMMENDATION                      | CONCLUSION   |
|---|--|-------------------------------------|--|
| <input type="checkbox"/> Grade A (Excellent)            | <input checked="" type="checkbox"/> Grade A: Priority Publishing     | Google Search:                      | <input type="checkbox"/> Accept                        |
| <input checked="" type="checkbox"/> Grade B (Very good) | <input type="checkbox"/> Grade B: minor language polishing           | <input type="checkbox"/> Existed    | <input type="checkbox"/> High priority for publication |
| <input type="checkbox"/> Grade C (Good)                 | <input type="checkbox"/> Grade C: a great deal of language polishing | <input type="checkbox"/> No records | <input type="checkbox"/> Rejection                     |
| <input type="checkbox"/> Grade D (Fair)                 | <input type="checkbox"/> Grade D: rejected                           | <input type="checkbox"/> Existed    | <input checked="" type="checkbox"/> Minor revision     |
| <input type="checkbox"/> Grade E (Poor)                 |  | <input type="checkbox"/> No records | <input type="checkbox"/> Major revision                |

## COMMENTS TO AUTHORS

The authors review some of the most relevant studies performed using different Magnetic Resonance Imaging techniques and analysis in patients with hepatic encephalopathy. This article provides an appropriate overview of the utility of MRI in the study of the cerebral alterations in HE and the possible implications of the results obtained with the different techniques for the understanding of the mechanisms involved in the pathogenesis of HE and in monitoring of the progress of HE and of the possible beneficial effects of treatments. The review on MRI techniques, results and implications is comprehensive and appropriate. However, there are two main points which must be corrected in the introductory section and in some parts of the text because they do not reflect properly the current knowledge on the pathogenesis of HE. The main points to correct are: 1. Role of astrocyte swelling and cytotoxic edema in the pathogenesis of HE: On page 5, The authors say: "Pathogenesis of HE. The most crucial and widely accepted hypothesis for HE is hyperammonemia with various sources of serum ammonia[13-15]. Hyperammonemia leads to excess uptake of ammonia by astrocytes representing the principal target. Then, increased ammonia and glutamate are converted to form abundant glutamine under the catalysis of glutamine synthase, which contributes to increased osmotic pressure. However, astrocytes swelling may not happen immediately due to the exist of osmotic-regulatory mechanisms by depletion of intracellular osmolyte until decompensation. As decompensation continues, astrocytes undergo morphologic changes leading to Alzheimer type 2 astrocytosis." Along the text the data are also presented considering that astrocyte swelling is responsible for HE. This is not correct. It is now clearly demonstrated that cytotoxic edema does not play a role in minimal HE. This has been recently reviewed in Nature Reviews Neuroscience. (2013) 14(12):851-858. Also the data from reference 62 (from the authors of the paper) commented on



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page 15 (copied below) clearly show that decreased functional connectivity was also detected between some regions without abnormal structural connectivity: "Investigators combined DTI and resting-state fMRI to investigate brain changes in MHE in a single institute study,[62] and found MHE patients have both disturbed structural and functional connectivity within the DMN. The decreased functional connectivity was also detected between some regions without abnormal structural connectivity, suggesting that the former may be more sensitive in detecting the early abnormalities of MHE. This study extends our understanding of the pathophysiology of MHE". This supports that functional impairment is not a consequence of structural alterations, but of alterations in neuronal communication (e.g. altered neurotransmission). This has been clearly demonstrated in animal models of HE (see for example Cauli et al; Liver Int. 2013 Jun 20. doi: 10.1111/liv.12258. PMID: 23869990: Cerebral oedema is not responsible for motor or cognitive deficits in rats with hepatic encephalopathy). Therefore 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

2. "Hepatic encephalopathy (HE) is a neuropsychiatric complication of end-stage liver diseases" 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 ( see Metabolic Brain Disease; 2012, 27(1):51-58). This must be also corrected in the bsract and along the text. Minor point:

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