

**Dear Editors,**

On behalf of all the authors, I would like to thank you for your letter and for reviewers' comments concerning our manuscript entitled "The compromised therapeutic value of pediatric liver transplantation in ethylmalonic encephalopathy: A case report and review of literature" (Manuscript NO: 56537). Those comments are all valuable and very helpful for revising and improving our paper. We have carefully considered the reviewers' critical comments and insightful suggestions, responded to these comments and suggestions point-by-point, and revised the manuscript accordingly. In the revised manuscript, you will find the alterations that we made in response to the reviewers. All changes made to the text are underlined so that they may be easily identified. In this response to reviewer letter, we also indicated how we have dealt with the reviewers' comments. Please find enclosed the edited manuscript in Word format (file name: Revised manuscript.docx)

**Title:** The compromised therapeutic value of pediatric liver transplantation in ethylmalonic encephalopathy: A case report and review of literature

**Authors List:** Guang-Peng Zhou, Wei Qu, Zhi-Jun Zhu, Li-Ying Sun, Lin Wei, Zhi-Gui Zeng, Ying Liu

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

**Manuscript NO:** 56537

The manuscript has been improved according to the suggestions of reviewers and Editorial Office.

**Comments:**

**Reviewer # 1**

Comment 1: This is an important case report and hence it is worthy of publication. I have some comments with respect to enhancing the manuscript. Reference is made to the OMIM website in the first sentence of the Introduction section of the manuscript. This needs to be included in the References - <https://www.omim.org/entry/602473>

*Response: Thank you for your review and constructive comments. According to your comments, we have added this paper into the References (Page 5, line 2-3).*

Comment 2: There is some published literature out of China pertaining to the incidence of ethylmalonic encephalopathy, this should be referred to - Diagnosis and therapeutic monitoring of inborn errors of metabolism in 00,077 newborns from Jining city in China. Yang et al. BMC Pediatrics, 2018, 118, 110. <https://link.springer.com/article/10.1186/s12887-018-1090-2>

*Response: We agree that the content about the incidence of ethylmalonic encephalopathy is very important, so we have added relevant content about the incidence of ethylmalonic encephalopathy and cited this paper in the References (Page 5, line 6-9).*

Comment 3: In addition, there is a Liver Transplant Registry in China which does report from time to time. Has this case been reported to the Registry and if so are you aware of how many other children have been transplanted for metabolic disorders in China to date? It is important to also report cases to a central registry so that their outcomes can be tracked.

*Response: This case has been reported to China Liver Transplant Registry (CLTR). Since we only have access to data on liver transplant recipients of our liver transplant center, we entrusted the staff of CLTR to search for data about liver transplantation for ethylmalonic encephalopathy in the CLTR. They found out that as of June 18, 2020, our case is the only case of liver transplantation for ethylmalonic encephalopathy in the CLTR.*

Comment 4: Finally, the discussion section does not quite encapsulate all of the factors that may contribute to improved patient outcomes for this condition, noting that your patient did have a novel gene mutation. It is possible that there is a spectrum of phenotypes of this disorder partly due to the variation in the nature of the gene mutations. This may partly explain the difference in outcomes seen to date with liver transplantation in the handful of cases that have been reported. I noted with interest that the best result to date was seen with a non-related donor liver (ie the case transplanted with the deceased donor liver), which raises the question as to whether live donor liver transplantation with a related donor is truly the best option (although it may be the only option in the absence of deceased donors). So there seem to be genetic factors, recipient factors (not all which are currently understood) and possibly factors related to the organ donor which contribute to the outcomes. If this can all be covered off in the discussion section.

*Response: This comment is of important guiding significance to our study. The undefined genotype-phenotype correlation and the use of a heterozygous carrier donor in living donor liver transplantation may also lead to the suboptimal clinical outcomes of our patient after liver transplantation. We have further discussed these possible factors related to patient outcomes after liver transplantation in the discussion section (Page 11, line 3-5 and 24-28; Page 12, line 1-7).*

## **Reviewer # 2**

Comment 1: There are minor grammar changes that need to be made.

*Response: Thank you for your review and valuable comments. According to your comments, we have sent this revised manuscript to a native-English speaking medical editor for further edition for English language.*

Comment 2: Since this a very rare condition, it would be interesting to

mention other treatment strategies that may be used in EE such as hemodialysis (Acute and Chronic Management in an Atypical Case of Ethylmalonic Encephalopathy. Kitzler TM, Gupta IR, Osterman B, Poulin C, Trakadis Y, Waters PJ, Buhas DC. JIMD Rep. 2019; 45:57-63) or intravenous N-acetylcysteine (Kılıç, M., Dedeoğlu, Ö., Göçmen, R. et al. Successful treatment of a patient with ethylmalonic encephalopathy by intravenous N-acetylcysteine. Metab Brain Dis 32, 293–296 (2017).)

*Response: We agree that the content about other treatment strategies that may be used in EE is important, so we added relevant content in the introduction section (Page 5, line 21-28; Page 6, line 1-2).*

#### **Science Editor:**

1 Scientific quality: The manuscript describes a case report of the pediatric liver transplantation in ethylmalonic encephalopathy. The topic is within the scope of the WJG. (1) Classification: Grade B and Grade B; (2) Summary of the Peer-Review Report: The case is very well presented and the comparison to the other cases described in literature is very clear. There are minor grammar changes that need to be made. Since this a very rare condition, it would be interesting to mention other treatment strategies that may be used in EE. Finally, the discussion section does not quite encapsulate all of the factors that may contribute to improved patient outcomes for this condition. The authors need to add more details in the “discussion” section. The questions raised by the reviewers should be answered; and (3) Format: There is 1 table and 3 figures. A total of 10 references are cited, including 3 references published in the last 3 years. There are no self-citations. 2 Language evaluation: Classification: Grade A and Grade B. A language editing certificate issued by MedE was provided. 3 Academic norms and rules: The authors provided the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement, the Signed Informed Consent Form and the CARE Checklist-2016. No academic misconduct was found in the CrossCheck detection and Bing

search. 4 Supplementary comments: This is an unsolicited manuscript. The study was supported by Capital Research Project of Specialty Clinical Application; and Capital Special Program for Health Research and Development. The topic has not previously been published in the WJG. The corresponding author has published 3 articles in the BPG.

*Response: Thank you for the consideration of this paper and for your comments. The questions raised by the reviewers have been answered point-by-point. In addition, according to reviewers' comments and suggestions, another 4 references are cited (Reference 1, 4, 9, and 10), and a total of 14 references are cited now.*

5 Issues raised: (1) I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

*Response: Approval documents of two grants have been uploaded.*

(2) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

*Response: The new file with .pptx extension have been added, including original figures.*

6 Re-Review: Required. 7 Recommendation: Conditionally accepted. (Man Liu)

#### **Editorial Office Director**

I have checked the comments written by the science editor.

*Response: Thank you for the consideration of this paper and for your comments.*

**Company Editor-in-Chief:**

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

*Response: Thank you for the consideration of this paper and for your comments.*

Finally, we wish to thank the Editors and the Reviewers for their valuable comments and suggestions that helped us to increase the value of our paper. We do hope that the revised manuscript is now acceptable for publication in *World Journal of Gastroenterology*.

Yours sincerely,

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