

Botucatu, April 26, 2021

To

Professor Lian-Sheng Ma

Science Editor, Company Editor-in-Chief, Editorial Office

Baishideng Publishing Group Inc

RE: World Journal of Gastroenterology Manuscript NO: 64197, entitled " Challenges in the diagnosis of intestinal neuronal dysplasia type B: A look beyond the number of ganglion cells".

We would like to thank the Editorial Committee for the attention to our manuscript. We thank the reviewers for their comments and constructive criticism regarding our manuscript and enclose the answers to the reviewers' comments, point by point, below. The reviewers' comments are shown in bold. We feel that our manuscript has improved after the revisions. All changes have been incorporated in a revised version of our manuscript. The modifications performed in the present revised manuscript are outlined in blue.

Thanking you very much in advance for your kind attention,

Sincerely yours,

Pedro Luiz Toledo de Arruda Lourenção, MD, PhD

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Reviewer # 1: We thank Reviewer #1 for the pertinent comments and constructive suggestions. We have made some changes to improve readability. The comments are answered point by point.

- 1) The title of this manuscript is interesting and challenging. As a gastroenterology, IND type B, is not a familiar term to us, unfortunately although we are interested in the etiopathogenesis of intractable constipation. As a gastroenterologist, I think this article is too long and distracted although I can fully understand that the diagnostic definition or criteria as well as the true existence of IND type B is not established yet, so the authors needed to explain them in detail. If you are generous to help us to understand the importance of new diagnostic criteria (because this journal is mostly for GI doctors), it will be better to summarize the uncomfortably long and many sentences about previous reference articles into a few table such as 1) comparison between Hirschsprung disease vs. IND type B, 2) New definition vs. previous definition history, 3) IHCs and their feature, and so forth.**

Really, the uncertainties that persist regarding the definition and diagnostic criteria for IND-B require very detailed explanations, making the manuscript long and distracted. We removed some sentences with specific information that hindered the readability of the manuscript. We have added new tables that summarize information presented in many sentences. Table 1 (on page 29) compares Hirschsprung's disease and intestinal neuronal dysplasia type B (IND-B) regarding the main clinical and histopathological aspects. Table 2 (on page 29) summarises the main histopathological criteria used for the diagnosis of IND-B. Table 3 (on page 30) shows the pattern of immunohistochemical expression of the main markers used for the diagnosis of intestinal neuronal dysplasia type B.

- 2) In addition, conclusion is likely to be indecisive. If you suggest the new presumptive diagnostic criteria with IHC, it will be more informative and understandable.**

The lack of consensus regarding the criteria used by different centers for the histopathological diagnosis of IND-B makes it difficult to establish reasoned

conclusions. We restructured the "Conclusion" section on pages 14 and 15, presenting this limitation and highlighting the impact of using immunohistochemical markers to clarify aspects of the etiopathogenesis and the diagnosis of IND-B.

Science Editor: We thank the scientific editor for considerations and clarify that the presented self-citations are closely related to the topic of this review. We uploaded the approved grant application form and the original figure documents.