Dear Editors and Reviewers,

The authors thank the editors and reviewers for their constructive suggestions. We have carefully addressed the reviewers' suggestions and modified our manuscript accordingly.

Please find below a point-by-point response to the reviewers' comments and concerns. The revised changes are highlighted in yellow.

Sincerely,

Sohn

Comments from reviewer 1 (Reviewer's code: 03207387)

The case highlights the necessity to be alert to bradycardia and T-wave abnormalities that may occur with intravenous steroid pulse therapy if the patient has genetic factors that may contribute to abnormal potassium channel function. This manuscript presented the hypothesis that mutations in the HNF-4a gene are a genetic susceptibility factor for bradycardia and raises a new question: What genetic factors should we consider when using glucocorticoids? Clearly, this case provides new insights into the mechanisms of corticosteroid-induced bradycardia.

Authors' response:

→ We feel very grateful to the reviewer for agreeing with us to the main intention of the manuscript.

Here are some suggestions: 1)This article presents a patient with MS and MODY. Since high-dose corticosteroid therapy is used commonly to treat autoimmune and inflammatory diseases, MS should be a secondary condition in this case report. I am afraid the title, keywords, and conclusion of this manuscript make the readers feel that the topic is not prominent enough to catch the key points. The reason for the bradycardia in this case is speculated to be related to the heterozygous mutation of the HNF4A gene that causes MODY and the use of glucocorticoids, so the role of MS in it should not be emphasized.

Authors' response:

We revised the manuscript, and modified the title accordingly, to put emphasis on the comorbid HNF4A variant.

"Maturity-onset diabetes of the young" was added to the keywords, to emphasize the patient's comorbid factor that may potentially lead to corticosteroid-induced bradycardia.

2)I suggest to supplement the information of the mutation (c.1045C>T [p.Gln349*]) in HNF4Agene. Whether the mutation is inherited in an autosomal dominant (AD) manner in previous reports? The parents of the index patient have no history of diabetes and do not meet the characteristics of AD. It is recommended that parents and grandparents finish the genetic

test to validate co-segregation analysis on other members of this family.

Authors' response:

→ We supplemented the information of the c.1045C>T variant, which was predicted (in silico) to be in a highly conserved position in exon 8.

→ We agree that familial study, including genetic trio study, is very informative and crucial to draw causal inference in genetic disorders. However, after genetic counseling, her father was unwilling to proceed genetic screening, because he has been taking regular annual health checkups, and thus was reluctant to undergo further diagnostic evaluation which might require additional cost or have little to do with patient management.

3)The authors mentioned that the blood potassium of the patient was normal. How many times have the blood potassium been tested, and was it normal every time? As mentioned in Discussion, "Patients with HNF4A mutation have defective proximal tubule functions[7, 8], and are prone to urinary loss of serum potassium". Has 24-hour urine potassium been tested? Have you supplemented the patient with potassium during intravenous steroid pulse therapy?

Authors' response:

→ The patient's HNF4A variant was not known during the admission period, since the results of genetic testing only became available after 1 month at the outpatient clinic. Therefore, we did not collect 24-hour urine for evaluation. We described this limitation in the main text.

→ Serum potassium level was tested every 2~3 days on average, and all measured values were within normal limits, except for Day 15. We did not supplement potassium during the bradycardia event (Day 11~ Day 14). However, we supplemented potassium per os (potassium chloride 600 mg three times a day) on Day 15, after her heart rate returned to normal. On Day 15, the potassium level was 3.4 mmol/L. Corticosteroid was administered until Day 13. She was discharged from our hospital on Day 16. (Fig. 1(B))

4)The exact etiology of steroid-induced bradycardia is unknown, but several mechanisms have been proposed. It is recommended to increase the literature review in the discussion. Potential references: "Stroeder J, Evans C, Mansell H. Corticosteroid-induced bradycardia: Case report and review of the literature. Can Pharm J (Ott). 2015 Sep;148(5):235-40. doi: 10.1177/1715163515597451. PMID: 26445579; PMCID: PMC4561462."“Üsküdar Cansu D, Bodakçi E, Korkmaz C. Dose-dependent bradycardia as a rare side effect of corticosteroids: a case report and review of the literature. Rheumatol Int. 2018 Dec;38(12):2337-2343. doi: 10.1007/s00296-018-4167-1. Epub 2018 Oct 1. PMID: 30276424."

Authors' response:

→ Thank you for your thoughtful advice. I also included other relevant references in addition to the references you recommended.

5)The conclusions in the abstract and the "conclusion" section are not specific. It is better to briefly present the gene found in this case and its possible role.

Authors' response:

→ We appreciate the reviewer for the kindly comments. In the “conclusion” section, we included the specific gene and its possible role related to dysfunctional potassium channel or potassium homeostasis. We also briefly referred ‘HNF4A mutation’ in the abstract, according to word limit (~20 words) for conclusion in the abstract.

Comments from reviewer 2 (Reviewer's code: 05688164)

Sohn SY and colleagues in the present case report, entitled "Corticosteroid-induced bradycardia and T-wave abnormalities in a patient with multiple sclerosis and HNF4α mutation: A case report" present a case report on the emergence of bradycardia and T-wave abnormalities under corticosteroid therapy in a patient with multiple sclerosis (MS) and maturity-onset diabetes of the young associated with hepatocyte nuclear factor 4-alpha (HNF4A) gene mutation. For this purpose, authors present an important case that highlighted need for special clinical attention to the occurrence of bradycardia and T-wave abnormalities under corticosteroid treatment for MS patients, especially comorbid with diabetes and with predisposing factors such as genetic mutation. The main strength of this case report is that it addresses an interesting and valuable report, attracting more careful attention of physicians who administer corticosteroid therapy for the treatment of MS, especially when patients have some comorbidities. In general, I think the report of this manuscript is really interesting and the authors' fascinating observations on this timely topic may be of interest to the readers of World Journal of Clinical Cases.

Authors' response:

→ Thanks for your positive comments.

However, some comments, as well as some crucial evidence that should be included to reinforce the authors' argumentation, needed to be addressed to improve the quality of the manuscript, its adequacy, and thus its readability prior to the publication in the present form. My overall judgment is to publish this review after the authors have carefully considered my suggestions below, in particular reshaping parts of the Introduction and Discussion sections, and by adding more evidence.

Authors' response:

→ Thank you for your kindly comments. We added another paragraph in the Introduction section, expanded the Discussion section, and also added relevant literature according to your advice.

Please consider the following comments: 1. Introduction: This section is too concise and needs to be expanded including background regarding the treatment of multiple sclerosis (MS), side effects in general, the comorbidity which requires a special attention in general and particularly to diabetics, genetic polymorphism in MS and the previous case including the mutation in particular and association with diabetes, and the uniqueness of this case.

Authors' response:

→ We expanded the "introduction" section by adding descriptions and literature about treatment, comorbid condition (in brief) in MS patients. However, we tried not to overly focus on MS itself. We postulated that corticosteroid-induced bradycardia occurred owing to the HNF4A mutation, since the mutated gene may influence potassium channel (Kir) or potassium homeostasis. As far as we are aware, HNF4A variant has not been known to be related with MS. We described the HNF4A gene in detail, in the Discussion section.

2. History of past illness: The section is too short. If there is nothing else describe, please state so.

Authors' response:

→ We expanded this section by adding pediatric history (macrosomia at birth), which suggest that the patient harbored HNF4A variant from birth.

3. Physical examination: This is section needs to expand including negative findings of relevant examinations.

Authors' response:

→ We described the neurological exam in more detail.

4. Discussion: I would ask the authors to discuss limitations, weaknesses, future directions, other possible options for treatment, and biomarkers, among others. Here, authors can describe in detail and report all the technical issues brought to the surface. Suggested references: https://doi.org/10.3390/biomedicines8100406.

Authors' response:

→ We added limitations (Page 10, line 19, highlighted in yellow), and in the last paragraph of the "Discussion" section, we provided direction for future researches (Page 10, line 28, highlighted in yellow). In this patient, other possible treatment options would be to minimize MS recurrence, by controlling the disease activity with efficacious DMT (Page 9, line 20, highlighted in yellow). Also, we included the suggested reference.

5. In my opinion, I think the conclusions paragraph, despite being well organized, is too thin and does not clearly describe what the authors think is the take home message. I believe that this section would benefit from some thoughtful as well as in-depth considerations by the authors, because as it stands, it is very descriptive but not enough theoretical as a discussion should be. Authors should make an effort, trying to explain the theoretical implication as well as the translational application of their research.

Authors' response:

→ The precise pathomechanism of corticosteroid-induced bradycardia remains elusive. We wanted to focus on the HNF4A variant, which can theoretically exert a major role in potassium homeostasis or inwardly rectifying potassium channel (Kir), and can finally lead to T-wave abnormalities on ECG. We presented our inference mainly in the "Discussion" section.

6. References: Presenting more references certainly reinforces more solid evidence to support this case study and raise importance to pay more careful attention to comorbidity, and present valuable challenges to avoid the emergence of possible complications. Overall, the manuscript contains one figure and 18 references.

Authors' response:

→ We added more references, up to 32, to strengthen evidence for the present case study. Also, we modified the figures in 2 parts (Figure 1 & Figure 2).

I believe that this manuscript might carry important value presenting the potential complication under the treatment of MS in patients with comorbidity.

Authors' response:

→ The authors are grateful for the reviewer's insightful feedback, which helped us to greatly improve our manuscript.