

PEER-REVIEW REPORT

Name of journal: *World Journal of Clinical Cases*

Manuscript NO: 71645

Title: Corticosteroid-induced bradycardia and T-wave abnormalities in a patient with multiple sclerosis and HNF4 α mutation: A case report

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03207387

Position: Peer Reviewer

Academic degree: MD

Professional title: Dean

Reviewer's Country/Territory: China

Author's Country/Territory: South Korea

Manuscript submission date: 2021-09-24

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-09-24 23:58

Reviewer performed review: 2021-10-05 10:51

Review time: 10 Days and 10 Hours

Scientific quality	☐ Grade A: Excellent ☐ Grade B: Very good ☒ Grade C: Good ☐ Grade D: Fair ☐ Grade E: Do not publish
Language quality	☐ Grade A: Priority publishing ☒ Grade B: Minor language polishing ☐ Grade C: A great deal of language polishing ☐ Grade D: Rejection
Conclusion	☐ Accept (High priority) ☐ Accept (General priority) ☐ Minor revision ☒ Major revision ☐ Rejection
Re-review	☒ Yes ☐ No

Peer-reviewer statements	Peer-Review: [☒] Anonymous [☐] Onymous Conflicts-of-Interest: [☐] Yes [☒] No
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SPECIFIC COMMENTS TO AUTHORS

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. 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. 2) I suggest to supplement the information of the mutation (c.1045C>T [p.Gln349*]) in HNF4A gene. 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. 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? 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." 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.

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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05688164

Position: Peer Reviewer

Academic degree: BSc, MD, PhD

Professional title: Research Fellow

Reviewer's Country/Territory: Hungary

Author's Country/Territory: South Korea

Manuscript submission date: 2021-09-24

Reviewer chosen by: Qi-Gu Yao (Online Science Editor)

Reviewer accepted review: 2022-02-20 08:06

Reviewer performed review: 2022-02-20 10:08

Review time: 2 Hours

Scientific quality	☐ Grade A: Excellent ☐ Grade B: Very good ☒ Grade C: Good ☐ Grade D: Fair ☐ Grade E: Do not publish
Language quality	☐ Grade A: Priority publishing ☒ Grade B: Minor language polishing ☐ Grade C: A great deal of language polishing ☐ Grade D: Rejection
Conclusion	☐ Accept (High priority) ☐ Accept (General priority) ☐ Minor revision ☒ Major revision ☐ Rejection
Re-review	☒ Yes ☐ No

Peer-reviewer statements	Peer-Review: [☐] Anonymous [☒] Onymous Conflicts-of-Interest: [☐] Yes [☒] No
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SPECIFIC COMMENTS TO AUTHORS

20 February 2022 Review report on the manuscript titled “Corticosteroid-induced bradycardia and T-wave abnormalities in a patient with multiple sclerosis and HNF4 α mutation: A case report” by Sohn SY et al, submitted to World Journal of Clinical Cases Manuscript ID: 71645 Dear Authors, Sohn SY and colleagues in the present case report, entitled “Corticosteroid-induced bradycardia and T-wave abnormalities in a patient with multiple sclerosis and HNF4 α 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. 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. 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. 2. History of past illness: The section is too short. If there is nothing else describe, please state so. 3. Physical examination: This is section needs to expand including negative findings of relevant examinations. 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>. 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. 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. I believe that this manuscript might carry important value presenting the potential complication under the treatment of MS in patients with comorbidity. I hope that, after these careful revisions, the manuscript can meet the Journal's high standards for publication. Thus, I reconsider this manuscript

after major revision and I am available for a new round of revision of this article. I
declare no conflict of interest regarding this manuscript. Best regards, Reviewer

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Clinical Cases*

Manuscript NO: 71645

Title: Corticosteroid-induced bradycardia in MS and MODY due to HNF4A mutation: A case report

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05688164

Position: Peer Reviewer

Academic degree: BSc, MD, PhD

Professional title: Research Fellow

Reviewer's Country/Territory: Hungary

Author's Country/Territory: South Korea

Manuscript submission date: 2021-09-24

Reviewer chosen by: Yun-Xiaojian Wu

Reviewer accepted review: 2022-04-12 13:51

Reviewer performed review: 2022-04-12 14:17

Review time: 1 Hour

Scientific quality	☐ Grade A: Excellent ☒ Grade B: Very good ☐ Grade C: Good ☐ Grade D: Fair ☐ Grade E: Do not publish
Language quality	☐ Grade A: Priority publishing ☒ Grade B: Minor language polishing ☐ Grade C: A great deal of language polishing ☐ Grade D: Rejection
Conclusion	☐ Accept (High priority) ☒ Accept (General priority) ☐ Minor revision ☐ Major revision ☐ Rejection
Peer-reviewer	Peer-Review: ☒ Anonymous ☐ Onymous

statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

12 April 2022 2nd Round review report on the manuscript titled "Corticosteroid-induced bradycardia and T-wave abnormalities in a patient with multiple sclerosis and HNF4 α mutation: A case report" by Sohn SY et al, submitted to World Journal of Clinical Cases Manuscript ID: 71645 Dear Authors, The authors did an excellent work clarifying the questions I have raised in the previous round of review. Currently, this paper is a well-written, timely piece of research and provides a useful study addressing an interesting and innovative question, presenting an important case that highlighted need for special clinical attention to the occurrence of bradycardia and T-wave abnormalities under corticosteroid treatment for multiple sclerosis patients, especially comorbid with diabetes and with predisposing factors such as genetic mutation. Overall, this is a timely and needed work, thus I believe that manuscript now meets the Journal's standards for publication. I am always available for other reviews of such interesting and important articles. I look forward to seeing further study on this issue by these authors in the future. Thank you for your work. I declare no conflict of interest regarding this manuscript. Best regards, Reviewer