Author’s response to reviews

Title: Long-term follow-up in a Chinese child with congenital lipoid adrenal hyperplasia due to a StAR gene mutation

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Version: 2 Date: 04 Oct 2018

Author’s response to reviews:

Dear Editor:

Thank you for your kind letter titled “Your submission to BMC Endocrine Disorders - BEND-D-18-00178R1” on September 11, 2018. We revised the manuscript in accordance with the reviewers’ comments and carefully proof-read the manuscript to minimize typographical, grammatical, and bibliographical errors.

We describe our revisions according to the reviewers’ comments below.

Part A (Reviewer 1)

1. The reviewer’s comment: The case report is interesting, but in my opinion it is too long.

For example:
Considering that CLAH is a well known disease and the reported clinical scenario is absolutely typical, table 1 describing laboratory data is not so useful. Moreover, lots of data are lacking and the table looks almost empty.

The description of the growth pattern is too long and not so useful. We may suppose that the reported growth deceleration was not a typical clinical feature directly related to CLAH, but it was the result of the long-lasting poor hormonal balance.

The fact that adrenal glands were found very small at CT scan should be discussed with more details. At what age did the child undergo adrenal CT scan? How long after the start of steroid therapy? Steroid therapy could have contributed to the decrease of adrenal gland size.

Page 4, line 91 There is probably a mistake. Hypokalemia should be replaced with hyperkalemia.

The authors’ answer: Thank you very much for the thoughtful advice, which greatly benefited the revision of this manuscript. We have shortened our manuscript according to the reviewer’s suggestions. We have amended some details about the adrenal glands on CT scans in Case presentation, page 5, lines 99-102. We have replaced hypokalemia with hyperkalemia in Case presentation, page 3, line 67. We have simplified the description of the growth pattern of CLAH in Case presentation, page 6, lines 117-120. Table 1 looks almost empty as you indicated. The second reviewer suggested that we add some details about treatments in Table 1. Therefore, we have simplified and amended some details in Table 1. If you decide that Table 1 is unnecessary after reading the revision, we will delete Table 1 immediately. Again, we would like to express our deep appreciation for your thoughtful advice regarding the paper.

Part B (Reviewer 2)

1. The reviewer’s comment: Page 2, 45th line, and page 3, 48th line, should the "OMIN" be a mistake? OMIM is well known, but not "OMIN".

The authors’ answer: Thank you for your careful review. I apologize for my carelessness. We have corrected the mistake regarding "OMIM" in Background, page 2, line 45, and page 3, line 49.

2. The reviewer’s comment: Page 3, 51th line, there is a sentence said "but there are only 17 confirmed cases of CLAH in Chinese patients". We believe it should be presented as published or reported cases, not confirmed cases since some cases didn't get published. Please be careful for the described words you used.

The authors’ answer: Thank you for the helpful advice. Only 17 Chinese cases of CLAH have been published. We have amended the paper in Background, page 3, line 52.
3. The reviewer’s comment: Page 3, 53-54th line, there is a sentence "All affected individuals are phenotypically female regardless of their gonadal sex [1]." Same to the above opinion, the author should be careful for the descriptions. As classic CLAH, the phenotype must be female whatever the sex chromosome is. But for non-classic CLAH, the phenotype may have variations. Pls modify this sentence properly.

The authors’ answer: Thank you for the advice regarding the imprecisely written sentence. We have amended the sentence according your advice in Background, page 3, lines 54-55.

4. The reviewer’s comment: Page 3 64-66th line, the sentence "However, her compliance was poor, and she was not followed up regularly. There were several episodes of adrenal crisis before 13 years of age. No adverse events were recorded". Pls give detailed information about whether poor compliance is also indicated poor treatment compliance.

The authors’ answer: Thank you for the advice. The patient did not take her medications according the doctor’s advice. She often took medication only 1 time per day or 3-7 days per week. She also did not visit the doctor regularly and had no suitable tests to assess treatment effects. Therefore, her compliance is discussed in Case presentation, page 4, lines 73-76.

5. The reviewer’s comment: Page 3 68th line, The sentence "The patient was alert", What does alert mean? Pls give detailed information or modify the description properly.

The authors’ answer: Thank you for this advice. To shorten the manuscript, we deleted the sentence in Case presentation.

6. The reviewer’s comment: Page 3 68th line, The sentence "her height, weight and body mass index (BMI) were 148.7 m (-1.3 SDS), 35.3 kg (-1.5 SDS) and 15.96 kg/m2 ". Pls correct the height, the meter is not the correct unit.

The authors’ Answer: Thank you for your advice regarding the unit for height, which we described incorrectly. We corrected the mistake in Case presentation, page 4, line 80.

7. The reviewer’s comment: Page 3 71th line, the sentence "Normal external female genitalia were observed with a normal clitoris and vaginal orifice." Pls delete the word "normal" since the patient is a 46 XY DSD.

The authors’ answer: Thank you for your advice regarding this imprecisely written sentence. We deleted the word "normal" and have amended the sentences in Case presentation, page 4, lines 82-84.
8. The reviewer’s comment: In addition to the correction of the above opinion. In this paper the clinical manifestation, physical examination were listed separately. This kind of description was a bit messy. Pls give the information chronologically. The important lab value also should be given in the context in addition to the tables of lab data.

The authors’ answer: Thank you for your advice. We have amended the descriptions of the clinical manifestations and physical examination according the reviewer’s advice in Case presentation, page 3, line 66 to page 5, line 104.

9. The reviewer’s comment: The condition of birth was recommended to list before the medical history chronologically.

The authors’ answer: Thank you for the advice. We have amended the condition of birth before the medical history chronologically in Case presentation, page 3, lines 63-64.

10. The reviewer’s comment: Although the gene sequencing were done in the patient and her father, it should also be done to her two sisters to confirm whether there is carrier.

The authors’ answer: Thank you for the advice. We had suggested that her two sisters be tested for the StAR gene to confirm whether either sibling is a carrier. Unfortunately, however, her father and sisters refused a gene analysis. Therefore, we cannot assess her sisters’ StAR gene sequences. We have discribed the situation in Gene analysis, page 7, line 46.

11. The reviewer’s comment: The significant point is a small adrenal for the patients. But the discussion about that is very limited in the paper. Could the author search some literatures to figure out whether there is reasonable speculation.

The authors’ answer: Thank you for your advice. In CLAHs due to mutation of the StAR gene, small adrenal glands represent a rare clinical manifestation, and we searched the literature to find the reason for this. Only one paper reported a small adrenal gland in one CLAH patient with a StAR gene mutation without reasonable speculation. Reported cases of StAR gene mutations of Q77X or Q258X indicated that the adrenal glands were normal in size or enlarged. We have read many studies but have not found any reasonable speculation regarding this manifestation. We have discribed the situation in Discussion, page 10, lines 208-212.

12. The reviewer’s comment: Pls add the treatment details in the table 1.

The authors’ answer: Thank you for the advice. We have amended the treatment details in Table 1.
13. The reviewer’s comment: Since the cases of CLAH usually has hypogonadism, the bone age was behind the actual age for most of the cases. But this patient has the age matched bone age. Could the author give some pictures to show the bone age?

The authors’ answer: Thank you for your advice. We added pictures related to bone age in the paper as Figure 2. The pictures taken at another hospital at the ages of five and fifteen years were not available because of improper preservation by the patient’s father.

We sincerely appreciate the reviewers’ comments and suggestions, which have been valuable for improving the quality of our manuscript. All the line and page numbers indicated above refer to the revised manuscript.

Thank you and all the reviewers for the thoughtful advice.

Sincerely yours,

Xiu Zhao