Author’s response to reviews

Title: Clinical, Neuroimaging, Biochemical, and Genetic Features in Six Chinese Patients with Adrenomyeloneuropathy

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Author’s response to reviews:

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Clinical, Neuroimaging, Biochemical, and Genetic Features in Cases of Chinese Patients with Adrenomyeloneuropathy” (ID: NURL-D-18-00841R2). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied the comments carefully and have now seriously made the corrections in the revised version. We highlight the changes in the revision by using blue-colored text. Lastly, we are sorry for a delay in the submission of the revision due to the predefined academic schedule. The main corrections in the paper and the response to the reviewer’s comments are as follows:

Responds to the editor’s comments:

Q1: Reviewer 2 has commented that the manuscript would be more suitable as a case report. However, as this is a case series, please keep the manuscript as a research article and ensure it meets our guidelines for a research article. In addition, please revise the title to make it clear that this is a case series of 6 individuals.
Response 1: The manuscript meets the guidelines for a research article, and following the Editor’s suggestion, we have now modified the title to “Clinical, Neuroimaging, Biochemical, and Genetic Features in Six Chinese Patients with Adrenomyeloneuropathy” as it shown in Line 1-2.

Q2: In figure 2, please increase the size of the black box to cover more of the participant’s face.

Response 2: Thanks for your advice, we have modified the figure 2 as shown in FIG2.

Q3: In the section “Ethics approval and consent to participate” in the Declarations, please give the reference numbers for the ethical approval.

Response 3: The reference numbers for the ethical approval (S2016-021-01) has been added, see Line 290.

Q4: I am afraid the quality of the English used throughout your manuscript does not currently meet our requirements. We recommend that you ask a native English speaking colleague to help you copyedit the paper. If this is not possible, you may need to use a professional language editing service. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication.

Response 4: Thanks a lot for your kind suggestion, we have invited a professional English institute (American Journal Experts, AJE) to help us to polish the full text from format, spelling and grammar. We highlights all the changes by using blue-colored text.

Responds to the reviewer’s comments:

Reviewer #1:

Q1: The AMN patients have been reported in several articles from Chinese origin, for example Neurodegener Dis. 2018;18(2-3):156-164. The authors should modify the description in the revision.

Response 1: We are very sorry for our imprecision of description in the section of Conclusions. We have modified the first sentence to “In conclusion, this study aimed at illuminating basic features from the clinical, neuroimaging, biochemical, and genetic aspects of some Chinese AMN patients.” see Line 250-251.

Q2: Peripheral neuropathy was frequently accompanied with AMN, what about in these patients? Please give detailed data about NCV.
Response 2: Thanks for the reviewer’s constructive suggestions. The detailed data about NCV can be obtained from the attached document: “S1.” According to Reviewer 2’s suggestions, we didn’t take this part into the body.

Q3. In the discussion section, there is a lack of further analysis of gene mutations, especially for de novo mutation. In these cohort, how to reflect the irrelevance of genotype and phenotype.

Response 3: Thanks for the reviewer’s constructive suggestions. According to your advice, we have analyzed the de novo mutation further (see Line 242-247). In our cohort, although they each had the same genotype, the various clinical manifestations of patients 1, 2, 4, and 5 were consistent with the AMN phenotype, which is inconsistent with previously reported results (see Line 196-199). This means that there is absence of a genotype–phenotype correlation.

Q4. The language need copy-edit by native speaker.

Response 4: Considering the Editor’s suggestion, we have invited a professional English institute (American Journal Experts, AJE) to help us polish the full text from format, spelling and grammar. We marked all the changes on language problems with blue in the revision.

Reviewer #2:

Li et al report 6 adult X-ALD patients with the phenotypes of Addison’s disease, AMN and progression to cerebral X-ALD in adulthood. They genotyped 5 of those patients and reported biochemical and neuroimaging results. They also identified a novel variant in one of the patients.

This study is a small case series reporting 6 X-ALD patients with adult presentations. The information that the authors have reported, has been known for many years. The study did not report anything new. There are some grammar errors that makes difficult to understand what the authors report.

There are following questions, which should be answered:

Q1. Manuscript is too long for the dataset. There are too many details for routine investigations such as MRI, NCV, electrophysiology.

Response 1: Thanks for the reviewer’s suggestion. Actually, the manuscript is a clinical retrospective study. So far, there are still lack of detailed reports on clinical aspects of AMN patients in China. Thus, we think it is necessary to describe these related information about MRI, NCV, electrophysiology.

Q2. The message of the manuscript is not clearly written what the study team trying to give.
Response 2: We appreciate the reviewer’s suggestion a lot. As we have responded to Q1, we try to depict the clinical, neuroimaging, biochemical, and genetic features of Chinese AMN patients based on our real cases, which showed some different features compared to previous findings. Firstly, we identified a novel frameshift mutation of ABCD1 gene in a Chinese AMN patient, which could enrich the ALD database. Secondly, in our cohort, patient 5 only manifest as myeloneuropathy with adrenal involvement sparing. This means that when encounter with patients manifest like spastic paraplegia, we shouldn’t ignore the screening of VLCFA. Finally, we think that emotional trauma (such as divorce) is an important factor that may induce or aggravate the formation of intracranial lesions in AMN patients by clinical observation, which was not reported before (see Line 215-220 in the revision).

Q3. This manuscript is more suitable in the format of Case Report, instead of a Research Article.

Response 3: Thanks for the reviewer’s suggestion. As we totally collected 6 patients of AMN during last 6 years. This paper should be more suitable in the format of a case series. But following to the editor’s suggestions, we would still keep the manuscript as a research article and ensure that it meets the guidelines for a research article.

Q4. It is not clear, if the study team had all those AMN/X-ALD patients and reviewed their charts retrospectively, or enrolled cases to investigate for X-ALD/AMN.

Response 4: Thanks for the reviewer’s question. We enrolled all patients cured at Chinese PLA General Hospital who meet the inclusion criteria below from August 2012 to January 2018: (a) adult onset with spastic paraparesis, (b) cases with mutations of the ABCD1 gene or/and increased plasma levels of VLCFA, particularly the proportions of C24:0/C22:0 and C26:0/C22:0 (See the chapter “Methods”, Line 92-98 in the revision), and their charts retrospectively.

Q5. Why do investigator say that AMN is the most common adult form of X-ALD, if the majority of the patients have Addison disease in their cohort?

Response 5: We are grateful for the reviewer’s question. Firstly, according to the report by Engelen et al., there were 60-66% patients belong to phenotype of AMN in all X-ALD patients1 (see Table1 in his article). Secondly, on the basis of our own data, there were four patients with childhood cerebral ALD, one patient with adolescent cerebral ALD, two patients with adult cerebral ALD, six patients with AMN and one woman with X-ALD. In our cohort, there were five patients with Addison disease in all six patients (see table 1). This indicated that AMN is the most common adult form of X-ALD.

Q6. Study team reports 6 patients, but genetic test results of 5 patients. What is the information for genetic test result for the patient 3?

Response 6: We appreciate the reviewer’s suggestion a lot. As we have responded to Q1, we try to depict the clinical, neuroimaging, biochemical, and genetic features of Chinese AMN patients based on our real cases, which showed some different features compared to previous findings. Firstly, we identified a novel frameshift mutation of ABCD1 gene in a Chinese AMN patient, which could enrich the ALD database. Secondly, in our cohort, patient 5 only manifest as myeloneuropathy with adrenal involvement sparing. This means that when encounter with patients manifest like spastic paraplegia, we shouldn’t ignore the screening of VLCFA. Finally, we think that emotional trauma (such as divorce) is an important factor that may induce or aggravate the formation of intracranial lesions in AMN patients by clinical observation, which was not reported before (see Line 215-220 in the revision).
Response 6: We are sorry about the negligence of noting this important information on Patient 3. In fact, patient 3 refused to perform genetic test for economic reasons. So we didn’t have the genetic test results of patient 3 (see Line 118-119 in the revision).

Q7. What are the targeted and specific treatment options for AMN patients that the diagnosis will change the outcome of the disease?

Response 7: Thanks for the reviewer’s question. Firstly, steroid replacement therapy should be given when patients have Addison’s disease. Secondly, Lorenzo’s oil is a dietary therapy based on oral administration of oleic acid (C18:1) and erucic acid (C22:1), both in triglyceride form, that normalizes plasma C26:0 levels within 1 month in most patients with ALD. Actually, patient 1 received the therapeutic regimen with oral Lorenzo’s oil, his condition was still aggravated. Thirdly, haematopoietic stem cell transplantation (HSCT) remains the only therapeutic intervention for cerebral ALD. In our cohort, patient 1 received HSCT treatment in March of 2019. We are following up on his condition. Finally, genetic counseling was offered to the parents of AMN and their family to detect: 1) carriers who can be offered prenatal diagnosis, and 2) asymptomatic or presymptomatic men or women who can benefit from therapeutic interventions. Regular follow-up in presymptomatic males can prevent serious morbidity and mortality.

Q8. For the patient 6 with cerebral form of the disease, how did study group manage this patient? How quick was the disease progression? Did they look into bone marrow transplantation option for the cerebral form of the disease?

Response 8: Thanks for the reviewer’s question. First of all, we gave the patient steriod replacement therapy, because of educational and economic reasons, the patient didn’t have a regular steroid replacement therapy. Due to the Loes score of patient 6 was 20 (a score >9), the outcome of HSCT would be poor based on the results performed in previous cases of cerebral ALD.2,3 Thus, we didn’t recommend the patient to receive HSCT treatment. During the last telephone follow-up in June of 2019, the patient's family informed us that the patient was unable to take care of himself totally and even didn’t recognize his family.

Q9. What was the Loes score of patient 6?

Response 9: Thanks for the reviewer’s question. According to the formula by Loes et al 4,5, the Loes score of patient 6 was 20.

Q10. What do authors try to say with the following? "It is noteworthy that the psychiatric symptoms of patient 6 were significantly aggravated after divorce." Do they think that psychiatric problems are the result of the divorce, not the other way around?

Response 10: Thanks for the reviewer’s question. Because the patient’s mental state was normal before divorce. However, about half a year later after the divorce, the patient’s mental state,
walking ability and verbal ability showed significant deterioration (see Line 215-216 in the revision). Due to irregular clinical management, we didn't get the data of brain MRI changes of the patient before and after divorce. But this is a very interesting clinical phenomenon, we think the divorce may trigger or aggravate the development of intracranial lesions.

Q11. Was is reported in the literature that stress can initiate cerebral disease? The references are related to head trauma and does not support what the authors wrote in the following sentence: "This suggested that the development of cerebral AMN might be triggered or aggravated by environmental factors (i.e., trauma, mental stimulation, etc)27-29.

Response 11: Thanks for the reviewer’s constructive suggestion. Up to now, there are no reports about that stress can initiate cerebral disease. I am sorry for our imprecise expression. According to previous reports, head trauma may be a possible environmental trigger6,7, but other modifiers (both genetic and environmental) have not yet been identified. We think that mental stimulation (such as divorce) may be an environmental factor, which initiates or aggravates cerebral disease (see Line 216-220 in the revision).

Q12. The following sentence should be re-written, as the neurologist would not neglect the results, rather would not have sufficient knowledge to interpret the result: "Nevertheless, it’s likely that this percentage were underestimated, which may be attributed to part of neurologists who tend to neglect the diagnostic tests on AMN as adrenal function is normal24."

Response 12: Thanks for the reviewer’s constructive suggestion. We have modified the sentence to “Nevertheless, it’s likely that this percentage were underestimated, which may be attributed to part of neurologists who are still lack of sufficient data to interpret the result as adrenal function is normal.” as it shown in Line 209-211 in the revision.

Q13. Five patients with skin pigmentation in childhood, were they treated or investigated for adrenal insufficiency? If not did they have any symptoms?

Response 13: Thanks for the reviewer’s suggestion. Five patients were all investigated for adrenal insufficiency (see Line 103-105 in the revision). Patient 1 and patient 3 had received hydrocortisone therapy regularly, the other three patients didn’t have a regular steroid replacement therapy (see Line 139-140 in the revision). Other symptoms include fatigue, dizziness and so on (we did not mentioned these in the manuscript).

Q14. Please summarize clinical characteristics of patients in table 1 which are listed in results under the subheading of “Clinical Characteristics”. This will remove the duplicate information and shorten the manuscript.

Response 14: According to the reviewer’s suggestion. We have summarized some critical clinical characteristics of patients in table 1. After a summary and integration, we added one
index in it (see table 1 in the revision) and remove the duplicate information under the subheading of “Clinical Characteristics” (see Line 122-124, 131-132, 145-147).

Q15. Please add the reference ranges for VLCFA in the table 2, first row in brackets instead of having those underneath of the table.

Response 15: Thanks for the reviewer’s constructive suggestion. We have modified it following the reviewer’s suggestions (see table 2).

Q16. There are grammar and language issues that should be corrected. Some of those are listed below:

a. Please read through the manuscript to correct some language issues.

b. Change "cured" to "followed"

c. Change "conditions" to "inclusion criteria"

d. Change "strangely" to "interestingly"

e. Change "speculate" to "think"

Response 16: Thanks for the reviewer’s constructive suggestions. We have invited a professional English institute (American Journal Experts, AJE) to help us polish the full text from format, spelling and grammar. We marked all the changes on language problems with blue in the revision.

We have tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in blue in revised paper.

We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.


