Author’s response to reviews

Title: Antibody-LGI 1 autoimmune encephalitis manifesting as rapidly progressive dementia and hyponatremia: a case report and literature review

Authors:
Xuanting Li (lxtlingone@163.com)
Junliang Yuan (yuan_doctor@163.com)
Lei Liu (pathologyliu@163.com)
Wenli Hu (huwenli@sina.com)

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Author’s response to reviews:

(Please find the Answering Reviewers letter for more details, uploaded as supplementary material)

Response to reviewers

Dear Editors,

Thank you very much for your letter, and the comments. According to the editor and reviewers’ comments and requests, we have made extensive modification based on our original manuscript. All corrections and supplementary materials are labeled in pink for the editor, green for the Reviewer #1, blue for the Reviewer #2 in this letter. Our detailed point-by-point responses to the concerns are as follows.

Response to reviewers

Editor comments

Many thanks for the comments and suggestion from the editor. All corrections and supplementary materials are labeled in pink for the editor in our revised version of manuscript.

Comment 1

Technical Comments: Please provide Declarations header and note that III manuscripts must contain the following sections under the heading 'Declarations':
Ethics approval and consent to participate

Consent for publication

Availability of data and material

Competing interests

Funding

Authors' contributions

Acknowledgements

Authors' information (optional).

[Reply] Many thanks for this comment. We have read the requirements of the journal style carefully, and ensured that our revised manuscript conformed to the journal requirements.

Comment 2

Clinically the cognitive decline is most important but not well described in the manuscript. Were other cognitive tests apart from the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) done? If not, I recommend a better clinical description of the syndrome.

[Reply] Many thanks for this suggestion. According to the prior studies about the LGI1-AE1-3, the MMSE and MoCA were the most common scales to assess the cognitive decline, however, we did not perform the other cognitive tests. As for the MMSE, due to the orientation (-5), attention and calculation (-3), recall (-2), write a sentence (-1), the final score of MMSE was 19. As for MOCA, visuospatial/executive function (-3), calculation (-1), language (-1), abstraction (-1), memory (-5), orientation (-4), the final score of MOCA was 15.

Comment 3

Please remove “significant” when significance was not shown by a statistical test.

[Reply] We fully accept this criticism and have removed “significant” and correct the expression, showing as “After the combined treatment of intravenous immunoglobulin and glucocorticoid, the patient’s clinical symptoms improved obviously” in the Abstract section on page 2, line 15-17, “Fifteen days after his admission, he recovered obviously and discharged from our department with mild memory impairment. During 30 days’ follow-up, his symptoms were in
complete remission with immunomodulation” in the Case Presentation section on page 7, line 13-16, and “Secondly, our case presented with obvious significantly memory impairment, after the immunomodulation, the cognitive disorders fully recovered” on page 10, line 1, 2.

Comment 4

Please add in the discussion that the clinical remission upon methylprednisolone and IVIG does not prove therapeutic efficacy of these drugs, however, untreated cases often do not improve (relevant literature might be cited).

[Reply] We accept this comment and advice. We have added this information in the Discussion and Conclusions section (page 8, line 1-3), showing as “The treatment with high-dose steroids, IVIG and/or plasma exchange was considered to be first-line therapy, however, the clinical remission upon methylprednisolone and IVIG does not prove therapeutic efficacy of these drugs4”.

Reviewer #1

Many thanks for this reviewer’s comments. All corrections and supplementary materials are labeled in green for the Reviewer #1 in our new version of manuscript.

Comment 1

The authors describe a rather typical case of LGI1 encephalitis with predominant memory impairment. As autoantibody-associated diseases are increasingly appreciated differential diagnoses in dementia, the case illustrates the need for consideration of autoimmunity in diseases of memory and cognition and therefore adds to the literature.

[Reply] Many thanks for the positive appraisal.

Comment 2

Abstract: "the clinical symptoms improved significantly" --> which statistical test?

[Reply] We fully accept this reviewer’s criticism. For the significance was not shown by a statistical test, we have removed “significant” and correct the expression, showing as “After the combined treatment of intravenous immunoglobulin and glucocorticoid, the patient’s clinical symptoms improved obviously” in the Abstract section on page 2, line 15-17, and “Fifteen days after his admission, he recovered obviously and discharged from our department with mild
memory impairment. During 30 days’ follow-up, his symptoms were in complete remission with immunomodulation” in the Case Presentation section on page 7, line 13-16, and “Secondly, our case presented with obvious significantly memory impairment, after the immunomodulation, the cognitive disorders fully recovered” on page 10, line 1, 2.

Comment 3

Abstract: all the imaging data (5 figures!) are not mentioned in the abstract.

[Reply] Many thanks for the reviewer’s criticism. According to the reviewer’s good advice, we have rewritten the Case presentation section of Abstract, showing as “Herein, we reported a male patient presenting as rapidly progressive dementia and hyponatremia. He had antibodies targeting LGI1 both in the cerebrospinal fluid and serum, which demonstrated the diagnosis of typical anti-LGI1 AE. The scores of Mini-Mental State Examination and Montreal Cognitive Assessment were 19/30 and 15/30, respectively. Cranial magnetic resonance images indicated hyperintensities in bilateral hippocampus. The findings of brain arterial spin labeling and Fluorine-18-fluorodeoxyglucose positron emission tomography showed no abnormal perfusion/metabolism. After the combined treatment of intravenous immunoglobulin and glucocorticoid, the patient’s clinical symptoms improved obviously.” on page 2, line 8-17.

Comment 4

Abstract: "case also illustrates that this excellently treatable condition" --> often less well treatable, almost all patients develop atrophy.

[Reply] Many thanks for the reviewer’s criticism. As we know, some prior studies have suggested the majority of LGI1-Ab AE patients had a better prognosis after immunomodulator treatment4-7. However, according to some other studies, poor clinical outcome following LGII encephalitis was associated with global brain atrophy and disintegration of white matter tracts8. We have changed to this description in the Abstract section as follows: “The better recognition will be great importance for the early diagnosis, essential treatment, even a better prognosis” on page 3, line 4-5.

Comment 5

Abstract: "can be easily misdiagnosed in face of dementia or cognitive decline" --> I suggest changing to "can be easily misdiagnosed as neurodegenerative dementia or cognitive decline".
[Reply] Many thanks for the reviewer’s good advice. Taking into consideration Comment 4 and 5, we have changed the description as follows: “The better recognition will be great importance for the early diagnosis, essential treatment, even a better prognosis” on page 3, line 4, 5.

Comment 6
Case Presentation: "short-term memory" --> rather anterograde amnesia?

[Reply] We fully accept this comment. We have changed it as follows: “A 56-year-old man presented with fever for three weeks and memory decline for two weeks, especially deficits in anterograde amnesia” in Case Presentation section on page 5, line 9, 10.

Comment 6
Case Presentation: "other biomarkers of AE" --> which are the other biomarkers of AE?

[Reply] We accept the reviewer’s criticism and good advice. We have added the other biomarkers of AE, tumor markers, and paraneoplastic neuronal antibodies, showing as “however, the other biomarkers of AE (NMDAR-Ab, AMPAR2-Ab, GABABR-Ab, Caspr2-Ab), tumor markers (CEA, AFP, CA125, CA19-9, CA15-3, CA724, SCCAg, NSE, T-PSA, CYFRA21-1) and paraneoplastic neuronal antibodies (anti-Hu, -Ri, -Yo, -Ma/Ta, -Amphiphysin, -CV2, -SOX1, -Tr) were all unremarkable” on page 5, line 21, 22 and page 6, line 1, 2.

Comment 8
Discussion: "ASL is noninvasive, and it is a useful tool to early diagnose anti-LGI1 AE" --> I am not aware of any proof that ASL is accepted to be useful for the early diagnosis of LGI1 encephalitis.

[Reply] We accept the reviewer’s criticism. This description was changed to this: “Different from invasive 18F-FDG PET, ASL is a noninvasive tool with high sensitivity to changes in regional CBF” in Discussion and Conclusions section on page 9, line 11-13.

Comment 9
Figures: One could potentially panel all (reduced number of) images into one figure.
[Reply] We fully accept the reviewer’s great advice. The Figure 1 was cancelled and the Figure 2 and 3 were combined together as new Figure 1.

Comment 10

Figures: Fig. 1: this is a routine assay, no figure is needed to visualize. If figure preferred, than comparison to untransfected HEK cells needed.

[Reply] We fully accept the reviewer’s great advice. The Figure 1 was cancelled.

Comment 11

Figures: Fig. 2: one or two figures are more than enough to show MRI changes.

[Reply] We fully accept the reviewer’s great advice. We have combined the previous Figure 2 and Figure 3 together as new Figure 1.

Figure 1. Cranial magnetic resonance images (MRI) of this patient. T2-weighted fluid-attenuated inversion recovery (a) and the corresponding plane in diffusion weighted imaging (b) sequences showed hyperintensities of bilateral hippocampus. Repeated MRI showed some abnormal hyperintensities particularly in the left hippocampus 12 days after the initial MRI scan (c, d).

Comment 12

Figures: Fig. 3: in contrast to the figure legend, the FLAIR image shows persistent hyperintensities, in particular in the left hippocampus (which is also what one would expect after 12 days).

[Reply] We fully accept this criticism. The legend was changed as follows: “Repeated MRI showed some abnormal hyperintensities particularly in the left hippocampus 12 days after the initial MRI scan (c, d)” as the legend of new Figure 1.

Comment 13

Figures: Fig. 4: you would not expect a tumor in the brain, reduce number of PET images.
[Reply] We fully accept this criticism. The legend of Figure 4 was changed as follows: “Fluorine-18-fluorodeoxyglucose positron emission tomography showed no abnormal metabolism in the brain”.

Figure 4. Fluorine-18-fluorodeoxyglucose positron emission tomography showed no abnormal metabolism in the brain.

Comment 14

Discussion: Fig. 4: looks like striatum hypermetabolism which is common in LGI1 encephalitis, please comment (hard to judge from the small low-resolution images).

[Reply] Thanks for the reviewer’s advice. Indeed, striatum hypermetabolism is common in LGI1 encephalitis9. However, according to our PET data, we did not find this phenomenon of striatum hypermetabolism.

Reviewer #2:

Many thanks for this reviewer’s comments. All corrections and supplementary materials are labeled in blue for the Reviewer #2 in our new version of manuscript.

Comment 1

The manuscript is well-written and covers a relevant subject. It extends (so far very low) information in the literature on Antibody-LTI 1 autoimmune encephalitis manifesting as rapidly progressive dementia and hyponatremia. The case is well-presented both concerning the content and the length of the article. The conclusions which the authors draw are in a modest tone and avoid generalization and too much speculation. Overall, the case is worth to be published in BMC Neurology.

[Reply] Many thanks for the positive appraisal.
Comment 2

As a (minor) suggestion, the authors might slightly tone down some of their conclusions regarding the ASL technique and better imply that more cases are needed to validate them better.

[Reply] Thanks for the criticism, and we fully accepted this advice. We have done as required in the Discussion and Conclusions section of our revised manuscript as follows: “Further prospective studies with larger sample sizes will be needed to utilize ASL to validate such findings” on page 10, line 13, 14. And we have changed the description about the ASL technique to this: “Different from invasive 18F-FDG PET, ASL is a noninvasive tool with high sensitivity to changes in regional CBF” in Discussion and Conclusions section on page 9, line 11-13.

We have revised the manuscript in line with all the editor and reviewers’ comments and we hope that the new manuscript can be acceptable for publication. If you have any questions, please feel free to contact us.

Many thanks for your processing on our work.

Best regards,

Xuanting Li

References


