Author's response to reviews

**Title:** Anti-N-methyl-D-aspartate receptor encephalitis with serum anti-thyroid antibodies and IgM antibodies against Epstein-Barr virus viral capsid antigen: a case report and one year follow-up

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**Author's response to reviews:** see over
Dear Editor-in-Chief,

Thank you very much for your latest letter regarding our manuscript entitled

“Anti-N-Methyl-D- aspartate receptor encephalitis with serum anti-thyroid antibodies and IgM antibodies against Epstein-Barr virus viral capsid antigen: a case report and one year follow-up”. We have revised the manuscript according to the comments and suggestions of all three reviewers and highlighted the changes with pink color in the manuscript, while the changes made during first revision are still in blue. Besides, we responded point by point to the comments as listed below. We have also asked another native-English speaker with professional background to edit our manuscript completely. We hope this revised version is acceptable for publication in your journal.

If you have any questions, please don’t hesitate to contact me as soon as possible.

Looking forward to hearing from you soon.

Best wishes!

Yours sincerely,

Lei Liu MD
Report of Reviewer 1:

Major Compulsory Revisions:
The authors have satisfactorily addressed the issues raised in the initial review.

Minor Essential Revisions:
The authors have satisfactorily addressed the issues raised in the initial review.
The manuscript still requires minor editing for clarity of written English prior to publication.

Discretionary Revisions:
The authors have satisfactorily addressed the issues raised in the initial review.
Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published.

Response: Thank you for understanding the merit of this paper and the efforts we have made in the revision. This time we have asked another native-English speaker with professional background to edit our manuscript.
Report of Reviewer 2:

Major Compulsory Revisions:

1. The authors explain that no epileptiform activity was recorded during the course of illness. Would it be more prudent to replace the term "seizures" (implying epileptic seizures) by "paroxysmal events"? See reference of case-report of anti-NMDAR encephalitis where no epileptiform seizures could be found despite "bursts of agitation". Dev Med Child Neurol. 2011 Aug; 53(8):764-7. doi:10.1111/j.1469-8749.2011.03956.x. Epub 2011 May 19. Paroxysmal EEG pattern in a child with N-methyl-D-aspartate receptor antibody encephalitis. Gataullina S, Plouin P, Vincent A, Scalais E, Nuttin C, Dulac O.

Response: We have followed your precious construction to replace the term "seizures" by "oral-facial dyskinesias and extremities convulsions "or "paroxysmal events" (Case, para 3, line 11; Case para 4, line 2).

2. The authors attribute mild improvement to intravenous immunoglobulin therapy and IV steroids (although she got intubated during that time), and major improvement due to surgery and resection of teratoma. In the conclusion, it is stated that "we proved that aggressive ...may be essential factors enabling prompt and full recovery…”

It may be more prudent to state that the authors believe that these therapies helped, but that more evidence is needed from other cases and controlled studies. If the authors believe that that it is not possible that factors related to the surgery (use of anesthetic, benzodiazepine, induction of sleep) may account for the improvement, they should state that. The evidence of effectiveness of IVIG and IV steroids does not seem not very convincing.

Response: Discussion, para 6, line 10-12: Although many experts recommended IVIG and IV steroids for anti-NMDAR encephalitis [1, 2], these are still lack of controlled studies to evaluate the effectiveness of above mentioned first line immunotherapies. And we call for such further studies in our latest manuscript.


In our humble opinion, factors related to the surgery including anesthetics or induction of sleep may not be responsible for patient’s clinical improvements, for propofol and midazolam administered during endotracheal intubation hadn’t change the course of her illness (Discussion, para 6, line 12-15).

3. The authors believe it is too far-fetched to give their opinion on the type of future studies that are needed to elucidate the pathophysiology and optimal treatment for such cases. On the contrary, I would welcome recommendations for such future studies and this case-report provides such an opportunity.

Response: Controlled studies are expected to compare the concomitant infectious or inflammatory status of patients with and without prodromal flu-like symptoms and may shed new light on the pathophysiology of anti-NMDAR encephalitis (Discussion, para 4, line 19-21).

We also call for controlled studies and more cases to prove the effectiveness of first line immunotherapies, such as IV immunoglobulin and IV steroids in anti-NMDAR encephalitis in our latest manuscript (Discussion, para 6, line 10-12).

4. Although the report focuses on medical factors and etiologies, the psychiatric presentation is compatible with acute psychosis and in particular with acute catatonia given the motor and autonomic symptoms (for discussion see: Am J Psychiatry. 2011 Jul; 168(7):749-50; author reply 750. Anti-NMDA receptorencephalitis versus pediatric catatonia. Dhossche D, Fink M, Shorter E, Wachtel LE).

It would be useful to know if the girl was functioning well in school and in family situations before falling ill. Any unusual or severe stressors? Was a drug screen performed in order to confirm absence of drug or medication use? The evidence that there were no psychosocial or drug-related precipitants of this syndrome should be explicated.

Response: Although the patient was lack of severe stressors and functioned very well in daily life before falling ill, we totally agree with you that her psychiatric
presentation was compatible with acute catatonia and cited two more references. Nevertheless, without aggressive management of the observable symptoms of catatonia, the most profound improvements in psychiatric and behavioral symptoms occurred after the teratoma had been resected (Discussion, para 6, line 2-7).

Blood and urine screenings for drug abuse and intoxication had already been performed in emergency room with negative findings (Case, para 1, line 13).
Report of Reviewer 3:

This report outlines specific concerns following reassessment of earlier draft. I appreciate the care that the authors have taken in attempting to address each compulsory issue previously identified.

I submit to the authors and Journal Editors the following recommendations for revision. Major compulsory revisions have been addressed satisfactorily. Additional minor essential and discretionary revisions are included below. The article would benefit from further attention directed towards general readability / English phrasing.

Response: Thank you for understanding the merit of this paper and the efforts we have made in the revision. This time we have asked another native-English speaker with professional background to edit our manuscript.

Major Compulsory Revisions
--None.

Minor Essential Revisions
1. Conclusion: A case study does not offer “proof” or “prove” concepts. Please soften the statements made in conclusions.

   Response: We have softened the statements in conclusion, such as replacing “prove” with “support”.

Discretionary Revisions
1. Abstract, Patient: Suggest change to Objectives: Suggest change to “An immature ovarian teratoma was found; removal of the tumour resulted in full recovery of the patient.”

2. Abstract, Results: Suggest change to “She was discharged symptom free. Titres of anti-thyroid peroxidise and anti-thyroglobulin antibodies remained elevated.”

3. Abstract, Conclusions: Suggest change to “… receptor encephalitis and support the idea that neuronal and thyroid autoimmunities represent a pathogenic spectrum.”

4. Background, paragraph 1: Suggest change to “… functional NMDA receptors that predominantly affects…” I also suggest you exclude “on admission” at the end of this paragraph.
5. Case presentation, paragraph 3: Suggest change to “Pelvic lymph nodes and peritoneal washings...”

6. Case presentation, paragraph 4: Suggest change to “One day following resection of the teratoma, the patient was successfully weaned from the ventilator. Seizures remained controlled on valproic acid and oxcarbazepine.”

7. Discussion, paragraph 3: Suggest change to “... in this case has not been previously reported.”

8. Discussion, paragraph 4: Suggest change golden standard to “gold standard.”

Response: We cherish your generous suggestions in grammar and have followed all your instructions in discretionary revisions completely.