Author's response to reviews

Title: Anti-N-methyl-D-aspartate Receptor Encephalitis Associated with an Ovarian Teratoma: Two Cases Report and Anesthesia Considerations

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Author's response to reviews: see over
Dear Dr. Chiara Lazzeri,

Re: Manuscript reference No. 9762394931713864

Please find attached a revised version of our manuscript “Anti-N-methyl-D-aspartate Receptor Encephalitis Associated with an Ovarian Teratoma: Two Cases Report and Anesthesia Considerations”, which we would like to resubmit for publication as a case report in BMC Anesthesiology.

Your comments and those of the reviewers were highly insightful and enabled us to greatly improve the quality of our manuscript. In the following pages are our point-by-point responses to each of the comments of the reviewers as well as your own comments.

Revisions in the text are shown using red types for additions and revisions. In accordance with reviewer #1’s suggestion, we have replaced the figure of EEG to Figure 2, and corrected legends. In accordance with reviewer #2’s suggestion, we presented the cases again in detail one by one, added the discussion in anaesthetics that act at NMDAR. Native English speakers have reviewed the manuscript again and made some language corrections.

The other revisions have been responded according to reviewer’s suggestion point-by-point. We added Figure 1 to describe the cases from surgery to pathology.

We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in BMC Anesthesiology.

We shall look forward to hearing from you at your earliest convenience.

Yours sincerely,

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Responses to the comments of Reviewer #1 : Merce Falip

1. Please explain EEG abnormalities found in both patients and describe seizures with more detail.

   Response: *we describe the details of case 1 in line 77-78, page 4; and case 2 in line 121-123, page 6.*

2. Do the seizures recurred?

   Response: *Yes, the seizures recurred when we stopped the antiepileptic drugs.*

3. The second patients a part of seizures suffered confusion. Was a none convulsive status epilepticus excluded?

   Response: *We did not distinguish seizures with confusion or convulsive status epilepticus. In fact, two patients have been treated with antiepileptic drugs since administration.*

4. Were both patients treated with antiepileptic drugs?

   Response: *Yes, two patients have been treated with antiepileptic drugs since administration.*

5. Was a loading dose of antiepileptic drugs administered during the surgery ?.

   Response: *No, we did not use loading dose of antiepileptic drugs except modarolam and propofol for anesthesia induction.*

6. Was the ovarian teratoma confirmed by anatomopathology ?

   Response: *Yes, the ovarian teratoma was confirmed by anatomopathology. We have added the anatomopathology result in table 1 and figure 1.*

7. “Patients received gammaglobulins (20g*5 d). It is usual to administrate 400mgr*Kg*day during 5 days . So gammaglobulins dose must be different because patients weight was different.

   Response: *Yes, we have made the revision in text.*

8. Hyperthermia increases neuronal damage. Did you treat it in the second patient? Please commend in discussion the need to avoid hyperthermia in neurologically ill patients.

   Response: *We used aspirin to treat hyperthermia in the second patient, and we add the description in line 111-112, page 6. We did future discussion in line 172-183, page 9-10.*

9. In the figure 1A the quality of the EEG trace is poor probably because 50Hz filter is off or because there are a lot of artefact. This quality is not acceptable for publication.

   In both figure 1A and 1B you must add a legend including the filters used (low and high), the voltatge per mm and the seconds per mm. Also you must use the international 10-20 system for electrodes denomination .FB1 does not exist in this system, the correct international term is FP1 . The electrocardiogram channel is also important and you do not have to erase it.
Response: We have revised and added the EEG parameter in Figure 2. We have selected new typical EEG under the help of EEG specialist, and replaced the Figure 1 in initial manuscript to Figure 2 in revision version.

Responses to the comments of Reviewer #2: Maribel Acién

1. Abstract-Background: “Ovarian teratoma is the only confirmed tumour associated with anti-NMDAR antibodies”. The anti-NMDAR syndrome although initially associated to tumours in the ovary, it has now been described in men and in children.

Response: Yes, we have deleted the “only” in Abstract-Background (line 32-33, page 2) and in Background (line 55-56, page 3). We made a mistake due to the old reference [3].

2. Abstract-Keywords: “Teratoma” is missing.

Response: We have added “Teratoma” in Abstract-Keywords (line 50, page 3).

3. Case presentation: Because the title is “case presentation and anaesthesia considerations”, more emphasis should be done in the description of the cases. I am missing the difficulties in reaching the diagnosis, delay and specially, the surgical piece pathology (oophorectomy vs tumour resection, tumour size, histology...) Case presentation: It would be easier to follow the complete presentation of one case and then of the other.

Response: We represented two cases in details one by one (line 66-157, page 4-8). We described two cases in diagnose, delay, special and surgical piece pathology et al in new presentation. In fact, both patients underwent tumour resection otherwise oophorectomy, “oophorectomy” have been corrected to “resection of the ovarian teratoma” through the manuscript. We presented the operation scene, ovarian teratoma and pathology in Figure 2.

4. Discussion: It is mentioned that propofol inhibits NMDAR and that anaesthetics that act at NMDAR should be avoided, but this is one of the anaesthetics that was used in the cases. Further discussion on this point would be interesting.

Response: Although there are several reports demonstrate that propofol also inhibits NMDAR in clinically relevant concentrations. GABA_A receptors play a major role in inducing anaesthesia. Propofol was utilised to induce and maintain anaesthesia for the two patients in this report. Ideally, controversial anesthetics that likely act at NMDARs should be avoided.

We added above further discussion in line 204-208, page 11.

5. Pelvic ultrasound and pelvic MRI are opposite. Also, in the case presentation patient is said to have been operated the 9th of June, but in the Table the NMDAR determinations and examinations are said to have been done afterwards. And finally, it is said patient rejected being tested BEFORE discharge.

Response: The second patient underwent right ovarian teratoma. We have corrected the pelvic MRI result in table. The second patient was operated on June 26, 2014. we have corrected in in line 129, page 6. The second patient rejected further testing for NMDAR antibodies after July 7, 2014. We revised it in table’s legend.
6. First paragraph- The sentence "Ectopic NMDAR expression damages immune tolerance, eventually leading to anti-NMDAR encephalitis" should come earlier in the paragraph. Second paragraph- First sentence is missing the verb or part of the sentence. And lines 142-144, reference [14] second time, is meaningless.

Response: We have move the sentence “Ectopic NMDAR expression damages immune tolerance, eventually leading to anti-NMDAR encephalitis” to line 162-163, page 9.

Second paragraph- First sentence was revised to “Anesthetics work by interacting with the ion channel targets that regulate synaptic transmission and membrane potentials in key brain and spinal cord regions. The ion channel targets are differentially sensitive to various anesthetic agents.” In line 184-186, page 10.

We have deleted the repeated reference [14] in line 199-202, page 10.

7. Figure 1: B: Generalized –activity.

Response: “Generalized –activity” was revised to “Generalised rhythmic delta activity” in figure 2:B legend.

8. Needs some language corrections before being published

Response: we have corrected the misspelling according to reviewer #2. Native English speakers have reviewed the manuscript again and made some language corrections.