Author's response to reviews

Title: Anti-NMDA-receptor antibody detected in encephalitis, schizophrenia, and narcolepsy with psychotic features

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Author's response to reviews: see over
Dear Dr. Catherine Olino,

Thank you for your email of February 22, 2012, regarding our manuscript, “MS: 1093311888610954, Anti-NMDA receptor antibody and psychiatric manifestations”. We appreciate the reviewer’s valuable and constructive comments on our manuscript. I attach here our 2nd revised manuscript, as well as a point-by-point response to the reviewer’s comments.

We feel that the revised manuscript is revised accordingly to the reviewer’s comments, and it is now significantly improved over the initial submission. We believe that it is now suitable for publication in BMC Psychiatry.

Thank you in advance for your kind consideration of publishing of our manuscript. We greatly appreciate your guidance and feedback.

Sincerely,

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Reviewer's comments:

The manuscript by Tsutsui et al., reports on the identification of anti-NMDA-receptor antibody in 10 patients. The findings are very interesting and important and extend recent work to Schizophrenia and Narcolepsy with psychotic features. Unfortunately, the writing and the organization of the manuscript are very poor and need thorough revision. The paper should be proofed by a native English speaking scientist. I just mention a few:

We carefully proofread throughout the manuscript.

The title is not informative and a title such as “Anti-NMDA-receptor antibody detected in encephalitis, schizophrenia and narcolepsy with psychotic features” would be much more informative.

We changed the title as the reviewer suggested.

How the paper is written, it’s not clear if some of the reported cases have already been published or if all are new ones. This important point should be clarified.

We described the published cases in the method as below.

Case reports for 1, 2, 4, 9, 10 were previously published (Tsutsui 2010, Tsutsui 2011(a), Tsutsui 2011(b), Suda 2011, Maeda 2006, Takahashi 2011).

The abstract and introduction are almost identical! Therefore the introduction must be rewritten.

We rewrote the abstract and introduction, and minimized overlaps.
The overall organization is very difficult to follow. The authors should make reference to their table in a short paragraph then report the typical cases followed by a summary of common/differential symptoms and features of all 10 cases.

We improved the first paragraph of the each group as below.

(Panel A) Typical clinical pictures of anti-NMDAR encephalitis: We reviewed a case of acute limbic encephalitis (NMDAR antibody was detected retrospectively) diagnosed after improvement of psychotic symptoms by mECT. This case was first diagnosed as schizophrenia based on catatonia-like symptoms, auditory hallucinations, and delusions. Two other positive cases presented with psychosis, convulsions and were treated with steroid pulse therapy.

(Panel B) Narcolepsy cases with severe psychosis: We had previously reported a case with Parkinson’s disease (PD) comorbid with hypocretin (orexin) deficient narcolepsy (Maeda 2004, Takahashi 2011). In this patient, severe psychosis presented subsequently to the diseases above, and has been treated by mECT in addition to anti-psychotics with a successful outcome. NMDAR antibody was detected retrospectively. The two other positive cases had narcolepsy with severe psychosis without neurodegenerative disease.

(Panel C) Psychiatry cases: In addition to these cases, we also found 4 antibody positive patients out of 51 patients with schizophrenia or schizo-affective disorders (group C). The neurological symptoms were mild in these cases, and mECT was effective in 3 cases. These 4 cases were female, two cases had convulsions (cases 7, 8), and two cases had ovarian tumors (cases 8, 10).

I have also doubts that the classification with 3 groups as well as individuals (A1-B-C1, etc) is really appropriate. Maybe a numbering from 1 to 10 is enough and in the text the authors can make reference to encephalitis (cases 1-3) schizophrenia (cases 4-6), and narcolepsy (cases 7-10). The term sleep disorder is definitely not appropriate and narcolepsy with cataplexy and psychotic features (maybe abbreviated in NCP) would be much better.
We changed the classification of A1-B1-C1 to cases 1-3(A), 4-6(B), 7-10(C) and the term sleep disorder is changed to narcolepsy with psychosis. However, we did not change the order of the disease groups, since the total number of the subjects is relatively large in the schizophrenia group.

We completely changed the writing as the reviewer suggested.

Abstract: under methods number of patients in each group is missing (except for schizophrenia). 3d line ...groups for comparison (delete the). Under conclusion ...we found 7 Japanese cases with anti-NMDA-receptor antibody associated with various... Last sentence: Our results call for further discussion...

Throughout the manuscript either use antibody or antibodies. My understanding is that antibody is more appropriate since not many different antibodies have been detected.

Introduction: ...causative role of...First sentence needs to be referenced. 3d paragraph: In addition to 3 conventional cases (maybe typical is better than conventional), ...we recently diagnosed and not experienced.

Methods: ...into 3 clinical groups for comparison. 2d paragraph. Five narcolepsy with severe...were also included. End of the paragraph: measured for comparison with group-B. 3d paragraph: Antibody detection were performed by Dr. Dalmau’s lab in cases 1, 2, 4, and in Dr. Tanaka (?) for the others.

Results: ...is presented in Table 1. 2d paragraph: no previous psychiatric, neurologic, or family history...Later: ...CSF and brain SPECT were performed. Brain SPECT showed decrease blood flux in... 3d paragraph: Examination for tumors was not performed...6th paragraph: ...were negative for anti-NMDAR antibody.

Under Group B: Thus patient has subsequently presented severe psychosis.......with successful outcome. 2d paragraph: He suffered from EDS at high school...later...mean sleep latency was shortened to 2 min. later...Finally...with successful outcome. Later...NMDAR antibody was detected in both serum and CSF of this patient. Last paragraph: ...and found 2 antibody positive patients...

Under Group C: first paragraph:...mECT was effective in 3 cases. 2d paragraph: A 26 y old female patient had normal...Later: ...junior high school. The next sentence starting
with. Although is not clear at all. Next sentence: She was diagnosed with depression and received X (name the treatment) treatment in a clinic. Next sentence: a hypomanic episode at age 17. 3d paragraph: the patient had insomnia and hypobulia at age 22. Next sentence...so she was transferred to a closed ward. End of paragraph: anti-psychotics based on schizophrenia diagnosis. Next paragraph:...by abdominal ultrasonography. Next paragraph: She was positive for anti-NMDAR antibody. Next paragraph:...schizophrenic and resistance to pharmacological treatments...
Under Discussion: are resistant to pharmacological...
Under NMDAR and psychiatric symptoms, end of the 2d paragraph: ...fatal condition, if the diagnosis is made rapidly, effective treatments are available. Next paragraph: ...most favorable outcome occurs...second sentence: Also, a good clinical outcome was reported...last paragraph: ...of consciousness.
Under The prevalence of...2d paragraph: ...examined cases that fulfilled.... Last sentence under Atypical psychosis:...in these psychotic patients.
Under mECT effects, 2d paragraph: ...full recovery was only obtained after...5th paragraph: ...redifine this new class of psychotic disorders positive for anti-NMDAR antibody. later: ...symptoms of psychosis and psychotic patients who are drug resistant but respond relatively well to mECT. Next paragraph: We did not measure the CSF antibody in the majority of our cases and future prospective studies should include paired serum-CSF antibody measures.