Author’s response to reviews

Title: Differences and diversity of autoimmune-mediated encephalitis in 77 cases from a single tertiary care center

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Author’s response to reviews:

Dear BMC Neurology Editors,

Please consider our second-revised manuscript, “Differences and diversity of autoimmune-mediated encephalitis in 77 cases from a single tertiary care center” for publication in BMC Neurology.

We appreciate the interest that the editors and reviewers have shown in our manuscript and the constructive criticism they have given. We have addressed the concerns of the reviewers. More specifically, we have rewritten some section and included a point-by-point response to the reviewers. Changes to the text and footnotes of the tables in the manuscript are marked in red. We are grateful for the valuable comments and hope that this revised version will be suitable for publication at BMC Neurology.

Thank you again for your kind consideration.

Sincerely yours,

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Reviewer reports:

Technical Comments:

1. Please confirm whether informed consent, written or verbal, was obtained from all participants and clearly state this in your manuscript. If verbal, please state the reason and whether the ethics committee approved this procedure. If the need for consent was waived by an IRB or is deemed unnecessary according to national regulations, please clearly state this, including the name of the IRB or a reference to the relevant legislation.

We have added “Since the study was mainly retrospective, the need for individual consent was waived by The Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.” to the Declaration section.

2. The individual contributions of ALL authors to the manuscript should be specified in the Authors’ Contributions section. We note that the initials for Chanikarn Sonpee are missing.

We have added “KW and CS performed the autoantibody tests and analyzed the results.” To the Author’s contributions.

3. In the 'Funding' statement, please declare the role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

We have added “Data collection and statistical analysis of this study were supported by the Ratchadapiseksompotch Fund…” to the Funding part.

PEER REVIEWER COMMENTS:

REQUESTED REVISIONS:

The manuscript would benefit from focused editing with the following goals:

1. Reduction of repeated information (especially prominent in the results + discussion); the high degree of repetition will frustrate many readers.

We have removed as much repetition as possible. In the Discussion, any repeated information from the Results is used as a basis for comparison with other studies. We have also inserted subheadings in both the Results and Discussion sections to make it easier for readers to navigate the manuscript.

2. Eliminate (duplicated) information in the text that is already presented in tables / figures. E.g., restatement of disease-associated tumors in the text when this information is clearly presented in Table 1.

We deleted several sentences such as “These were ovarian teratoma (anti-NMDA), non-small cell lung cancer (anti-AMPA2) and adenocarcinoma of the stomach (anti-GABAb).” “One patient with coexisting anti-Ri had seizure as the presenting symptom while the other with NMO antibody presented with behavioral change, abnormal movement and hemiparesis.” and
“Ovarian teratoma was found in one case. No other tumors were identified.” from the Results section.

3. Standardization of terminology. At times the authors refer to autoimmune encephalitis, immune-mediated encephalitis, autoantibody-mediated encephalitis,

“Autoimmune encephalitis” is now used throughout the manuscript

4. Control of acronyms. At various times the authors use NMDAr or NMDA receptor, GABA-R / GABA / GABA receptor, anti-NMDAR encephalitis / anti-NMDA encephalitis, etc.

We have corrected these and ensured that acronyms are used consistently.

5. English language editing to eliminate passive phrasing where possible, and improve readability.

When appropriate, active phrases are now used instead of passive ones.

Several errors in statistics are revealed on cursory review.

- 2 tailed Fisher exact for mortality (1/31 vs 4/25; p=0.16—not 0.09)
- P value for outcome (mRS) calculations in Table 1, recalculated to be 0.25 (reported as 0.09).

We corrected all the p-value according to the reviewer’s comments.

- Non-parametric measures (Mann-Whitney U test, not Student's T-test) should be used to evaluate continuous variables (e.g., hospital stay) given suspected non-normal distribution of data and relatively small sample size. Similarly, should report median and range for all values (not average and SD).

Median and range have been added to Table 2.

Recommendations for further revision are divided by manuscript section.

Abstract

- The Background is irrelevant and does little to inform the goals / motivation for this study. A better use of space would be to define AE, and state that there are two general categories of disease-associated antibodies that can be tested for. Then, state the major problem (i.e., cost and resources required to complete testing), and the rationale for this project.

We appreciated your advice and re-wrote the Background to reflect this.

- Methods: The location of KCMH should be stated. It is generally not necessary to provide specific details on statistics in the Abstract.
As your suggestion, we deleted the statistical details and added the location of KCMH.

- Results: State results as directly as possible, without commenting on "insignificant differences"

We have deleted “although this was statistically insignificant” and “significant differences” from the paragraph.

- Conclusions: This retrospective cross-sectional study at a single center cannot / does not define "prevalence" of a disease. Furthermore, the patients with neuronal surface antibodies were encountered more frequently than patients with intracellular antibodies is patently false (40% vs 32%). This first sentence should be eliminated in its entirety.

The first sentence has been removed.

Introduction

- The Authors cite a population specific to Olmstead County, Minnesota to support incidence / prevalence of AE (Reference 1). This is not acceptable.

We agreed with your comment and deleted reference Ann Neurol. 2018; 83(1):166-77 from the manuscript.

- I agree with Reviewer 2 that the Introduction is too long, and fails to clearly articulate the problem which this data addresses. It is not clear what review of the pathogeneses of neuronal surface Ab vs. intracellular Ab adds to this manuscript, or how it is relevant to interpretation of results. The Authors are advised to reframe the Introduction to reflect the key points outlined in the Abstract Background (above).

Thank you for your advice. We have rewritten the introduction to reflect this and ensured that our aims are clearly pointed out.

Methods

- The section labelled "laboratory investigations" includes several measures that are not laboratory investigations (e.g., chest x-ray, CT scans, etc).

“laboratory investigations” has been changed to “investigations”.

- Diagnostic criteria used to define patients with "Hashimoto's encephalitis" should be defined.

This has been added to the Selection Criteria.

- There is no mention of ovarian ultrasound (abdominal and/or transvaginal) used to screen patients for tmdarumor.

We added “Pelvic examination and ultrasonography were performed in female patients with anti-Yo and anti-NMDAr” to the Investigations.
Results

- The assumed goal of this manuscript was to compare clinical, radiological and laboratory findings in patients with neuronal surface Ab vs. intracellular antibodies. This should be the focus of the results. Patients that did not fit within these categories should be excluded from analyses and not discussed further as they do not support the main objectives of the study (NPLE, Hashimoto's, antibody-negative cases). There is far too much subdividing of patients with antibody-associated encephalitis, leading to an unnecessarily bulky and repetitious results section. In cases associated with multiple autoantibodies, I recommend logical assignment to a primary category (neuronal surface vs. intracellular) based on clinical judgement. Under this methodology all cases would be assigned to the neuronal surface Ab (perhaps with the exception of the one cause with NMDAR and anti-Ri Ab—although presentation in an 18 y.o. without tumor makes it exceedingly unlikely that Ri autoantibody was clinically relevant).

Thank you for your suggestion and we agree that the main goal of the manuscript is to differentiate patients with neuronal surface vs intracellular antibodies. However, given that each antibody is likely to have different consequences to patients, we believe that assigning patient with multiple autoantibodies to a primary category may influence the outcome and unintentionally introduce bias. Hence, we think it is more prudent to keep this as a separate category.

With regards to other groups of antibodies (systemic immune disease, antibody-negative etc), we appreciate that they do not contribute to differentiation between the neuronal surface vs intracellular antibodies groups. However, our other goal is to report the incidence of autoimmune encephalitis in this tertiary centre and describe their clinical presentation (we have made changes to the Abstract and Introduction to reflect this more clearly). By doing so, we have described non-classical paraneoplastic autoantibodies such as anti-recoverin, anti-titin and anti-SOX1, which are usually not considered as the cause of paraneoplastic CNS disease. We believe that this adds value to the manuscript and should be kept in.

- Summary results should be summarized; that is, age should be presented as median and range. Arbitrary divisions are not helpful (e.g., "Twenty-two patients were less than 45 years old").

Age is now presented as median and range, and arbitrary divisions have been removed.

- Neuroradiologic descriptions are not sufficient. "Temporal lobe lesion"—T2? T1? Hemorrhage / tumor / stroke / edema?

T2-weighted images were used. This has been added.

- Doses of treatments provided should be indicated. It should be clearly stated that tumors were treated when present.

We provided the doses/cycles of IVIg, prednisolone and plasmapheresis to the section. “Tumors were appropriated treated upon discovery” has been added.
- The Authors refer to "outcome" at several points in the text and tables (and in the Discussion). Unless I am mistaken this should read "outcome at discharge from hospital". This recommendation includes clarification of statements such as "recovery rate and morbidity" (Discussion).

“At discharge from hospital” has been added after “outcome” and “recovery rate and morbidity” throughout the manuscript

- Do not present male:female ratios. It is sufficient to state the number (%) of females (or males).

We deleted the male:female ratios from the manuscript and added percentage male instead.

- Causes of death should be articulated.

We described the causes of death of intracellular group in the manuscript.

Discussion

- This study does not describe the "epidemiology", but rather clinical, radiological and laboratory findings in patients with AE diagnosed and treated at your tertiary care hospital in Bankok, Thailand.

We replaced that sentence with “This study described the clinical, radiological and laboratory findings in patients with autoimmune encephalitis diagnosed and treated at a tertiary care hospital in Bangkok, Thailand.”

- Do not discuss results that have not been presented in the Results section (e.g., movement disorder subtype in NMDAR encephalitis).

We have added the movement disorder subtype of anti-NMDAR encephalitis to Table 1 under the Results section.

Conclusion

- The Conclusions should clearly address the primary objective of the study, without mention of additional extraneous information. To this end, I recommend that you eliminate the position statement (first sentence) and mention of "several subgroups”—the majority of which are contrived and unnecessary.

Thank you for your advice. We deleted the first two sentences from the Conclusion.