Reviewer’s report

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

Version: 1 Date: 22 Aug 2019

Reviewer: Reviewer 2

Reviewer's report:

PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses one or several testable research questions? (Brief or other article types: is there a clear objective?)
No - there are minor issues

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?
Yes - the approach is appropriate

EXECUTION - Are the experiments and analyses performed with sufficient technical rigor to allow confidence in the results?
Yes - experiments and analyses were performed appropriately

STATISTICS - Is the use of statistics in the manuscript appropriate?
No - there are issues with the statistics in the study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?
No - there are minor issues

OVERALL MANUSCRIPT POTENTIAL - Has the author addressed your concerns sufficiently for you to now recommend the work as a technically sound contribution? If not, can further revisions be made to make the work technically sound?
Probably - with minor revisions

PEER REVIEWER COMMENTS:

GENERAL COMMENTS: This manuscript presents a comprehensive overview of the presenting features of consecutive patients with autoimmune encephalitis encountered at a tertiary care hospital in Bangkok, Thailand. The manuscript has been revised in response to reviewer comments, which were predominantly minor. In some cases, the authors chose to respond only to the reviewer, without making changes to the manuscript. Responses that provide additional information concerning the cohort should be integrated within the text (e.g., causes of death).

Reviewer 2 encourages the authors to provide a more focused introduction, which clearly delineates the purpose/objective of this manuscript. The authors provide an impassioned response to the reviewer, which clearly articulates the challenges associated with performing
costly assays in resource poor countries, and the resultant interest in testing limited sets of
antibodies. The authors response is convincing, and provides an important counter-
perspective to the prevailing view that everyone should be tested for everything. I encourage
the authors to reframe their "background" paragraph (abstract) and introduction to clearly
state this important problem, which supports the need for this study, and informs the
conclusions.

The current manuscript version does not have major flaws that would preclude from eventual
publication. However, best practices require more clear statement of manuscript purpose /
rationale / goals, and a clearer presentation of results (necessary to ensure accurate
interpretation of information). Finally, known limitations associated with the work should be
discussed. To this end, the authors should revise their discussion to include review of
standard applicable limitations to case reviews of rare disorders (retrospective, dependent on
available records, applicable cases likely overlooked), and should discuss additional issues
specific to this work. These include limitations associated with testing (initial use of serum)
and access to treatment (as discussed in response to reviewers), as well as generalizability of
results from a single center. The discussion paragraph concerning antibody-negative patients
could be included in this section.

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.

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.

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

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

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

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).
- 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).
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.
- Methods: The location of KCMH should be stated. It is generally not necessary to provide specific details on statistics in the Abstract.
- Results: State results as directly as possible, without commenting on "insignificant differences"
- 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.

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

Methods
- The section labelled "laboratory investigations" includes several measures that are not laboratory investigations (e.g., chest x-ray, CT scans, etc).
- Diagnostic criteria used to define patients with "Hashimoto's encephalitis" should be defined.
- There is no mention of ovarian ultrasound (abdominal and/or transvaginal) used to screen patients for tumor.

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 form 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).
- 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").
- Neuroradiologic descriptions are not sufficient. "Temporal lobe lesion"—T2? T1? Hemmorhage / tumor / stroke / edema?
- Doses of treatments provided should be indicated. It should be clearly stated that tumors were treated when present.
- 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).
- Do not present male:female ratios. It is sufficient to state the number (%) of females (or males).
- Causes of death should be articulated.

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

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.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:
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