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 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 taken in our manuscript and the constructive criticism they have given. We have addressed the major concerns of the reviewers. More specifically, we have added more appropriated references 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 publish in BMC Neurology.

Thank you again for consideration of our revised manuscript.

Sincerely yours,

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Reviewer reports:

Sarosh Irani (Reviewer 1):
Introduction.

P3 - "Thus, with several novel......" This sentence only highlights rare antibodies. Better to rewrite and include LGI1, GABAB, CASPR2, GABA. These are far commoner.

We rewrote the sentence with the suggested antibodies and added a few more. “Additionally, with several novel neuronal antibodies discovered recently such as LGI1, CASPR2, GABA-A/B, anti-dopamine2 receptor, anti-DPPX, anti-IgLON5 and neurexin-3α (8-15)”

if you are not analysing including the 'vesicular' category, there seems no need to include this in the introduction.

We removed the phrase “and those that are found predominantly in the synaptic vesicles (e.g.,GAD65 and amphiphysin)” from the paragraph and changed the group name from “intracellular/synaptic vesicle” to “intracellular”.

Methods

Was this consecutive or selected in some way? 10 per year - seems low form a large catchment. So, are the authors saying that there really were only 77 positive results in 7 years? What was the distribution of those results between 2010 and 2017?

We included every patient from 2010-2017. There were very few patients initially (2 cases in 2010), which gradually increased to 15-18 cases annually in 2016-17. Since we are one of the main referral centers in Thailand, this may be due to an increased awareness of autoimmune encephalitis from hospitals in rural parts of Thailand in recent years.

How were the patients identified for the study? - be much clearer; which antibodies? Serum and or CSF? For retrospective testing (2010-13), how were the cases to test identified?

Our center has a record of every patient who was tested for autoantibodies, so we reviewed these records and identified the patients. The names of antibodies tested are listed under ‘Laboratory investigations’. In 2010-2013, due to a limited budget, we only tested the serum initially. If the result was negative then we proceeded to CSF testing. Since 2014, there was a change in the National Health Insurance policy, so we could test both the serum and CSF (if patient did not had the contraindication for lumbar puncture).

Was CT pelvis included in the workup? (only chest / abdomen mentioned)

Yes, CT pelvis was included. This has been added to the manuscript.

Were brain sections stained in addition to the transfected cells?

No, we only used the method suggested by EUROIMMUN® to perform IIF.

What was the inter-rater reliability of the test interpretations?
We passed the quality assessment in “Autoantibodies against neuronal antigens” that host by IfQ-Lubeck (an institution of the EUROIMMUN Medizinische Labordiagnostika AG) with 100% correct results.

Results

Did the distribution of positives amongst 24 provinces also reflect the number of patients from each province? If so, this is worth omitting.

We had removed the details about the distribution of provinces and region.

It is important to show whether antibodies in Table 1 were present in serum and CSF or just one. Please note NMDAR-antibodies should be included only if present in CSF.

We added the columns for “number of CSF positive patients” and “number of serum positive patients” to Table 1 to show this distinction. For anti-NMDAr cases without CSF data, we diagnosed these patients using the criteria of probable anti-NMDA receptor encephalitis as proposed by Graus et al. (Lancet Neurol 2016; 15: 391–404.).

Interesting to see few LGI1/CASPR2 cases. How can this be explained? Were the patients screened mainly <60 years?

Yes, the majority of patients in our study were middle aged (mean age 40 years old). This has been added to the Discussion section.

Can the age distribution of tested and positive cases be shown in a stacked bar chart?

We have already shown the age range of positive cases in Table 1.

Is HLA-DRB1*07:01 / 11*01 present in Thai populations (see Binks et al 2018 Brain)

We do not have data with regards to HLA-DRB1*07:01 / 11*01 and the Thai population. However, since Binks et al. had identified this in the Chinese population, it is likely to be present in the Thai population as well. Unfortunately, we currently cannot have this test at present.

Can the authors clarify if the stiff people had GAD antibodies?

We can confirm that the stiff patient in our study did not have anti-GAD. We used both the immunoblot and immunofluorescence techniques and the results were negative for anti-GAD.

They mention two LGI1 in the table, but 4 in the text - please clarify.

There were only 2 LGI1 patients in our study. We had rewritten the sentence to make this clearer. “Among the nine patients with abnormal movements, five had chorea/dyskinesia (all had anti-NMDA with one patient also presented with catatonia), two had faciobrachial dystonic seizures (both had anti-LGI1), one had stiff-person syndrome (anti-AMPA2), and one had myoclonus (anti-GABA).”
Why did so few NMDAR-antibody cases present with psychosis / mood? - maybe best to pool with behaviour given Al-Diwani et al 2019 Lancet Psychiatry

We adopted the definition of Behaviour and catatonia according to Al-Diwani et al and added this to the Method section.

I'm not sure it is worth mentioning the clinical features of the less/non-diagnostic antibodies e.g. SOX / titin / GAD / recoverin. Maybe it would be better if the authors list the cases which were typical / classical for what is already known of the syndromes (and say little more), but focus on the ones where the clinical observations were more novel.

The cases and their classical findings had been added to the paragraph. Additionally, we added the point that anti-titin/SOX1 often presented with other classical autoantibodies, however, this was not the case in our population, which may demonstrate that these autoantibodies were directly responsible for the neurological symptoms seen.

Why did one patient die?

The patient with anti-GABA had status epilepticus and the cause of death was sepsis due to ventilator-associated pneumonia.

Can the authors make it very clear how patients were treated? It seems they received very few immunotherapies. Also, can the authors show how long after disease onset they were treated?

As a public hospital with limited government funding and the high cost of immunotherapy, we could not afford to offer it to all patients and every prescription of IVIG had to be approved by a committee. However, we have been receiving more funding from 2014 and strive to treat every patient to the best of our capabilities. We have also added the duration of disease onset to treatment to Table 2.

Can the authors show mRS 0-1 in the table 2?

We have added the statistics of mRS 0-1 to table 2.

Referencing

The authors have omitted several relevant references including those relating to

LGI1 (Thompson et al 2018 Brain, Gadoth et al 2017 Ann Neurol), AMPA/GABA (Patit-Pedrol et al 2014 Lancet Neurol, Dogan-Onugeren et al 2016 JNNP), NMDAR (Al-Diwani et al 2019 Lancet psych, Varley et al 2018 JNNP). When citing these, it will be useful to see the authors reflect on whether their findings were present in the Thai cohort.

We would like to thank the reviewer for highlighting these studies to us. We have added them to the manuscript and included comparisons to the Thai cohort.

“This is likely because LGI1 antibodies were more common among elderly patients with antibody-associated CNS syndrome (29, 30), while the majority of patients in this study were middle-aged (mean age of 40). Both cases of anti-LGI1 encephalitis in our study had
faciobracial dystonic seizure (FBDS) that responded to immunotherapy rather than antiepileptic drugs, which is similarly reported by Thompson et al. (31). Additionally, these two patients were more than 50 years old and only had CNS manifestations—a finding that is consistent with Gadoth et al. (32).” was added to Discussion.

“Among the two cases of anti-AMPA antibody encephalitis, one had SCLC, which was the most commonly associated tumor according to Onugoren et al. (33).” was added to Discussion

Patit-Pedrol et al 2014 Lancet Neurol as reference number (15).

“We used the descriptions of psychopathological features according to Al-Diwani et al (25). in our study.” was added to the Selection Criteria.

“However, we did not find dystonia as common as suggested by Varley et al (42). and there was only one case of catatonia in our study.” Was added to Discussion

Please remove the Paterson et al reference which is now not relevant given our knowledge about the more irrelevant VGKC antibodies.

This reference has been removed.

Can the authors compare / contrast their findings to those from the South Korean group whose ethic population may be more similar amongst major papers published in the field.

This has been added to the Discussion. “However, in our study, only two cases (9%) of ovarian tumor were found at the first immediate tumor screening despite a thorough investigation with abdominal and pelvic CT and pelvic ultrasonography. Interestingly, this is consistent with anti-NMDA encephalitis case series in China by Wang et al (26). and Korea by Lim et al (39)., which found that ovarian tumor was present in four (8%) and two (9%) patients respectively.”

There are also lots (?10) different reviews cited - would be better just to choose 2/3 to avoid repetition.


Jin-Sun Jun (Reviewer 2):

1. This is a single-center study, which limits the generalization of the results. Thus, the discussion and conclusion of this manuscript should be toned down. Especially, you should revise this sentence "Our study revealed the epidemiology of different autoantibodies in autoimmune encephalitis in a Thai population". I don't think that the data from a single
tertiary care center represent the population data. Only multicenter or nationwide data should be considered as the population data. Similarly, the conclusion "we recommend that suspected patients should be screened for both the neuronal surface and intracellular/synaptic vesicle antibodies, regarding any clinical presentation." This expression is too strong.

We appreciate that this is a single center study and changed the term ‘revealed’ to ‘described’ and ‘population’ to ‘patients’. However, we would like to point out that we are a major referral center in Thailand, and we are one of a few hospitals in the country with the facility to screen for autoantibodies in patients.

With regards to the recommendation, we believe that this is justified because our data have shown that patients from both groups of autoimmune encephalitis have very similar clinical presentations, neuroimaging and CSF profile. Therefore, it is likely to be in the patient’s best interests for us to be prudent and screen for both groups of antibodies.

2. The objective of this study remains unclear, even although the introduction session is a little bit long. I don't agree that "The choice of antibodies to be tested for is based on clinical presentations and the physician's judgement." Considering that the early immune therapy should be considered for better outcome in patients with autoimmune encephalitis, early diagnosis is very important in these patients. The choice of antibodies may make the diagnosis of autoimmune encephalitis delay.

We completely agree that the early diagnosis is vital in these patients. However, as a public hospital in a developing country, our resources are extremely limited, and these autoantibodies assays were very costly. Thus, we were keen to compare the differences between the two major groups of autoimmune encephalitis. Had there been a significant difference, we would be able to save cost by testing only one panel instead of two and allocate our resources to other areas of care such as better treatments. Furthermore, our results could be applicable to other developing countries in South East Asia such as Cambodia and Laos who could benefit from this cost saving strategy as well. Unfortunately, the differences were not significant enough and we believe it is prudent to continue testing for both groups of autoantibodies.

3. I don't understand that the Table 2 is located in the discussion session. You should transfer this table and relevant contents to the result section.

We have transferred Table 2 to the Results section.

4. How many patients were tested for autoantibodies, and how many patients among them were positive for autoantibody testing? You should describe the inclusion process of the patients in detail.

The breakdown of patients and what they were positive for could be seen in Figure 1 at the end of the manuscript (Page 23). 77 patients with suspected immune-mediated encephalitis were tested. 74 were positive for autoantibodies and 3 were antibody negative. The inclusion criteria and definitions have been made clearer under Selection Criteria in Methods.