Author's response to reviews

Title: Neuromyelitis optica spectrum disorders without and with autoimmune diseases

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Author's response to reviews: see over
Response

MS: 1045091991290486
Title: Neuromyelitis optica spectrum disorders with non-organ-specific autoimmune diseases and with organ-specific autoimmune diseases
Authors: Bingjun Zhang, Yi Zhong, Yanqiang Wang, Yongqiang Dai, Wei Qiu, Lei Zhang, Haiyan Li and Zhengqi Lu

Dear Dr. Handel and Santos,

Thank you very much for your letter and advice. We have revised the manuscript, and would like to re-submit it for your consideration. We have addressed the comments raised by the reviewers, and the amendments are highlighted in red in the revised manuscript. Point by point responses to the reviewers’ comments are listed below this letter.

We hope that the revised version of the manuscript is now acceptable for publication in your journal.

I look forward to hearing from you soon.

With best wishes,

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We would like to express our sincere thanks to the reviewers for the constructive and positive comments.

Replies to Reviewer #1

Major comments

1) Could the authors clarify what specific autoimmune panel they tested/included for organ-specific autoimmunity? Although autoimmune myasthenia gravis has been mentioned as an organ-specific autoimmune disease in the introduction, there is no mention of anti-AChR or MUSK antibodies in the Table. In addition, could they clarify whether they tested the specific antibodies for autoimmune diabetes, autoimmune gastritis, autoimmune hepatitis etc. Did all patients undergo these tests before categorizing them into the two categories of non-organ specific and organ specific autoimmune diseases? For instance, patients with non-organ specific autoimmune disease could have co-existing organ-specific autoimmune diseases: for instance, autoimmune myasthenia gravis can co-exist with SLE etc.

Answer: In fact, the high frequency co-morbid specific autoimmune diseases were thyroid diseases in Asian NMOSD patients. In our MS Center, ANAs, ENAs, ANCAs, RFs, immunoglobulins, complements, and thyroid indexes testing were performed for most NMOSD patients (Method section). As shown in the flowchart, several patients were excluded for not enough testing.

Anti-AChR, MUSK, and other organ-specific antibodies testing were not routinely performed unless the patients have the clinical symptoms and signs. In our MS center, none patient was suspected for autoimmune diabetes, autoimmune gastritis, and autoimmune hepatitis.

As a retrospective study, all patients undergo these tests before categorizing them into the two categories.

2) Did the author compare the clinical features of NMOSD with or without autoimmune disease (non-organ specific and organ specific diseases put together)?

Answer: The data of NMOSD without autoimmune disease have been added in the revised version.

3) Did the authors carefully look for transient hyper-CKemia (Muscle Nerve. 2014. doi: 10.1002/mus.24298 and Neurology 2010;74(19):1543-5) and hyponatremia between NMOSD with or without autoimmune disease?

Answer: Serum CK in all NMOSD patients with autoimmune disease was normal.
Frequency of hyponatremia was low in NMOSD patients with autoimmune diseases (2/40). However, the data have not been added in the revised version.

4) It might be better to recast the study as comparison of NMOSD with or without other autoimmunity. Since the authors have a higher number of NMOSD cases (around 170) from a single centre, this comparison might have better clinical relevance or could yield interesting or useful findings than the present format of comparing NMOSD with non-organ specific vs. organ specific autoimmunity. Please note that the previous paper on this topic was multicentre-based (JAMA Neurol. 2008;65(1):78-83)

Answer: The data of NMOSD without autoimmune disease have been added in the revised version.

5) How many (or percentage) of the NMOSD cases had co-existing auto-antibodies without clinical autoimmune disease?

Answer: Autoantibodies were detectable in 18.3% (21/115) NMOSD without autoimmune disease (ANA 16, SSA 2, SSB 1, RF 2). The data have been added in the Table 2 of the revised version.

6) Since the titer of auto-antibody panel such as ANA was not known, could there be a technical problem in categorizing patients? For instance, incidental low titre of ANA might be classified as non-organ specific autoimmunity.

Answer: Thanks for your question and nice suggestion. As mentioned in the discussion, titers unknown are one of limitations in our study. However, according to the criteria, titers of auto-antibodies are one of items, but not requisite for the diagnose of autoimmune diseases. In our study, autoimmune diseases were diagnosed strictly according to the criteria. We considered the titers unknown have little effect on the categorizing patients.

Minor comments
1) In Page 3, line 2, under introduction, NMO is described as an idiopathic condition. Since NMO is established as an autoimmune disease, this should be changed.

Answer: The sentence has been modified in the Introduction section (page 3, paragraph 1, line 2) of the revised version to address this issue.

2) In page 5, line 65, under statistical analysis, instead of median plus or minus range, the format has to be median (range).
Answer: Corrections have been made in the revised version.

Replies to Reviewer #2

1. There are multiple grammatical mistakes throughout the manuscript which should be corrected.

Answer: Corrections have been made in the revised version.

2. Since the authors use small cohorts of patients, they should include power calculations for their ability to detect differences between the cohorts.

Answer: NMOSD patients without autoimmune disease were included in our study in the revised version. The numbers of NMOSD patients add up to 155 in the cohorts.

3. The authors should expand on why they chose to look specifically at the two subgroups of patients that they report here and precisely how these groups are defined.

Answer: Thanks for this precious advice. Several sentences have been added in the Introduction section (page 3, paragraph 1, line 11-15) and the Method section (page 4, paragraph 1 line 32-38) of the revised version to address this issue.

“However, few systemic studies have focused on the relationship between NMOSD without and with autoimmune diseases, and NMOSD with non-organ-specific and organ-specific autoimmune diseases. The characteristics of different NMOSDs, particularly NMOSD with non-organ-specific and organ-specific autoimmune diseases, were not studied enough.”

“Other included were: (a) all of these patients whose serum samples were tested for NMO-IgG, autoreactive antibodies (antinuclear antibodies (ANAs), extractable nuclear antigen autoantibodies (ENAs), rheumatoid factors (RFs) anti-neutrophil cytoplasmic antibodies (ANCAs)), immunoglobulins, complements, thyroid hormones and autoantibodies; and (b) also MRI of the brain and spinal cord available for review. Non-organ-specific autoimmune diseases (e.g. SLE,[7] SS,[8] RA,[9] UCTD[10]), and organ-specific autoimmune diseases (e.g. thyroid diseases) were diagnosed by neurologists/rheumatologists/endocrinologists according to the criteria and typology guidelines. Clinical data and MRI scans were collected from these individuals, a group that including 115 NMOSD patients without autoimmune diseases and 40 with autoimmune diseases (20 with non-organ-specific autoimmune diseases and 18 with organ-specific autoimmune diseases).”
4. The authors should include the data on NMO patients without co-morbid autoimmune disorders (i.e. the 132 patients excluded from this study) to allow the reader to draw conclusions related to the importance of patients having autoimmune disorders in addition to underlying NMO.

Answer: Thanks for this precious advice. The data of NMOSD without autoimmune disease have been added in the revised version.

5. How can the authors be sure that any differences observed (particularly related to auto-antibody frequency) are not simply due to the non-organ-specific autoimmune disease and unrelated to the NMO diagnosis?

Answer: Thanks for your question and nice suggestion. The data of NMOSD without autoimmune disease have been added in the revised version. Autoantibodies were also detectable in 18.3% (21/115) NMOSD without autoimmune diseases (ANA 16, SSA 2, SSB 1, RF 2). However, antibodies seropositivity was significantly higher in NMOSD patients with autoimmune diseases and non-organ-specific autoimmune disease (p < 0.05).

6. In figure 1 the numbers do not add up (170 patients are at the top and those without co-morbid autoimmune disease are not shown as being excluded in this).

Answer: The new Figure 1 has been added in the revised version.