Author's response to reviews

Title: Association between neuromyelitis optica and tuberculosis in a Chinese population

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Author's response to reviews: see over
Dear Editor:

Thanks for your reply. We have confirmed that patient consent was obtained for the use of MRI images, and stated it in the methods following your suggestion. We wish to resubmit our manuscript again. We have addressed all of the editor and Reviewers’ comments as follows:

**Edit:**

1. **Please include an ethics statement.**

   Research involving human subjects, human material, or human data, must have been performed in accordance with the Declaration of Helsinki and must have been approved by an appropriate ethics committee. A statement detailing what ethical approval has been obtained, including the name of the ethics committee and the reference number where appropriate, must appear in all manuscripts.

   Response: We have included the ethics statement in “methods” section. Ethical approval was given by the medical ethics committee of the third affiliated hospital of Sun Yat-sen University with the following reference number:[2007]33.

2. **Please include the name of the institutional review board that approved this study in the manuscript.**

   Response: We have include the name of the institutional review board (the medical ethics committee of the third affiliated hospital of Sun Yat-sen University) that approved this study in the manuscript.

3. After reading through your manuscript, we feel that the quality of written English needs to be improved before the manuscript can be considered further. We advise you to seek the assistance of a fluent English speaking colleague, or to have a professional editing service correct your language. Please ensure that particular attention is paid to the abstract. Please also ensure that your revised manuscript conforms to the journal style.

   Response: We have employed a professional scientific editing service (Praveen Paul, Edanz) to fix the grammatical errors and improve the overall readability of the text. We have also revised our manuscript and it has conformed to the journal style.

**Response to reviewer 1 (ilya kister)**

**Major revision:**

1. The authors have not studied the association of TB and NMO, but only of ‘active pulmonary TB’ and NMO. This point needs to be emphasized. It is possible that history of distant or treated TB is a ‘risk factor’ for development of NMO later on in life. This paper does not address this broader association. If the
authors have the data on “TB history” of their NMO pts and controls (and not just active PTB), it would be helpful to include it. Even if results are accepted, there may still be an association between TB and NMO.

Response: The reviewer’s comment is highly appreciated. However, due to the limitation of retrospective design, we have no more data of history of distant TB or treated TB in our series. We have emphasized this limitation in “Conclusion” section.

2. It may be difficult, as the authors acknowledge, to know what the etiology of myelitis is in a patient with TB. Absence of NMO antibody in and of itself is insufficient to disprove that myelitis is not NMO related. As many 30% of NMO cases are NMO IgG negative (at least with ELISA tests), and it is not clear whether how many pts with TB myelitis/optic neuritis in this series were tested.

Response: According to the suggestion, we have included these detailed data in Table 2.

3. Absence of relapses in TB myelitis cases is difficult to interpret as we don’t know how long the patients have been followed. Perhaps some of these ‘TB myelitis’ patients would relapse if followed long enough. I think duration of follow up is important to variable that needs to be included if available (or discussed explicitly even if unavailable).

Response: The reviewer’s comments are most helpful. We have got follow-up data in most of our patients by telephone and outpatient system and have included the follow-up duration in Table 2.

4. It seems that the strongest argument against the 10 TB myelitis cases being related to NMO or other autoimmune disease was presence of meningeal enhancement and concomitant tuberculoma. It was not clear to me how many of these 10 pts had one or both of these findings.

Response: We have added these information in “Results” section. Ten TBM patients had myelitis (spinal meningitis, n=2; tuberculoma, n=1; meningitis combined with tuberculoma, n=2; focal spinal lesions with hydrocephalus, meningitis or tuberculoma in brain MRI, n=2; clinical manifestations indicating myelitis, n=3)

Minor comments on ‘Methods’ section

1. “All patients with NMO fulfilled the 2006 Wingerchuk criteria 10 (the 1999 Wingerchuk diagnostic criteria were used for several cases owing to a lack of NMO-IgG data11).” How many were diagnosed by 2006 criteria and how many by 1999 only?
Response: We have described the number of NMO cases fulfilling 2006 criteria and 1999 criteria respectively in “Results” section. (sixteen-seven patients were diagnosed by 2006 criteria and twenty-one by 1999 criteria)

2. “Because of distinct pathogenesis and therapy, the disorder related-“NMO-like” syndrome, which includes CNS infection and systemic autoimmune disorders with a focus on the spinal cord and optic nerves, was excluded if there is.” I am not sure what NMO-like syndrome refer to. Are these ‘NMO spectrum disorders’ – eg recurrent myelitis +NMO ab, etc?

Response: Yes, it mainly refers to NMOSD, especially optic neuritis or longitudinally extensive myelitis associated with systemic autoimmune disease. To make sure that NMO patients included in our study is idiopathic ones, we must excluded possible disorder related-“NMO-like” syndrome. Disorder related-“NMO-like syndrome” here refers to longitudinal extensive myelitis or optic neuritis, similar to clinical symptom of NMO, developing during the course of other diseases (systemic autoimmune disorders and other explanation for the syndrome suggested by Miller (see reference 12)). We have revised this statement accordingly. (Patients with evidence for sarcoidosis, vasculitis, clinically manifest systemic lupus erythematosus or Sjogren’s syndrome, or other explanation for optic neuritis or myelitis were excluded.)

3. Which test was used to determine NMO IgG? Cell-based, ELISA, etc?

Response: It has been revised in “Methods” section. Serum NMO-IgG antibodies were tested using aquaporin 4-transfected cells from a commercial sampling kit (EUROIMMUN AG, Lu’beck, Germany) according to the manufacturer’s instructions.

Minor comments on ‘Results’ section

1. “Brain MRI showed small ischemic lesions” – Do authors mean ‘non-specific white matter lesions’. These may or may not be ischemic.

Response: Thanks for the comments. It has been revised in “Results” section.

2. “Some special MRI sequences including diffusion and magnetic resonance spectroscopy (MRS) were not performed, as they were not available during that period. However, considering the clinical data and consultations with the neurosurgeon, intramedullary tuberculoma could be excluded.” Unclear how consultation with neurosurgeon helped to exclude tuberculoma.

Response: Excluding tuberculoma was mainly based on the MRI features (no oval lesions with low T1-weighted image signal, typical ‘target sign’ T2-weighted image
signal, and nodular or rim enhancement) and discussion with neurosurgeons, and the later follow-up

3. “serum positive” – seropositive

Response: It has been revised in “Results” section.

4. “tuberculoma (42.9%) in spinal cord was common” - it would be helpful to define key imaging features of tuberculoma

Response: We have defined the key imaging features of tuberculoma in “Results” section.

5. “Six patients received additional immunosuppressants in remission” – this is surprising. The standard of care in most countries is to treat all NMO patients with immunosuppressants – any reason why only 6/88 pts were treated?

Response: NMO was thought to be a variant of MS by most Chinese neurologists until recently, and the immunosuppressants were not widely prescribed before.

6. “All TBM patients received anti-tuberculosis therapy “ – what did it consist of?

Response: we have described the detailed information in “Results” section. All TBM patients received anti-tuberculosis therapy (isoniazid, rifampicin, ethambutol plus pyrazinamide or streptomycin for 86 patients and isoniazid, rifampicin, ethambutol plus second-line drugs for other six patients).

7. Tables “Linear sign” – what is it?

Response: we have defined “linear lesions” in “Methods” section. (Linear lesions were defined on T2-weighted imaging on MRI as: 1) i) consecutive linear shape lesions on sagittal plane; ii) symmetric, with a preferential involvement in the central gray matter on axial plane, according to Misu et al)

Comments on 'Discussion'

1. “we report limited data showing that NMO-IgG was only detected in NMO patients, and not in patients with TBM” – is there a degree of tautology involved? If a patient with myelitis had PTB and no NMO, he will likely be diagnosed as TBM, while if he did have NMO Ab, he would be diagnosed as NMO?

Response: This sentence was removed.

Response to reviewer 2 (Diego Franciotto)
1. **Level of interest: An article of limited interest**

Response: Thanks for reviewer’s comments. We have emphasized the scientific value of our study in the manuscript. Although an association between NMO and TB has been suggested in a number of reports from different geographical regions, a definite association between the two conditions has not been conclusively demonstrated. Further investigation and clarification would be helpful in the diagnosis and treatment of patients who develop ‘NMO-like’ symptoms (longitudinal extensive myelitis and optic neuritis) during the course of TB.

2. **The authors compared demography, course, and CSF and neuroimaging features of NMO patients with those of patients with tuberculous meningitis (TBM), and found obvious and expected differences [e.g., NMO patients showed a higher relapse rate (75.0%) vs TBM patients (0%)]. Indeed, the two pathological conditions can be easily diagnosed presently, given the current knowledge and technologies.**

Response: Thanks for the comments. Although most of TBM patients, as the reviewer mentioned, can be differentiated from NMO patients, a tiny minority of TBM may incidentally mimic NMO in some aspects. NMO-IgG is high specific for diagnosis of NMO[ref 1, 2, 10], but NMO-IgG negativity cannot rule out its diagnosis absolutely. This is because NMO-IgG levels and even serostatus can vary during follow-up[ref 28]. Thus, diseases that mimic NMO, including CNS infections with a focus on the spinal cord and optic nerves, still have the potential to be diagnosed as NMO with NMO-IgG negativity. It’s an issue of clinical value whether NMO-like symptoms that develop during the course of TB (especially with NMO-IgG negativity) should be considered and diagnosed as NMO, because these two pathological conditions need different therapy. Our study, though with some disadvantages, provide some information and presumption about the association between these two pathological conditions.

We have reorganized this part of methods, results and discussion. We hope our efforts can make the reviewer satisfied.

3. **Quality of written English: Needs some language corrections before being Published**

Response: We have employed a professional scientific editing service (Praveen Paul, Edanz) to fix the grammatical errors and improve the overall readability of the text.

Yours sincerely,
Xueqiang HU