Author's response to reviews

Title: Clinical and electrophysiological features of post-traumatic Guillain-Barré syndrome

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Author’s response to reviews:

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Tjalf Ziemssen
Editorial Office
BMC Neurology

Re: Manuscript # NURL-D-16-00516

Dear Editor:

Thank you for your letter sent on 30/12/2016 regarding our manuscript “Clinical and electrophysiological features of post-traumatic Guillain-Barré syndrome”. We also appreciate the reviewers’ constructive and overall positive comments. Guided by their feedback, we have consulted an extensive amount of references which specifically address all the reviewers’ concerns. All the added content is incorporated into the revised manuscript, and these are indicated by tracked changes.

We are aware that scientific rigor is a major focus for the readers of BMC Neurology. Therefore, firstly, we apologize for mistakes in the original manuscript such as the wrong word
“havedescribed” and misusing inappropriate words. In addition, we added Declarations in the manuscript. We also described the electrodiagnostic study results as presented by numbers in a table instead of the graph presentation. These issues have been addressed in the revised version. Moreover, following the Reviewer’s suggestion, we performed a definition of post-traumatic GBS and added more details of patients.

With these appropriate revisions, we believe that we have thoroughly addressed each of the reviewers’ concerns. Importantly, we have now provided new information and clarified several issues that caused some confusion in the original submission.

Below, please find a point-by-point response to reviewers’ comments.

We thank you for your time and consideration in re-evaluating the manuscript.

Sincerely,

Junwei Hao, PhD.
(On behalf of all authors)

Point-by-point reply to the Reviewers’ comments

Reviewer #1:

1. Abstract
   - ‘also manifested damaged cranial …´ correct to ‘…also manifested with cranial…´
   - ‘and the short term prognosis was poor´ correct to ‘.. and the short term prognosis is poor …´
   - I am not sure whether ‘prevent morbidity and delay mortality´ is the right goal for GBS patients. I would write prevent morbidity and mortality.

Results
   - Page 8 Line 13: ‘notedshown’? Please correct
   - Page 9 Line 1 I would refer to ‘reduced F wave persistence´ and not ‘incidence´
   - Page 10 line 5 ‘havedescribed´ please correct
   - Line 19 Page 10 ‘most physician´ most physicians
- Line 22-23 ‘also’ is mentioned two times.

Reply: We apologize for our carelessness and thank the reviewer for noticing this. We have corrected the mistake in the revised manuscript.

2. Most of the patients had a high HFGS at discharge. Was there a control CSF examination performed at the phase of clinical recovery? A stable protein on CSF would indicate an ineffective treatment.

Reply: This is truly a valid concern and we thank the reviewer for pointing this out. Because of the retrospective nature of data collection, without a control CSF examination is indeed the limitation of our study. Meanwhile, some patients refused to undergo the invasive examination again at the phase of clinical recovery. Following the suggestion, we plan to undertake another study with a control examination in the future.

3. Was there a prolonged hospitalisation in an intensive care unit after the ‘traumatic event (surgery etc.)’ and before the begin of GBS for these six patients?

Reply: We thank the reviewers for pointing this out. Consistent with prior reports presented in Table 4, the average interval between trauma and the onset of GBS symptoms ranged from 8 to 14 days (average of 11.3 days).

4. The pathogenic role of most anti-ganglioside antibodies is not yet clearly recognised. Were there examinations for IgM GM1 antibodies?

Reply: We thank the reviewers for pointing this out. The acute phase serum of all patients was examined for anti-ganglioside antibodies. Although there remains some controversy regarding the relationship between the anti-ganglioside antibodies and GBS, some researchers suggest IgG antibodies are considered pathological[1]. In addition, tests for detecting these antibodies, especially those of the IgM class, have a limited positive value[2]. So, only IgG antibodies were measured in our study.

5. At the conclusions you refer to short term survival. Did any of the patients die?

Reply: We are sorry for using the inappropriate words and thank the reviewer for raising this. Following this suggestion, we have changed the statement in the revised manuscript.

The clinical presentations and laboratory findings described here played an important part in the diagnosis of post-traumatic GBS as likely immune-response related nerve damage. The characteristic outcome of the six patients studied was antecedent trauma, extremely severe disease, a poor prognosis and a delayed recovery. Such patients often have the axonal damage recorded here. Therefore, electrophysiological study is important for the diagnosis and identification of different subtypes of GBS. This means of establishing an early diagnosis and treatment may prevent morbidity and improve prognosis.
6. I would modify the discussion part on the pathogenetic background of post-trauma GBS in order to explain more clearly that the combination of immunosuppression after trauma, antecedent infections and genetic vulnerability may lead to autoimmune acute neuropathy in these cases.

Reply: This is truly a valid concern and we thank the reviewer for pointing this out. According to the reviewer’s suggestion, we improve the study and provide a modified statement in the revised manuscript.

Given the heterogeneity of the patients with post-traumatic GBS, it is postulated that the underlying mechanisms are based on a trauma-related affection of the cellular and humoral immunosystem. Trauma often leads to a transient immunosuppression and promotes clinical or subclinical exogenous infection. Immunosuppression could induce an alteration of immune tolerance and exogenous infection could elicit cross-reactive antibodies[3]. Both could promote an autoimmune attack on peripheral nerves and result in the occurrence of axonal-type GBS.

7. Why were high dose corticosteroids given for patient 4, as it already known that GBS does not actually respond on them?

Reply: We thank the reviewer for pointing this out. Actually, the patient 4 was presented with rapidly progressive weakness and severe respiratory failure after falling which made it difficult for us to distinguish GBS from an acute spinal cord injury. After his conditions was stable, we performed MRI and EMG which helped us diagnose GBS.

8. Why was there no plasmapheresis performed?

Reply: We thank the reviewer for raising this issue. Intravenous immunoglobulin and plasma exchange are efficacious treatments[2, 4]. No difference was found between IVIG and PE with respect to improvement in disability grade, the duration of mechanical ventilation, mortality, or residual disability[5]. IVIG has replaced PE as the preferred treatment in our center because of its greater convenience and availability.

9. What was the dosage of IVIG used?

Reply: This is truly a valid concern and we are sorry for describing it not clearly. Indeed, all patients analyzed in this study were treated with IVIG at a dose of 0.4 g/kg for 5 days[2, 5, 6]. We have described it in the part of Treatment, moderate improvement and outcomes.

Once GBS was confirmed, treatment with intravenous human immunoglobulin (and a large dose of corticosteroids in patient #4) was performed at a dose of 0.4 g/kg for 5 days.

10. As the electromyography was performed 10-14 days after symptom begin (which means at the nadir for most patients), I am not sure that the conclusion regarding the axonal character of the polyneuropathy is right. For some patients with very low cMAP at this time point, it could have been an aggressive demyelinating polyneuropathy at the beginning. Prolonged F wave latencies and the reduced F-wave persistence are an indication of demyelination.
Reply: We thank the reviewer for raising this issue. Because of the retrospective design of the data, needle examination was not performed. In our study, distal CMAP amplitude reduction was prominent in motor nerves, while distal latency and nerve conduction velocity were normal or slightly abnormal. The reduction of CMAP amplitudes was more severe than slowing of motor conduction, which were consistent with an axonal form of GBS[2, 7]. Although the underlying mechanism may be different from AIDP, such conduction abnormalities in the axonal type GBS may result in electrical inhomogeneity similar to that observed in demyelination. Conduction failure in the acute phase of axonal GBS has been attributed to lowered safety factors due to a dysfunction of the ion channels or due to microstructural changes at the nodes of Ranvier or paranodal regions caused by anti-ganglioside antibodies.

Reviewer #2:

1. In this manuscript, the authors describe five cases with the so-called post-traumatic GBS. Overall, the English is poor and needs extensive editing.

Reply: This is truly a valid concern and we thank the reviewers for pointing this out. We have invited a native speaker to help us improve the manuscript.

2. How were the patients detected? did the review the clinical data from all GBS patients from 2014-2016 and you found these cases? How many GBS patients were diagnosed in this time period in your hospital?

Reply: We thank the reviewers for pointing this out. We have added the specific criteria for GBS in Table 1 in the revised manuscript. Additionally, we apologize for describing the study’s methods not clearly. Our hospital is the biggest general hospital in the Tianjin city with a population of 16,000,000 inhabitants and provide acute neurological care for patients who are 16 years or older. Patents with GBS are treated only by neurologists in our city. Indeed, our group creates a database of GBS which has been recorded more than 200 patients who fulfilled the diagnostic criteria for GBS since 2014. We performed a retrospective analysis of these patients and collected 6 cases with GBS after trauma. Following the suggestion of reviewer, we have clarified this point in the Methods part.

4. The term "post-traumatic GBS" doesn't appear in the literature and has not been defined. So, first of all, we need a definition. The type of trauma is shown in the table; two are better defined as post-surgical, one is abortion, one mild traumatic brain injury (how mild? concussion, or just a tap on the head0. the other two are chest trauma and a fracture; again severity not mentioned. What was the situation of the patients after the trauma? sepsis? ICU admission or a critical situation? These all has to be clarified.

Reply: We thank the reviewer for raising this issue. Trauma is defined as any physical damage to the body caused by violence or accident or fracture etc. The concept of post-traumatic GBS was recently introduced and defined as GBS triggered by no risk factors other than trauma. The condition seems to occur after various types of trauma. In our study, post-traumatic patients include cases with post-surgery and post-injury. Although antecedent trauma has been described
to trigger GBS, its evidence is poor and based on case reports only[3]. The true incidence and causes of these processes are uncertain. The patients described here after trauma and before first symptom of GBS were alert and oriented with stable vital signs and without focal neurological deficits. No complications occurred before first symptom of GBS. The patient 2 was admitted to another hospital with a closed head injury after falling. The results of cranial CT imaging and magnetic resonance imaging were normal. The patient 4 was admitted with rib fracture after an accident. The results of chest CT revealed that the lung appeared normal. The patient 6 was admitted with femoral fracture after an accident. Following the suggestion of reviewer, we have emphasized it in the part of Characteristics of enrolled patients.

5. The clinical description lacks necessary details. These cases are not classic GBS. cranial nerves are involved in 5/6 but the nerves involved are 3, 4, 6 and 10th cranial nerves and there is no mention of facial nerve which is apparently the most frequently involved nerve. I would definitely need more clinical details.

Reply: We thank the reviewer for raising this issue. In about half of patients with GBS, serum antibodies to various gangliosides have been found in human peripheral nerves, including GM1, GD1b, GQ1b. These gangliosides have a specific tissue distribution in peripheral nerves and are organized in specialized functional microdomains[2, 4, 6]. GQ1b is localized in the paranodes of the human cranial nerves innervating the extraocular muscles[4, 6]. Patients with MFS overlap syndrome frequently have antibodies against GD1b and GQ1b, which are related to ataxia and ophthalmoplegia[2]. In addition, because of the relatively small sample size of our study, the results may not be consistent with that obtained from previous researches. According to the reviewer’s suggestion, we provide more details in the revised manuscript.

6. I would prefer to see the electrodiagnostic study results as presented by numbers in a table instead of the graph presentation.

Reply: We thank the reviewers for pointing this out. We have presented the electrodiagnostic study results by numbers in Table 3 in the revised manuscript.

7. The anti-ganglioside antibody titers and normative data are not provided.

Reply: We thank the reviewer for raising this issue. Because of the retrospective nature of the data and the limitation of our laboratory, anti-ganglioside antibody titers were not detected in our patients. Following the suggestion, we will explore a larger prospective and multi-center study in the future.

8. In the literature review, the authors have found only 35 cases, all after 2008, of which 30 are post-surgical.

Reply: This is truly a valid concern and we thank the reviewer for pointing this out. GBS typically is caused by an autoimmune attack of a peripheral nerve. Infection and vaccination have been considered as associated with its occurrence. Although the condition also occurs after surgery and injury, but its evidence is poor and based on case reports only. Then, we presented six reports with additional reports with post-traumatic GBS in the published literature, reviewed
their clinical features and found that trauma maybe a trigger for GBS and the axonal subtype of GBS after trauma was more common than the demyelinating subtype. In regard to the reported case and limitations of our study, it is hard to affirm whether there actually exists a cause-and-effect relationship between these two entities or if it is simply mere coincidence. We believe that further studies regarding the complex physiopathogenesis of the GBS will clarify such a singular and peculiar association. This first-ever reported case series of ganglioside-associated GBS after trauma may alert us to consideration of this diagnosis in patients with paralysis after trauma.

Editorial Policies:

1. In accordance with BioMed Central editorial policies and formatting guidelines, all manuscript submissions to BMC Neurology must contain a Declarations section which includes the mandatory sub-sections listed below. Please refer to the journal's Submission Guidelines web page for information regarding the criteria for each sub-section.

Reply: We are sorry for missing the Declarations section as per Journal format requirements. We have added in the reviewed manuscript.

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References


