Author’s response to reviews

Title: Case Report: GABAB receptor encephalitis in a patient diagnosed with Amyotrophic Lateral Sclerosis

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Version: 2 Date: 23 Aug 2018

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Response to Reviewers:

Editor Comments: Thank you for the submission of your work. At your convenience please see the referee comments below. This is an interesting and important report on clinical phenotype of GABA B receptor encephalitis which would be useful to the neurological community but require additional details of the clinical presentation, more specifically details needed to help conclude if the patient met clinical criteria for ALS and details of the assay used. If the patient did not meet El Escorial Criteria for ALS, as there are several atypical features listed in the clinical presentation for ALS, this should be addressed and conclusions regarding suggesting testing routine testing for GABA B encephalitis in ALS patients be tempered. We look forward to receiving your revised manuscript.

> We thank the Editor for the overall positive judgement. Our detailed response (please see below) addresses all points raised by the reviewers.

Tim Hagenacker (Reviewer 1):

The authors describe an interesting case which addresses a clinically relevant question. If there new forms of ALS-phenotypes which are caused by autoantibody production this suggests immunotherapies as treatment option. Although the manuscript describes the case in detail, I have some concerns that has to be added, or addressed in the discussion.

Has a tumor been ruled out by other methods, than CT-scan? PET? Autopsy? Breast radiography?

> A tumor-associated MND was not suspected initially. Therefore, only a whole body CT was performed. We added to the text that this CT was done with contrast agent.
Has a immunofixation been performed to rule out a lymphoma which is known to cause ALS-phenotype as well?

>Immunofixation was unsuspicious; this information has been added to the manuscript.

Please give where GABA-B ab has been tested? In which laboratory, which assay has been used?

>The antibody assay was performed in the commercial laboratory “Euroimmun” in Lübeck, Germany. It is a cell-based assay with GABA-B-R-expressing HEK cells. This information has been added to the manuscript.

Minor: l. 39-40: I think here is meant nerve conduction studies as well as myogramm. In Detail a electromyogramm does not offer insights in sesnory nerve function.

> We fully agree with the reviewer and changed the sentence accordingly. It now reads “Electromyography showed generalized acute denervation and chronic neurogenic changes”.

Defne Amado (Reviewer 2):

This is an interesting and unfortunate case, and was very interesting to read. The English was clear and the presentation straightforward. This extends the clinical presentation of GABA B encephalitis in clinically meaningful ways and will be important in assisting neurologists with diagnosing this relatively recently discovered (and likely under-diagnosed) condition. My concerns mainly center around the ALS component of the diagnosis, which is central to the paper and its conclusions. I do not feel an adequate case was made for a diagnosis of ALS. To me, the clinical presentation sounds like a case of autoimmune encephalitis that evolved to attack the peripheral sensory and motor nerves (in addition to the cerebellum and cognitive regions - so a multifocal general neuronal attack). There is at least one case report of GABA B autoimmune disease causing a sensory motor neuropathy (in that particular case, with anti-Hu antibodies), and in the case presented here, the only EMG data that are discussed involved both sensory and motor nerves, which both pre-date the ALS-like presentation and are atypical for ALS.

> We fully agree that it is more likely that the patient suffered from GABA-B-R encephalitis and as part of the encephalitis developed symptoms that fulfilled ALS criteria (see below). To clarify this point, we changed the passage in the discussion accordingly. It now reads “…we assume that the reported patient primarily developed GABABR encephalitis followed by a secondary manifestation of clinical ALS symptoms”. It is important to note, that the patient did not have clinical symptoms of sensory neuropathy and that the motor neuropathy clearly dominated in nerve conduction studies. The initial EMG actually showed pure motor neuropathy! We accordingly changed the text now stating “motor-dominant neuropathy”.
In addition, I did not see convincing evidence of upper motor neuron signs. I saw a mention of "slight limb spasticity" but this seems insufficient as a basis for diagnosis of ALS. Questions that would clarify this: -Was the patient hyperreflexic? -Was there true spasticity? -ALS-wise, was there spread between regions or was everything affected at once? (This is unclear in the manuscript - it says "fasciculations appeared in all extremities and tongue.... paresis and atrophy of limbs, shoulder girdle and hand muscles... evolved." Does this mean worsened, or spread from one region to another as is classic in ALS?)

>As suggested by the reviewer, we added further clinical details regarding reflexes, spasticity, spreading that help to follow the differential diagnosis of ALS in this case. It now reads in the case presentation: “Neurologic examination revealed a pseudobulbar syndrome resulting in dysarthria and mild dysphagia,...” and “Fasciculations appeared at the trunk and all extremities showing an asymmetric but generalized spreading pattern. Bulbar symptoms, paresis and atrophy of limbs, shoulder girdle and hand muscles evolved. There was an increased muscle tone without hyperreflexia. MEPs remained physiological”.

Was an EMG repeated when she presented with fasciculations in extremities and tongue, and importantly, at that time, was there sensory involvement? What about clinically - did the patient have sensory complaints or have sensory loss on neurologic exam? -Most specifically: Did the patient meet El Escorial criteria for a diagnosis of ALS?

>We added the clinical information requested by the reviewer. As described above, the patient did not have clinical symptoms of sensory neuropathy, and sensory neuropathy was (if at all present) clearly inferior to motor neuropathy. The data added to the manuscript now help to recapitulate that the diagnosis of probable ALS was made according to the revised El Escorial criteria. It now reads in the case presentation “The diagnosis of ALS was made (probable ALS according to revised El Escorial criteria) and treatment with riluzole started”.

I am not convinced from reading this manuscript that this could not just be called GABA B encephalitis with severe sensory motor axonal neuropathy, which would also be very interesting, but would require re-framing the paper. Importantly, many patients with GABA B encephalitis present with other concurrent autoantibodies and I did not see these mentioned in CSF or serum testing; the presence of VGKC or CASPR2 antibodies, for instance, would help to explain neuropathic aspects of the case.

>Please see the points above for our changes regarding the diagnostic criteria for ALS and the clarification about the lack of sensory neuropathy. The patient samples were (post mortem) analyzed not only for GABA-B-R antibodies, but also for approx. 30 further neuropil and onconeuronal antibodies which all returned negative. This has been added to the text: “…of GABABR IgG antibodies, while approximately 30 further antibodies (including LGII, Caspr2, GABAA and AMPA receptor) were negative”. We did not name all 30 antibodies for space restrictions.
In terms of the GABA B encephalitis component itself, there are some quite atypical features of this case as well. Nearly all GABA B patients present with seizures and fever (https://www.ncbi.nlm.nih.gov/pubmed/29166136; https://www.ncbi.nlm.nih.gov/pubmed/28974152), and these were not mentioned; if the patient did not manifest with these symptoms, they should at least be mentioned as a pertinent negative, as this is atypical.

> As suggested by the reviewer, we added the information to the manuscript that the patient did not have fever or epileptic seizures

Was an EEG done to confirm that the patient was not seizing? Additionally, the prominent cerebellar findings are unusual; another autoantibody could perhaps explain the cerebellar findings. I am not sure adequate autoantibody testing was done to confirm that all of the patient's clinical manifestations are due to the GABA B antibodies. If further testing is not possible, these alternate/additional possibilities should at least be mentioned in the discussion.

> There were no epileptiform discharges in repeated EEGs, this information has been added to the case presentation. The cerebellar findings are not characteristic, but were reported before, e.g. in the cited cases that benefited from immunotherapy (ref. #2, Hoftberger R et al., ref. #3, Jarius S et al., ref. #4, Mundiyanapurath S et al.). It is unlikely that another autoantibody accounted for the cerebellar syndrome, as all major autoantibodies were excluded, such as the “medusa head ataxia” antibodies anti-Yo, -Tr/DNER, -PCA2, -mGluR1, -Homer3, -ITPR1 or -ARHGAP26. We now state in the paper that we tested for approx. 30 further neuropil and onconeuronal antibodies which all returned negative. We did not name all 30 antibodies for space restrictions.

In terms of data presentation, the MRI data presented do not cover the regions that would be most interesting in a case of GABA B encephalitis, specifically the limbic regions; in the case presented, given the prominent dysmetria and saccadic eye movements it would be important to show the cerebellum as well. The abnormalities shown are typical for a 75-year-old patient and likely represent chronic small vessel ischemic changes; it is not clear that these are pathologically related to the process affecting her.

> As suggested by the reviewer, we modified the image panel and added MRI figures of the temporal lobe and the cerebellum.

In addition, given the diagnosis under consideration, EMG data should be a bit more detailed; and the MEP data is insufficiently described. Different components of the MEP are differentially affected in ALS (https://www.ncbi.nlm.nih.gov/pubmed/8891476; https://www.ncbi.nlm.nih.gov/pubmed/28068522) and I am not sure if this data is meant to support or refute the diagnosis (it does not support it).

> As suggested, we changed the EMG sentence which now reads “Electromyography showed generalized acute denervation and chronic neurogenic changes”. We did not add further data on
the MEP as we then would need to discard more important clinical information to keep with the word limit. Also, we feel that the additional clinical information in the revised version of the case report make further MEP details dispensable. From our experience, MEPs can well be normal in ALS, depending also on the time of disease.

In the discussion, I do not think it is fair to say "we cannot unambiguously determine whether she suffered... from ALS with laboratory abnormalities with unknown significance." I don't think that's a diagnostic possibility in the case presented. The patient had severe multisystem neurologic signs and symptoms that preceded the development of an ALS-like syndrome, and drawing this conclusion would mean disregarding those symptoms, and chalking the very-high GABA B antibody titer (which IS associated with at least some of those symptoms) up to "a lab abnormality of uncertain significance" does not seem accurate.

> We agree that the term “ALS with laboratory abnormalities with unknown significance” is not appropriate here and removed it. The respective paragraph was modified and now reads “Due to post-mortem identification of high-level GABABR autoantibodies and the lack of immunotherapy, we cannot unambiguously determine whether the patient suffered from autoimmune encephalitis. Given the similarity to published patients, we assume that our patient primarily developed GABABR encephalitis…”.

In summary, I think these are highly interesting findings with high general interest and clinical relevance, but require clarification, both in terms of workup and discussion of diagnostic considerations.

> We thank the reviewer for the positive judgement of our case report.