Reviewer’s report

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

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Reviewer: Defne Amado

Reviewer’s report:

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. 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?)

- 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?

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.

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. 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.

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. 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).

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.

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.

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No

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