Reviewer’s report

Title: Novel variants in a patient with late-onset hyperprolinemia type II: diagnostic key for status epilepticus and lactic acidosis

Version: 0 Date: 24 Oct 2019

Reviewer: Bjørnar Hassel

Reviewer's report:

Motte et al "A case report: Novel mutations in a late-onset hyperprolinemia type II: diagnostic key by status epilepticus and lactic acidosis"

This is a description of a patient whose epileptiform seizures may have been caused by hyperprolinemia, leading to P5C accumulation, which in turn may quench pyridoxine and cause pyridoxine-responsive seizures. The authors detected very high levels of proline and hydroxyproline in blood, urine, and CSF, but not P5C, in this elderly woman during an episode characterized by metabolic decompensation. Treatment with vitamin B6 (pyridoxine) appears to have helped. The paper is of potential interest, both because of the late onset nature of the patient's epilepsy and because of the genetic findings in the ALDH4A1 gene. However, the paper has been submitted prematurely, as the language leaves much to be desired and because the discussion appears to ignore the genetic findings that need discussion. The authors should follow the outline of the abstract through the rest of their communication.

Some examples of language problems:

Case presentation:
"...due to sudden difficulties in with (delete "in", insert "with") swallowing and (delete comma, insert "and") speech, slight vertical and horizontal eye movement disorder (Please specify: restricted movement? Ophtalmoplegia?), dysesthesia of the limbs ("pins and needles" Please specify distribution: glove and stocking?), and (insert "and") generalized areflexia. Muscle strength was normal but without any paresis."
Please use the full name: Miller Fisher syndrome.
Cerebral MRI showed no pathological findings, (comma) and a (delete "a") therapy with levetiracetam was started."
"accompanied from a vertical eye movement disorder with by vertical eye movement paresis (Ophtalmoplegia or gaze paresis?), a lactic acidosis..."
Lactate levels should be given with the same unit in serum and CSF, preferably in mmol/L. Divide mg/dL values by 11.2 to obtain mmol/L. (Lactate has mw 112, and you have to correct for the dL vs L).
"...no signs for of (delete "for", insert "of")a Wolff-Parkinson-White syndrome."
Correct "hyperkaliemia» to «hyperkalemia»

Discussion/Conclusion
The discussion should be re-written. As it reads now, the authors are looking for metabolic explanations for the disease and avoid discussing the genetic alterations they have identified. The discussion should focus on whether these are indeed mutations and whether they are pathogenic.

Table 1. (Amino acids in blood, urine and CSF).
Please provide a legend that includes units, presumably μmol/L.
The reference value for glutamate in blood ("glutamine acid") is clearly wrong. Specify also if these values are obtained in the fasted state or not. Most values are not relevant; proline and hydroxyproline are the relevant ones and could be given in the text, provided they are correct: Was U-proline actually >45 mmol/L?

Figure 1: The authors should expand the evidence in favor of these genetic findings being mutations and pathogenic. This should be done in the discussion section.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Unable to assess

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

**Quality of written English**
Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

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