Reviewer's report

Title: Long-term continuous N-carbamylglutamate treatment in frequently decompensated propionic acidemia: a case report

Version: 1 Date: 08 Jan 2018

Reviewer: Vicente Rubio Zamora

Reviewer's report:

1. Do you believe the case report is authentic?

Yes

2. Do you have any ethical concerns? Please consider if local Institutional Review Board approval or ethical approval was obtained (if appropriate) and if the patient (or their parent or guardian in the case of children under 18) gave written, informed consent to publish this case and any accompanying images. A statement to this effect should appear in the manuscript.

Comments: I already gave my answer for the original submission. No concerns

3. Does the Introduction explain the relevance of the case to the medical literature?

Yes

4. Does the article report the following information? Where information is missing, please specify.

a. The relevant patient information, including:

   - De-identified demographic information (age, gender, ethnicity)
   - Main symptoms of the patient
   - Medical, family and psychosocial history
   - Relevant past interventions and their outcomes

My previous concerns on this question have been answered
b. The relevant physical examination findings

My previous concern on this question has been satisfactorily addressed

c. Important dates and times in this case (if appropriate, organized as a timeline via a figure or table); if specific dates could lead to patient identification, consider including time relevant to initial presentation, i.e. initial presentation at \( T = 0 \), follow up at \( T = 1 \) month.

The new table 1 addresses my previous concern with respect to this issue.

d. Diagnostic assessments, including:
   - Diagnostic methods
   - Challenges (e.g., financial, language/cultural)
   - Reasoning and prognostic characteristics (e.g., staging), where applicable

OK

e. Types and mechanism of intervention

OK

f. A summary of the clinical course of all follow-up visits

Comments: Although I think that a figure would have been much more eloquent and easy to perceive, the fact is that Table 1 covers my previous query on this question.

5. Is the interpretation (discussion and conclusion) well balanced and supported by the case presented?

Comments: Please see my proposals listed in question 9 below

6. Is the anonymity of the patient protected? Please consider any identifying information in images such as facial features or nametags, whether the patient is named etc. If not, please detail below.

Yes
7. Is the Abstract representative of the case presented?

Comments: Yes. However, I continue not to agree on the use of "first" in lines 16-17 of the Abstract, particularly after Burlina's work on use for more of one year of NCG for organic acidaemia. Could the authors restate the sentence as follows?: "We report our clinical experience with continuous administration of NCG for 6 years in a patient with PA frequently presenting with hyperammonemia."

8. Does the case represent a useful contribution to the medical literature?

Comments: Yes

9. Additional comments for the author(s)?

I think a number of minor but substantial things deserve attention and change. I list them here:

Page 6, lines 10-17. I have important problems with the text "At 9 years of age, we initiated continuous treatment with oral NCG 100 mg/kg/day. Plasma ammonia levels and acid-base equilibrium normalized. After 6 months, the NCG dose was gradually reduced to a maintenance dosage of 50 mg/kg/day. Since initiation of NCG therapy...." This part of the text is not supported by any presented evidence, since it refers to the 6 months going from 9 years of age to 9.5 years of age. In addition, this sentence appears to imply that NCG normalized the acid-base equilibrium, with no proof given concerning this aspect. I think this part of the text should be more factual. Could it be changed to something like "In view of the frequency of metabolic events with abnormal ammonia levels, we introduced at 9 years of age continuous oral administration of NCG at a dose of 100 mg/kg/ day, although six months later we reduced the daily NCG dose to 50/mg/kg/day. Since initiation of NCG therapy....",

Page 7, line 32. I think that the sentence "We report the first long-term (6 years) clinical experience with continuous administration of NCG in a patient with secondary blockage of N-acetylglutamate synthase due to PA." is an overstatement concerning "the first". In addition, it is too hypothesis-driven concerning the mechanism. Therefore, I urge the authors to replace this sentence by "We report our highly positive clinical experience with continuous administration of NCG for 6 years in a PA patient who presented frequently with hyperammonemia believed to reflect secondary blockage of N-acetylglutamate synthase by PA metabolites [2,3]."

Page 7, lines 42-49, I have problems with the consideration that NCG stabilized multi-organ involvement. I would recommend splitting the sentence as follows: "Treatment was associated with a decrease in plasma ammonia levels and a durable reduction in the frequency of metabolic
decompensations. There were no clinically significant adverse reactions to therapy neither evidence of progress of multi-organ involvement.


Table 1. No admissions are reported from 10 to 15 years of age. Therefore, I find inappropriate to say in the title of this Table "mean ammonia levels at admission" since levels of ammonia are given for the period when there were no admissions. Please correct.

Table 2.

- Title: The expression "Patient characteristics" appears inappropriate. It could be replaced by "Protein and energy intake, body mass index (BMI)"

- Metabolites: I would replace "(μmol/L)" by "(μmol/L, number of measurements)" and then I would give the number of measurements after a comma following the figure for the standard deviation for each metabolite and condition. In this way notes a and b can be eliminated, as well as the strange figures in parentheses given in the column to the left for each metabolite.

- The figures for protein intake in Table 2 do not fit the data for protein intake given in Table 1. Please solve or clarify.

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