Reviewer’s report

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

Version: 0 Date: 19 Sep 2017

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: Such statement was listed in the appropriate part of the manuscript, and the authors stated that the corresponding ethical documents are available to the Editor of the Journal

3. Does the Introduction explain the relevance of the case to the medical literature?
   Yes/No
   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
No detail is given of the initial presentation at 2 days of age. Please describe it in detail, including all biochemical parameters. Or was the condition diagnosed as a newborn screening finding, perhaps with special biochemical surveillance prompted by the unresolved story of the previous sibling?

b. The relevant physical examination findings

In addition to the above, the levels of ammonia throughout the life of the patient should be given, including the levels at each admission.

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.

Not enough detail. As hyperammonemia is a more frequent finding in neonates and infants with organic acidemia than in later presentations, the authors should present at what ages did each admission take place along the life of the patient, both pre and post administration of carbamylglutamate.

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:

I would like to see a figure summarizing the life of the patient: a timeline, with ticks indicating admissions, and superimposed on it, the ammonia level at each admission and at interadmission periods.
5. Is the interpretation (discussion and conclusion) well balanced and supported by the case presented?

Comments:

Although hyperammonemia may be a relevant pathologic determinant in organic acidemias, I believe that this is not usually the main pathogenic manifestation in these disorders. Indeed, the ammonia levels given for this patient, although abnormal, are not extremely high as it may have been the case in a primary hyperammonemia. Therefore it is not clear to me whether the frequent admissions before carbamylglutamate was given were due to hyperammonemia or to the acid-base disturbance and intoxication due to the organic acidemia itself rather than to hyperammonemia. If hyperammonemia was not the major pathological determinant, do the authors imply that carbamylglutamate was beneficial for the organic acidemia itself, resulting in the decreased number of admissions after this drug was instituted? If this were the case, do the authors have a hypothesis on why carbamylglutamate should have any effect on the acidemia itself rather than on its hyperammonemnic manifestations?

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 would remove "the first" from line 5, and I would replace in line 6 "in a patient with secondary blockage of N-acetylglutamate synthase due to PA" by "in a patient with PA frequently presenting hyperammonemia". In addition, in line 10 I would revert the order of the levels of ammonia. There is no detail on multi-organ involvement and therefore, "stabilization of multi-organ involvement" in line 11 of the abstract should be removed.

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

Comments:

It may represent a useful contribution
9. Additional comments for the author(s)?

Please give primary quotations to key papers on the mechanism of NAGS activity interference by propionic acidemia, such as Coude FX, Sweetman L, Nyhan WL. Inhibition by propionyl-coenzyme A of N-acetylglutamate synthetase in rat liver mitochondria. A possible explanation for hyperammonemia in propionic and methylmalonic acidemia. J Clin Invest. 1979 Dec;64(6):1544-51.

and


Level of interest
Please indicate how interesting you found the manuscript:

An article of importance in its field

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

Acceptable
Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

1 & 4 yes. 2, 3, 5 and 6, No.

Because of my lifelong relation with carbamylglutamate (NCG) I am often invited by Orphan Europe (OE) to advise them, to talk in OE-sponsored seminars on biochemical bases of NCG use, including organic acidemia, receiving a fee for it. Nevertheless I feel objective

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal