Author’s response to reviews

Title: Proteinuria as a presenting sign of combined methylmalonic acidemia and homocysteinemia: case report

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Version: 2 Date: 13 May 2020

Author’s response to reviews:

Dear Editor,

We are grateful for the critique and thoughtful suggestions provided by you and reviewers for our manuscript entitled “Proteinuria as a presenting sign of combined methylmalonic acidemia and homocysteinemia: case report”. Based on these comments and suggestions, we have made careful modifications to the original manuscript. All changes made to the text are in red font. We hope that the new manuscript will meet the high standards of your excellent journal. Shown below are our point-by-point responses to the reviewer’s comments/questions.

Response to Reviewer 1:

1. Title should be changed to represent the purpose of report which is the link between Cobalamin C defect (MMACHC) and proteinuria presentation. I suggest changing it to (PROTINURIA AS PRESENTING SIGNS OF COMBINED METHYLMALONIC ACIDURIA AND HOMOCYSTINURIA: CASE REPORT).

Answer: The title has been changed to “Proteinuria as a presenting sign of combined methylmalonic acidemia and homocysteinemia: case report”.
2. Abstract: The author wrote in his abstract that the 2nd case is diagnosed as Imerslund-Gräsbeck syndrome, and in case presentation it was mention that the final diagnosis was Methylmalonic acidemia with hyperhomocysteinemia (MMACHC). It was not clear if the first diagnosis was misdiagnosis as Imerslund-Gräsbeck syndrome or there are two diagnosis at the sometime for case two. If possible, to make it clear in here or don't mention Imerslund-Gräsbeck syndrome in abstract.

Answer: In the Abstract, we have removed mention of the diagnosis of Imerslund–Gräsbeck syndrome.

3. Background: It is better to start the background with hyper-homocystinemia not elevated MMA, there is different mechanism in MUT cases and the associated renal tubulopathy than the hyper-homocysteinia.

Answer: We have described the pathogenesis and clinical manifestations of MMA combined with homocysteinemia in the Background section.

4. Case presentations: All-important finding mentioned, however for completeness it is better to include molecular findings and if other causes of hyper-homocystinemia were excluded including the Methylenetetrahydrofolate reductase C677T mutation. Please write the Plasma amino acid levels if done or not also the form of Vitamin B12 used in patient (dose, frequency and route).

Answer: We have added the results of comprehensive genetic analyses of peripheral blood-derived DNA and renal biopsy, levels of amino acids in blood and urine, as well as the dose, frequency and route of drugs in the two case presentations.

5. Discussion: (According to the type of defect, MMA can be divided into two categories: deficiency of methylmalonyl-CoA mutase and a disorder of metabolism of the coenzyme vitamin B12) delete this in the beginning it is just additional information and now the classifications are wider than this. The discussion is very long for case report. The molecular testing should be mention in the case personation, in this part. The author should go to the point here which is why proteinuria is and the link in his cases which is most likely due to elevated of homocysteine. This was toughed in many previous publication (PMID:20826746 and PMID: 11208992 and PMID: 16162814) those references should be included in the discussion because it explains why elevated homocysteine cause proteinuria (e.g. increased urinary excretion of albumin-bound Hcy).

Answer: Additional information (according to the type of defect, MMA can be divided into two categories: deficiency of methylmalonyl-CoA mutase and a disorder of metabolism of the coenzyme vitamin B12) has been deleted. We have reorganized the Discussion section, including molecular testing and analyses of the relationship between proteinuria and MMA with homocysteinemia in terms of pathology and pathogenesis.

Response to Reviewer 3:

1. This report would be significantly improved if the authors included figure with the renal pathology. These are lacking in the literature on these rare diseases and this would contribute more to the literature.

Answer: We have added pathology images of renal biopsy and discussed the relationship between proteinuria and MMA with homocysteinemia in terms of pathology and pathogenesis.

2. The Background section is too abbreviated needs many more details and references. Same is true for the discussion.

Answer: Similarities and differences between the two cases have been added to the Background and Discussion sections, including pathogenesis at the molecular level, clinical manifestations, treatment and prognosis.
3. Recommend that the authors have an English speaking colleague rereview the manuscript if possible. There are several mistakes that need corrected: a. They refer to urine as hematuria in many places: page 2 line 11, page 3 line 50 and others etc. b. He underwent physical examination should be reworded to: He underwent laboratory examination. c. They refer to genetic analysis when they mean biochemical analysis page 3 line 50. d. Hemochrome = ?hematocrit.

Answer: The native English-speaking scientists of Elixigen (Huntington Beach, CA, USA) helped to edit our manuscript.

4. Dates should not be included as this is somewhat identifiable information.

Answer: We have deleted identifiable information.

5. More details need to be provided about the biochemical values: what were the levels of the C3/C2 ratio? Methylmalonic acid? Did the Imerslund Grasbeck case have low B12?

Answer: We have added specific data for levels of amino acids in blood and urine and vitamin B12 in serum in the two case presentations.

6. More details about the treatment are needed. What type of vitamin B12 was used for treatment and frequency?

Answer: We have added the dose, frequency and route of drugs in the two case presentations.


Answer: We read an article named “A critical reappraisal of dietary practices in methylmalonic acidemia raises concerns about the safety of medical foods. Part 2: cobalamin C deficiency”. Then, we discussed diet management and protein restriction in the Discussion section.

8. For the cblC case it is very rare for the biochemistry to completely resolve. Was the homocysteine remeasured? How is the child's development? Vision?

Answer: In two cases, levels of metabolites in blood and urine were essentially normal after active treatment in the short-term. However, regular follow-up and medication adjustment according to follow-up results in the long-term were necessary. More details about the clinical outcome were added in the case-presentation part of the manuscript.

9. Too much detail is provided when discussion one paper about IGS page 5 lines 2-11. This could be summarized.

Answer: We have summarized the literature about IGS in the Discussion section.

10. Discussion needs to be more extensive. The majority is recapitulation of the results: Page 4 starting Case 1; Page 4 starting Case 2. a. Read and Review literature on the variants identified in MMACHC. b. Read and Review literature about cblC in China it is quite common in one region 1/3000 and there is quite a bit of literature that needs referenced.

Answer: We have reorganized the Discussion section, including the epidemiologic characteristics, molecular testing, and the relationship between proteinuria and MMA with homocysteinemia in terms of pathology and pathogenesis.

10. Please include more details about the clinical outcome in both cases.

Answer: In Case 1, proteinuria reversed, metabolite levels were controlled stably, and development was normal at ~1 year of follow-up. However, after four months, Case 2 continued to show proteinuria (2+) and was then lost to follow-up. More details about the clinical outcome were added in the case-presentation part of the manuscript.

We hope that these revisions are satisfactory, and that the revised version will be acceptable for publication in BMC Medical Genetics. We look forward to hearing from you at your earliest convenience.
Yours faithfully

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