Author’s response to reviews

Title: COL6A1 Mutation Leading to Bethlem Myopathy with Recurrent Hematuria: A Case Report

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Author’s response to reviews:

Dear Editor:

With reference to your decision letter about our manuscript entitled " COL6A1 Mutation Leading to Bethlem Myopathy with Recurrent Hematuria: A Case Report " (NURL-D-18-00403R1).

The authors wish to thank the reviewers for sparing their valuable time in reviewing our manuscript and also their very constructive suggestions. We have undertaken the revision and our responses to comments of reviewers are given below. We have highlighted the points and supplemented data added in this revised manuscript in red color.

We are thankful for giving us such a kind opportunity to revise manuscript for publication in your esteemed journal. In addition, we wish to thank you for your prompt response, and sparing your valuable time and resources to review our manuscript. It will be highly appreciated if you can kindly review and accept our manuscript.

with best regards
Responses to comments

Reviewer: 1

An interesting case report, concentrated on genetics and biochemistry. My comments:

1. the clinical findings are not enough described - e.g., face, tongue, shoulders, swallowing, handgrip, muscle contractions, etc

Response:

We thank the reviewer for the suggestion. We described the clinical findings in more detail and made some additional revision (in red color, p.3, 14 & 18).

2. EMG - polyspike and polyphasic MUP - but no duration and amplitude are added

Response:
The duration of polyphasic MUP was 8.9ms, and the amplitude was 450.7uV. The data were added to revised manuscript.

3. Unfortunately, renal biopsy was not performed.

Response:

We also deeply regret that biopsy was not performed due to his parents having rejected a renal biopsy and the high risk of this operation.

Thank you again for taking time to review our manuscript.

Reviewer: 2

The authors describe a case of a 14-year old boy with bethlem myopathy and recurrent hematuria. In the discussion, the possible connection between bethlem myopathy and hematuria are described, including the involvement of different collagens. This is an interesting idea of clinical relevance. I have some remarks:

1. On page 3, l45 the authors describe a "treatment". Which treatment did the patient receive?

Response:

The patient received idebenone 30mg tid for ten days as treatment, but the muscle weakness failed to improve.

2. Did the authors exclude other reasons for hematuria? Was renal function normal at discharge? As a renal biopsy could not be taken, I doubt that a kidney disease could be excluded properly.

Response:

Renal function was always normal at discharge. We also deeply regret that biopsy was not performed due to his parents having rejected a renal biopsy and the high risk of this operation. Nephrologists and urologists were invited to perform professional clinical assessment, and thoroughly auxiliary examinations have taken, including urine routine, urine red blood cell phase test, renal function, urinary ultrasound, contrast-enhanced CT scan and cystoscopy. The findings of red cell casts and percentage of abnormal erythrocytes confirmed the glomerular origin of hematuria. Cystoscopy was performed with no abnormal signs other than some blood clots. Abdominal ultrasonography and contrast-enhanced CT scan demonstrated no abnormal signs. And we have been followed this patient for 1.5 years, no sign of renal dysfunction was detected. Other reasons for hematuria could be excluded by these investigations.
3. Did the authors perform a collagen VI-stain (i.e. by immunofluorescence)? It would be interesting to know, if the mutation in the COL6A1-gene leads to a loss or reduction of collagen-VI fibers in skeletal muscle tissue.

Response:

We performed a collagen VI-stain by immunohistochemistry as suggested. The collagen-VI fibers were indistinguishable between the patient and the control (Supplementary Figure 1). The mutation does not interfere the protein expression of collagen-VI. This is in keeping with the result of previous study. [1] The amount of protein changes is not obvious, and the semi-quantitative methods such as immune protein imprinting are difficult to detect abnormalities in Bethlem Myopathy. [1]

4. Concerning language: Throughout the manuscript, the language has to be improved. I guess the reader will know, what the authors want to say, and is able to understand it. However, especially the discussion needs revision, as some parts are not clear. One example: "The missense mutation in COL6A1, c.877G>A, in the conserved Gly-X-Y motif in the triple helical domain, altered structure of the α1 chain and then the structure of collagen VI." (p. 4, ll 14-17) To accept the manuscript for publication, the manuscript, especially the "discussion and conclusions"-part, has to be edited.

Response:

We have used a reputable English language editing service of American Journal Experts, which was recommended by editors. Revisions were made and tracked in revised manuscript.

The authors wish to thank you again for your constructive suggestions.

References