

*The responses to the reviewers*

Dear reviewers,

We appreciate your comments concerning our manuscript entitled “The diagnosis of an intermediate case of maple syrup urine disease: A case report” (manuscript number: 80076). We have thoroughly evaluated the comments and have made revisions accordingly.

*Reviewer #1:*

*Scientific Quality: Grade A (Excellent)*

*Language Quality: Grade A (Priority publishing)*

*Conclusion: Accept (High priority)*

*Specific Comments to Authors: Nice paper outlining an mild case of maple syrup urine disease which was missed on presentation and subsequently diagnosed using genomic sequencing. Nothing to change,*

[We thank the reviewer for the careful review.](#)

*Reviewer #2:*

*Scientific Quality: Grade B (Very good)*

*Language Quality: Grade A (Priority publishing)*

*Conclusion: Minor revision*

*Specific Comments to Authors: Please add if the subject at present has maple syrup odor in his urine. If the odor is still absent at this age. Please refer few articles and discuss the reason why the odor could be absent in the urine and if similar findings were reported earlier because the absence of odor led to genetic analyses. Is the subject capable to speak now, what is the response towards stimuli on subject's muscles and lastly if there were seizures were observed at any point of time. Why the subject was suspected of having MSUD on what basis the suspect of MSUD arised? Mental retardation could be caused by numerous genetic disorders it is just a symptom. what were the physical examinations performed at triage that has to be mentioned in manuscript which is absent currently. The signed consent was obtained in the year 2017 if you have lost the subject please mention with year in the manuscript. Better to mention the age up to which the patient was followed up and diagnosis was continued. The term follow up is necessary to be present in the abstract along with the present age. This can be ignored but not the above comments, please add and forward to editor. English is very good although active sentences could be good but often avoided in case series*

*or reports so that part is fine.*

We thank the reviewer for the careful review and helpful comments. We would like to reply orderly:

*(1) Please add if the subject at present has maple syrup odor in his urine. If the odor is still absent at this age. Please refer few articles and discuss the reason why the odor could be absent in the urine and if similar findings were reported earlier because the absence of odor led to genetic analyses.*

During the follow-up until 6 years and 2 months of age, there was still no maple syrup odor in his urine. This description has been added as “Moreover, there was still no maple syrup odor in his urine” (refer to the Line 220-221 of the Supplementary Material—revised manuscript (clean copy)).

The reason why the odor could be absent in the urine has been further discussed as “In two previously reported intermittent patients of MSUD, maple syrup urine odor was noted during the episode of vomiting and diarrhea or high fever [13,14]. In our case, maple syrup odor was never present in his urine. The diagnosis of our case was achieved by a genetic analysis before acute metabolic crisis occurs, underlining the importance of genetic testing in early diagnosis of suspicious cases” (refer to the Line

312-317 of the Supplementary Material—revised manuscript (clean copy)).

*(2) Is the subject capable to speak now, what is the response towards stimuli on subject's muscles and lastly if there were seizures were observed at any point of time.*

The proband could speak now but his language delayed for about 1 year comparing with healthy peers. He had mild hypotonia without any pathological reflex. No seizure was observed.

These descriptions have been added as “He had mild hypotonia without any pathological reflex” (refer to the Line 130-131 of the Supplementary Material—revised manuscript (clean copy)) and “During the follow-up until 6 years and 2 months of age, ... He could walk and run stably but slowly with mild hypotonia. His cognition and language were delayed for about 1 year comparing with healthy peers, but his parents refused an intelligence test. No seizure was observed” (refer to the Line 216-221 of the Supplementary Material—revised manuscript (clean copy)).

*(3) Why the subject was suspected of having MSUD on what basis the suspect of MSUD arised? Mental retardation could be caused by numerous genetic disorders it is just a symptom.*

The first examination of plasma amino acid profiling at 8 months of age showed elevations of BCAAs, which met the specific amino acid

spectrum of MSUD. However, no maple syrup odor was noticed in his urine. Urine organic acid analysis revealed a small amount of 2-OH-isovaleric acid. Thus, the proband was requested a repeated sampling to exclude the impact of dietary factors and further define if he had MSUD. However, the second examination at 1 year and 1 months of age did not support the possible diagnosis of MSUD. The proband was then categorized as unexplained psychomotor retardation.

As mental retardation could be caused by numerous genetic disorders, there was no suspected genetic cause for the proband. Therefore, WES was performed. Surprisingly, the proband was identified as a MSUD patient with pathogenic compound heterozygous variant of the *BCKDHB* gene.

This process was described in the section “CASE PRESENTATION—Laboratory examination — Metabolic analysis” and “CASE PRESENTATION—Laboratory examination—Genetic analysis” (refer to the Line 149-182 of the Supplementary Material—revised manuscript (clean copy)).

*(4) what were the physical examinations performed at triage that has to be mentioned in manuscript which is absent currently.*

The physical examinations include the measurement of weight and height, visual examination and palpation of face, muscle and skeleton, and

auscultation and palpation of viscera. The physical examination has been added as “The proband’s weight and height were normal at presentation (Table 1) [15]. He didn’t show facial dysmorphism. He had mild hypotonia without any pathological reflex. No obvious abnormalities were shown in his skeleton and viscera” (refer to the Line 129-132 of the Supplementary Material—revised manuscript (clean copy)).

*(5) The signed consent was obtained in the year 2017 if you have lost the subject please mention with year in the manuscript. Better to mention the age up to which the patient was followed up and diagnosis was continued. The term follow up is necessary to be present in the abstract along with the present age.*

The follow-up was continued unregularly due to COVID-19. The follow-up at 5 years, 5 years and 8 months, and 6 years and 2 months of age have been added (refer to the section “OUTCOME AND FOLLOW-UP” (Line 216-225) of the Supplementary Material—revised manuscript (clean copy), and the revised tables and figures).

*Reviewer #3:*

*Scientific Quality: Grade B (Very good)*

*Language Quality: Grade B (Minor language polishing)*

*Conclusion: Accept (High priority)*

*Specific Comments to Authors: It was a nicely written case report.*

We thank the reviewer for the careful review. We have further edited our language.