Author’s response to reviews

Title: Stable clinical course in three siblings with late-onset isolated sulfite oxidase deficiency: a case series and literature review.

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Author’s response to reviews:

October 8, 2019

Dear editor,

Thank you very much for consideration of our manuscript “Spontaneous recovery of mild isolated sulfite oxidase deficiency cases in one family: a case series and literature review” (BPED-D-19-00217). We appreciate the thoughtful comments of the reviewers, and have revised the manuscript to reflect their criticisms.

Sincerely,

Yi Qu

Prof. Yi Qu
Department of Pediatrics,
West China Second University Hospital,
Sichuan University,
Response to reviewers

We appreciate the thoughtful comments of the reviewers, and have revised the manuscript to reflect their criticisms (see underlined).

1 Review report 1 (Brian Meyer)

This is a well-written case report. The introduction, laboratory testing and clinical descriptions are concise and informative. Results are interpreted within accepted clinical guidelines. The cases described do expand the clinical phenotype of ISOD and for the first time describe a mild late-onset form of the disease that resolves rather than deteriorates. The authors highlight the clinical significance of such finding and rightly suggest that ISOD be considered as a differential diagnosis in a wider spectrum of cases and importantly that age of onset and severity of symptoms associated with ISOD be carefully considered given the clear identification of mild and even self-resolving phenotypes. Figures, tables and supplementary information are well-presented and relevant. I would recommend some minor English language editing of the manuscript.

Response: We appreciate the reviewer’s encouraging comments. We have edited English language of this manuscript as the reviewer’s suggestion.

2 Reviewer 2 (Parayil Sankaran Bindu)

Authors describe a family of three siblings affected with the mild form of isolated sulfite oxidase deficiency ISOD and highlight "spontaneous recovery/stable clinical course" on follow up. The case is noteworthy since literature on late onset forms of ISOD is scarce and so also case description with long-term follow up. I have the following suggestions to improve the manuscript.

2.1 Title suggest modifying the title as 'stable clinical course in three siblings with late onset ISOD.

Response: We appreciate the reviewer’s suggestion. We have modified the title as “stable clinical course in three siblings with late onset ISOD”

2.2 Abstract Authors should make it clear that there are two forms of the ISOD when describing the background both in the abstract and main manuscript.
The first sentence "…by severe neurological impairment including dystonia, severe psychomotor restriction, refractory seizures, and lens dislocation" needs rewriting as well since dystonia or extrapyramidal manifestations are mainly described in late onset ISOD.

Response: We appreciate the reviewer’s suggestion. We have made it clear that there are two forms of the ISOD when describing the background both in the abstract and main manuscript. Besides, the first sentence has been rewritten according to the reviewer’s suggestion.

2.3 Case studies

2.3.1 Case 1- the case description should be more systematic

- It is worthwhile to mention the birth details

- The time points are not used consistently- November 2010 is mentioned in the beginning, but not later in any time. If you choose to use exact time points use it consistently [use either age at onset/ age of MRI /age at follow up etc.] or remove it.

- Was there any prodromal illness prior to onset of regression / was the diarrheal illness started before regression?

- Regression of motor skills and "mentality"- Can you replace mentality with another suitable word like 'cognition'/cognitive milestones.

Please mention the best milestones achieved premorbidly.

- Please describe the examination findings systematically- Any Dysmorphic features? Comment on eye movements/ tremor/ ataxia /involuntary movements.

- Growth parameters at presentation?

- Was a formal ophthalmological evaluation performed at the time of initial presentation or at any point in time? Please mention

- Investigations: I presume he has undergone a metabolic evaluation this time-, which was mentioned in the discussion. Please describe the negative evaluations here so that there is continuity

- Please describe the MRI brain findings using standard terminology- MRI brain showed T2 weighted…. hyper intense signal changes in bilateral basal ganglia. Are you sure that the brainstem signal changes were in cerebral peduncle and not in substantia nigra? Would you please provide better images of the brainstem? If diffusion weighted images are available please provide the pictures.

- ?What kind of treatment was given at this time?
- When describing the follow up, please mention the age first. Follow up at the age of 9.5 years… For ease of reading.

- Please mention centiles of the growth parameters.

- Has he undergone any developmental assessment or IQ testing on follow up?

Response:

- The birth details have been described in the revised manuscript.

- We have unified the description of time points in the revised manuscript.

- Diarrheal was the prodromal illness prior to onset of regression for 2 patients in our study, we have described it in the revised manuscript.

- We have replaced mentality with “cognition” according to the reviewer’s suggestion.

- We have mentioned the best milestones achieved premorbidly in the revised manuscript.

- No dysmorphic features, tremor, ataxia and involuntary movements were observed.

- Growth parameters and ophthalmological evaluation results have been added in the revised manuscript.

- We have added the data of metabolic evaluation in the revised manuscript.

- We carefully checked the neuro-imaging features with neuroimaging experts. We agree with your comments that the brainstem signal changes were in substantia nigra. We feel regret that diffusion weighted images and sagittal imaging are not available for the first 2 children in our study as neuroimaging data were performed in another hospital. We have changed the original description to “Brain magnetic resonance imaging (MRI) showed T2-weighted imaging (T2WI) and fluid-attenuated inversion recovery (FLAIR) high signal lesions limited to the bilateral globus pallidus and substantia nigra” according to the reviewer’s comments.

- He received supportive and physical therapy. We have added it in the revised manuscript.

- We have mentioned the ages when describing the follow up.

- We have added the ophthalmological examination and Wechsler Mental Development Scale results in the revised manuscript.

2.3.2 Case 2

- Please make it clear if there was a prodromal illness
- Was an ophthalmological evaluation performed?
- Briefly mention the extent of metabolic evaluation - was homocysteine done at this time? [From the table it appears this was done later]
- Was an EEG done in this child?
- Describe the MRI using standard terminology
- Video: It seems she has some choreiform movements, which becomes evident while walking. Please describe the gait [she is unsteady in addition]
- Please mention all the growth parameters and centile

Response:
- Diarrheal was the prodromal illness for the first two children in this study. We have described it in the revised manuscript.
- Ophthalmological evaluation, growth parameters and centile have been added in the revised manuscript.
- Homocysteine and sulfite level has been added in the revised manuscript.
- EEG was not done for this child.
- Standard terminology was used when describing the MRI abnormity (line ).
- We agree that she has some choreiform movements, which becomes evident while walking. We have described it in the revised manuscript.

2.3.3 Case 3
- The suggestions about the presentation of case and MRI are applicable to case three also.
- Please describe the video at follow up, especially the choreoathetoid movements

Response: We have made corresponding revisions according to the reviewer’s comments.

2.3.4 Investigations
- Please mention the important negative investigations undergone by patients while describing the case for ease of reading/describe them comprehensively under investigations separately
When was the exome sequencing performed? Specify the age at which this was performed

I presume that the sulfites and homocysteine were done after the exome sequencing? Please mention this accordingly

Response:

- We have added important negative investigations in the revised manuscript.

- Whole exome sequencing was performed at the age of 9 years for the first child, at the age of 5 years for the second child, and at the age of 4 years for the third child. We have added the ages that exome sequencing was performed.

- Detection for sulfites and homocysteine was done after the exome sequencing. We have mentioned this in the revised manuscript.

2.3.5 Discussion & Conclusion

- Would you please include discussion on the differential diagnoses of the MR imaging findings described in the patients?

Response: We have included discussion on the differential diagnoses of the MR imaging findings described in the patients.

- Please add a note on the predicted functional consequences of the reported mutation on enzyme activity.

Response: We have described the functional consequences of the reported mutation on enzyme activity in the “Background” part.

- The sentence "In present study, all five cases (genetic sequencing was not performed for five patients) harbored missense mutations of SUOX gene, which might be the cause of their milder presentation" is confusing since the present study involved only three patients - Authors might rewrite the sentence if they are referring to patients reported in literature. The next sentence "In our study, five patients showed decreased homocysteine level." Also should be modified.

- "Our results further suggested that decrease in homocysteine which was often ignored by the doctors needs to be aware in the diagnosis of ISOD" - Were the homocysteine results in your patients ignored in the beginning? This is not coming out from the study.

Response: We appreciate the reviewer’s comments. We have re-written the sentences and adjusted the statements in the revised manuscript to make the description much clearer.
- Can the authors include the three cases described also in the table when they are summarizing the cases in literature?

Response: Thanks for your suggestion, we have included our cases in the table when summarizing the cases in literature.

- "More than 90% of patients with ISOD"-please specify that this refers to "Classic ISOD"

Response : We agree that classic ISOD has severe abnormalities of cerebral and cerebellar atrophy and/or cystic white matter changes. We have re-written this sentence.

- Concluding paragraph-A: better description would be that they had a stable clinical course. As mentioned above, all three patients are left with mild sequelae from the neurological insult clinically though there is regression in MRI lesions

Response : We have re-written this concluding paragraph according to your comments. Thank you for your suggestion.

- Please provide legends to videos

Response: We have provided legends to videos.

- The entire manuscript needs copy editing

Response: We have edited the manuscript.

3 José Pedro Vieira, MD (Reviewer 3):

The authors report three cases of isolated sulphite oxidase deficiency with late onset, spontaneous recovery and a relatively mild clinical course. Patients presented with encephalopathy (decreased consciousness) in one patient, a generalized seizure in another patient, choreoathetosis in one patient and «hypotonia and acute regression» in all.

3.1

Information about lens dislocation is not provided.

The clinical description is, in my view, insufficient: acute onset means hours? Days? Was there a decreased level of consciousness? Cranial nerve examination was normal? Were there clinical signs of ataxia? Hypotonia and hypertonia that these patients sequentially revealed was bilateral? Generalized? Reflexes were normal?
Decreased? Hyperactive? Plantar responses were flexor? Ophthalmologic examination was normal?

Response:

- We have added the ophthalmologic examination results of the three patients in the revised manuscript.

- We have re-written the paragraphs in the revised manuscript to make clinical descriptions more detailed and systematic according to the reviewer’s suggestion.

- We have added the time of onset when describing the acute onset of disease.

- There were no cranial nerve examination abnormality, no ataxia for all cases. Reflexes examination results and level of consciousness have been added for each patient in the revised manuscript.

- Hypotonia and hypertonia that these patients sequentially revealed were bilateral and generalized.

- Ophthalmologic examination results were normal for these case series till the latest follow up.

3.2 MRI should be reported with details on which sequences were chosen to demonstrate the lesions and whether these lesions were hyper or hypointense in the text, not only in the legends

Pedunculus cerebri is not in common use in English Neurology literature. I would say from the pictures provided that the hyperintense lesions involve the substantia nigra (?)

Response: We have carefully checked the imaging features with neuroimaging experts and we agree with your comments that the brainstem signal changes were in substantia nigra. We feel regret that diffusion weighted images and sagittal imaging are not available since neuroimaging were performed in another hospital. We have changed the related statements in the revised manuscript. Besides, we also used standard terminology when describing the signal changes on MRI.

3.3 I would not state that bilateral lesions in the globus pallidus suggest ISOD as the differential diagnosis for these lesions is extensive; dislocated lens and/or low plasma homocysteine would be important clues for this diagnosis

I also point out that the patient reported in Reference 11 recovered spontaneously from acute, recurrent encephalopathy without any dietary management

Response: We appreciate the reviewer’s comments. We have added some descriptions to explain the differential diagnosis of ISOD.
The authors in Reference 11 mentioned “The patient was treated with a low protein diet and thiamine supplementation”. We think it is, in a broad sense, a kind of dietary therapy. However, the authors did not elaborate on whether the patient was treated with a diet with restriction of methionine, cysteine and taurine intake. We have added a statement that “Patient was treated with a low protein diet and thiamine supplementation” to the table.

3.4 Finally I detect many ortographic and syntathic issues that I respectfully suggest should be reviewed.

Response: Thanks for your suggestion, we have tried to address these issues in the revised manuscript.