Reviewer’s report

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

Version: 0 Date: 03 Sep 2019

Reviewer: Parayil Sankaran Bindu

Reviewer's report:

Tian et al 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

Title:

I suggest the clinical course of the patients could be better described as having a stable clinical course with spontaneous improvement in brain lesions. All the three patients seem to have mild neurological deficits on follow up, though the brain lesions have regressed. I agree that the clinical course is stable without any additional episodes or progressive neurological deterioration. I suggest modifying the title as 'stable clinical course in three siblings with late onset ISOD.

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.

Case studies

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?

Follow up

-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?

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

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

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

Discussion & Conclusion
- Would you please include 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.
- 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

- Can the authors include the three cases described also in the table when they are summarizing the cases in literature?

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

- 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

- Please provide legends to videos

-The entire manuscript needs copy editing

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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