Author’s response to reviews

Title: Primary care challenges of an obscure case of "Alice in Wonderland" syndrome in a patient with severe malaria in a resource-constrained setting: a case report

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Author’s response to reviews:

Comments and responses

Editor Comments:

Primary care challenges of an obscure case of "Alice in Wonderland" syndrome in a Patient with severe malaria in a resource-constrained setting: a case report

INFD-D-17-00916

Dear authors.

This is a well written report.

They are however some minor issues from the reviewers that you are requested to address as below:

Authors have described a rare case of AIWS in a patient with severe malaria

Comment 1: Did the patient have past history of malaria in particular?
Response: Many thanks for the comment. In the past, the child had been admitted and treated twice for malaria but symptoms of AIWS were not reported on these occasions. We apologize for omitting these details and we are indeed grateful that you brought this to our notice. The details have been included in the case presentation section page 4 lines 16-18

Comment 2: Please clarify on the blood smears and how the parasite count was done. As noted by the reviewer - "To confirm the diagnosis of malaria, a thick blood film analysis was done which was remarkable for hyperparasitaemia at 277,000 trophozoites/microliter - which species of malaria on thin smear? Authors have provided an explanation for this (even though they could have preserved a thin peripheral smear which could be read at a later date for species identification); however, treatment of severe malaria is the same for Plasmodium falciparum and plasmodium vivax malaria".

Response: Thank you for the comment. The blood smear and parasite count procedure that was used has been included in the case presentation page 4 lines 48-52. We agree with you that a thin smear could have been analyzed at a later date and we indeed deferred the thin blood film analysis given the critical setting. However, we later on noted that the peripheral smear for species identification was of poor quality and poorly preserved. This prevented us from reporting the species of Plasmodium involved as noted in the discussion section

Comment 3: Felix-Widal test- What is this? Is it a combination of Weil Felix & Widal test? Weil Felix is a non-specific test for diagnosis of rickettsial disease and Widal test is also insensitive and nonspecific for typhoid, which the authors have acknowledged.

Response: Thank you for the comment. We are sorry about that typographical mistake. We were indeed referring to the Widal test and this has been changed from Felix-Widal to Widal as indicated on page 5 line 4. We agree with you that the Widal test lacks sensitivity and specificity and we did point that out as a diagnostic challenge in the discussion section.

Comment 4: The boy might have had seizure because of hypoglycemia. Though the authors mention blood sugar of 50mg/dL prior to quinine administration (which is very well hypoglycemia), they do not mention the plasma glucose value when the boy developed convulsions…It could be quinine induced hypoglycemia as well.

Response: Thank you for the suggestion. Indeed, the convulsions could have been due to quinine induced hypoglycemia and we have now inserted your pertinent suggestion in the discussion section page 7 lines 27-29.
Comment 5: Hypoglycemia itself is known to produce various neurological manifestations including visual hallucinations. On presentation, the boy had hypoglycemia. Could this AIWS symptomatology be attributable to hypoglycemia induced by malaria?

Response: Thank you very much for the comment. We agree with you that hypoglycemia could trigger various neurological manifestations. However, in our case, we did not consider malaria-induced hypoglycemia as a cause of AIWS because for up to 2 days prior to presentation the recurrent visual symptoms in the severely-ill child had been resolving spontaneously without known interventions geared towards blood glucose correction during the episodes of visual disturbances.

Comment 6: Introduction - line 18, "Severe malaria is a life threatening..."). Suggest "Severe malaria may be a life threatening..."). - as today with improving management options, outcomes are more favourable, especially in older semi immune patients

Response: Thank you for the suggestion. Line 18 in the introduction now reads ‘Severe malaria may be a life threatening condition and it is frequently encountered in developing countries’

Reviewer reports:

Kavitha Saravu (Reviewer 1): Primary care challenges of an obscure case of "Alice in Wonderland" syndrome in a

Patient with severe malaria in a resource-constrained setting: a case report

INF-D-17-00916

Authors have described a rare case of AIWS in a case of malaria

Reviewer's comments:

Comment 1: Did the patient have past h/o malaria in particular?

Response: Thank you for the question. The boy’s past history was positive for previous episodes of malaria but without symptoms suggestive of AIWS. We apologize for omitting this detail which we have now included in the case presentation, page 4 lines 16-18.
Comment 2: To confirm the diagnosis of malaria, a thick blood film analysis was done which was remarkable for hyperparasitaemia at 277,000 trophozoites/microliter - which species of malaria on thin smear? Authors have provided an explanation for this (even though they could have preserved a thin peripheral smear which could be read at a later date for species identification); however, treatment of severe malaria is the same for Plasmodium falciparum and plasmodium vivax malaria.

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Comment 3: Felix-Widal test- What is this? Is it a combination of Weil Felix & Widal test? Weil Felix is a non-specific test for diagnosis of rickettsial disease and Widal test is also insensitive and nonspecific for typhoid, which the authors have acknowledged.

Response: Thank you for the comment. That was a typographical mistake on page 5 line 4. It is now written as Widal test. Indeed, we did acknowledge that the Widal test lacks sensitivity and specificity in the diagnosis of typhoid.

Comment 4: The boy might have had seizure because of hypoglycemia. Though the authors mention blood sugar of 50mg/dL prior to quinine administration (which is very well hypoglycemia), they do not mention the plasma glucose value when the boy developed convulsions…It could be quinine induced hypoglycemia as well.

Response: Thank you for the comment. Indeed, the convulsions could have been due to quinine induced hypoglycemia and we have now inserted your pertinent suggestion in the discussion section page 7 lines 27-29.

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known interventions geared towards blood glucose correction during episodes of visual disturbances

Harriet Mayanja (Reviewer 2): This is a well written case report on a rare syndrome but one which persons practicing in clinical medicine should at least be familiar with. It was new to me - but I found a article very informative. The write-up is clear and concise, with a good discussion taking in fact the noted limitations. The abstract is free standing and well summarized.

Response: Thank you very much for your kind and encouraging comments.

Minor discretionary corrections.

Comment a: Introduction - line 18, "Severe malaria is a life threatening...". I suggest "Severe malaria may be a life threatening...". - as today with improving management options, outcomes are more favourable

Response: Many thanks for the correction. Line 18 in the introduction section now reads ‘severe malaria may be a life threatening condition and it is frequently encountered in developing countries’

Comment b: Case presentation, page 4 line 50 - Felix-Widal test does not "rule out typhoid" - but this is ably clarified in the discussion.

Response: Thank you for the comment. This sentence of concern which was initially on page 4 line 50 has been modified to ‘The Widal test was used to check the possibility of typhoid and the titre was weakly positive’ as highlighted on page 5 lines 4-7

Otherwise I have no pertinent corrections or suggestions.

Response: Thank you for the kind suggestions