Author's response to reviews

Title: Severe falciparum malaria with dengue coinfection complicated by rhabdomyolysis and acute kidney injury: an unusual case with myoglobinemia, myoglobinuria but normal serum creatine kinase.

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Author's response to reviews: see over
Dear BMC ID editor and reviewers,

Thank you all for your kind review of our submitted manuscript titled “Severe falciparum malaria with dengue coinfection complicated by rhabdomyolysis and acute kidney injury: an unusual case with myoglobinemia, myoglobinuria but normal serum creatine kinase”.

Your comments have been most valuable.

On behalf of the authors, I would like to address the comments point-by-point.

Dr Idro’s valuable comments:

1. **My specialty is not nephrology but it is difficult to understand the conclusion that …in children with severe falciparum malaria and rhabdomyolysis, serum and urine myoglobin are better markers of acute renal failure than CK.** My understanding is that serum/plasma CK levels are a marker of muscle injury and creatinine levels for acute renal failure …which recent literature now refers to as acute kidney injury. Instead, the conclusion in the main text “The absence of raised serum CK alone does not exclude a diagnosis of rhabdomyolysis” is more appropriate. Throughout the text, consideration should be given to using acute kidney injury instead of acute renal failure.

   **Our reply:** We agree that “acute kidney injury” is the more appropriate terminology and this has been adopted to replace “renal failure” throughout the manuscript as suggested. We agree that creatine kinase levels are usually the more sensitive marker of muscle injury in rhabdomyolysis (1). However, there have been case reports of rhabdomyolysis with myoglobinemia and myoglobinuria without raised CK in the setting of Duchenne muscular dystrophy and malignant hyperthermia (2). We are trying to highlight this same perplexing situation seen in our patient with severe malaria and dengue co-infection.

2. **The second conclusion in the abstract “In the event of myoglobin-induced acute renal failure requiring dialysis, high-flux hemodiafiltration, rather than conventional hemodialysis, is the preferred modality to remove myoglobin” is also not justified on the basis of observation in a single case report.**

   **Our reply:** There is some evidence on the use of high-flux hemodiafiltration being more effective than conventional hemodialysis for myoglobin clearance in patients with myoglobin-induced AKI beyond our single case report (3 – 5). However, we agree that this is the only report in the setting of myoglobin-induced AKI in severe malaria. We have amended our manuscript comment to “In the event of myoglobin-induced AKI requiring dialysis, clinicians may consider using high-flux hemodiafiltration instead of conventional hemodialysis for more effective myoglobin removal.”

3. **In the background, the first statement on renal injury should be qualified further as the statement is true for adults and not children.**

   **Our reply:** We agree and the statement has been revised.
4. What was the level of parasitaemia – i.e. parasite density in the patient? Could this have affected the clinical picture?

Our reply: The level of parasitemia was pointed out in the manuscript “A blood film revealed *Plasmodium falciparum* in 4.0% of erythrocytes”. The WHO guidelines on malaria management (6) defines severe malaria as >2% parasitemia in areas of stable low-transmission or >5% parasitaemia in areas of stable high-transmission. Hence our patient’s relatively high 4% parasitemia burden may have caused more myocyte injury and release of myoglobin which contributed to the AKI needing renal replacement therapy.

Dr Mitra’s valuable comments:

(Major Compulsory)

1. The authors have not been able to explain how CPK has remained normal. In addition, there is swelling of both the thighs. (Ref: Case Presentation- generalized myalgia that was especially painful over bilateral thighs)

*Our reply:* We agree that creatine kinase levels are the more sensitive marker of muscle injury in rhabdomyolysis (1). However, there have been reports of rhabdomyolysis with myoglobinemia and myoglobinuria without raised CK in the setting of Duchenne muscular dystrophy and malignant hyperthermia (2). We are, however, unable to explain this phenomenon observed in our patient. Nevertheless, we hope to raise the awareness that the absence of raised serum CK does not exclude a diagnosis of rhabdomyolysis.

2. The statement "Myoglobin, either serum or urine, is a better marker for renal failure in this setting and should be tested" is confusing.

*Our reply:* We agree and have revised and clarified this point in the manuscript.


*Our reply:* We agree and have revised and clarified this point in the manuscript.

4. The number of references may be reduced.

*Our reply:* The references cited are necessary to support the points made and are relevant to the case.

5. The article needs to be re-written.

*Our reply:* The manuscript has been revised.

(Minor revisions)

1. Sentences needs to be restructured for clear understanding.

*Our reply:* The manuscript has been revised.

2. Avoid words like: mild transaminitis, tachycardic etc
Our reply: We have removed “tachycardic” and the word “mild” but “transaminitis” remains as it is an accurate reflection of the state of the liver dysfunction.

3. Legends in the X-axis be clear. Remove the days at each stage. It makes the graph clumsy.

Our reply: We agree. The x-axis on the graph has been simplified as suggested.

4. Discussion can be shortened.

Our reply: We have shortened the discussion as suggested.

References


We hope you would review the manuscript favourably for publication in your journal.

Thank you very much.

Yours truly,

Chian Yong LOW
On behalf of the authors