Author's response to reviews

Title: An Egyptian child with erythromelalgia responding to a new line of treatment: a case report and literature review

Authors:

Samir M Al-Minshawy (Sammmoner2@yahoo.com)
Abdel-Azeem M El-Mazary (abdelazeemhemed@yahoo.com)

Version: 5  
Date: 26 October 2013

Author's response to reviews: see over
Dear professor,

Thank you very much for consideration of our manuscript for publication in your journal. We have reviewed the manuscript according to your reviewer’s comments.

Editorial comments:

Journal of Medical Case Reports MS: 2117112311013867 - Case report
Erythromelalgia: An Egyptian case report with a new line of treatment and literature review

1. Please include the study design in your title, i.e. Case report. For example: A presenting with B in C: a case report.
   - We included the study design in our title and it became: An Egyptian child with erythromelalgia responding to a new line of treatment: a case report and literature review

2. Please include three to ten keywords representing the main content of the article, after the Abstract section.
   - We included keywords after the Abstract section: Keywords: Erythromelalgia, Egyptian children, cetirizine hydrochloride.

3. Please include a list of abbreviations used in the manuscript and their meanings after the Conclusions section.
   - We included a list of abbreviations used in the manuscript and their meanings after the Conclusions section as the reviewer indicates.

4. Please include an acknowledgement section at the end of the manuscript before the reference list. Please acknowledge anyone who contributed towards the study by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the
criteria for authorship. Please also include the source(s) of funding for all authors. Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements.

- We included an acknowledgement section at the end of the manuscript as the reviewer indicates.

5. Please include a figure title and legend section after the reference list.

- We included a figure title and legend section after the reference list.

The Journal of Medical Case Reports Editorial Team

Reviewer's report

Title: Case report Erythromelalgia: An Egyptian case report with a new line of treatment and literature review
Version: 3 Date: 7 September 2013
Reviewer: Stephen Waxman

Which of the following best describes what type of case report this is?: Other
If other, please specify: report of new purported response to therapy, anecdotal

Has the case been reported coherently?: No
Is the case report authentic?: Yes
Is the case report ethical?: Yes
Is there any missing information that you think must be added before publication?: Yes
Is this case worth reporting?: Yes
Is the case report persuasive?: Yes
Does the case report have explanatory value?: No
Does the case report have diagnostic value?: Yes
Will the case report make a difference to clinical practice?: No
Is the anonymity of the patient protected?: Yes

Comments to authors:
Does the case report have explanatory value? It does not provide new insights into pathophysiology. It does present a clear picture of this disorder from clinical perspective
Does the case report have diagnostic value? Yes, for clinicians who have not
seen this disorder. Will the case report make a difference to clinical practice? Not Clear, anecdotal

Comments to authors:
This article makes an interesting observation. The report is of course anecdotal and should be more clearly labeled as such. The manuscript should be revised as follows:

--1. The article describes anecdotal observations on a single patient (n=1). Chance association of a waxing-waning clinical course or a placebo response cannot be ruled out. This must be more explicitly noted in the Abstract and main text.

- As regards the chance association of a waxing-waning clinical course or a placebo response, we had explained the effect of treatment withdrawal in the abstract and main text as follows: When the child stopped cetirizine hydrochloride for one month as a test, the symptoms had been aggravated but relieved again when cetirizine therapy restarted again.

--2. Moreover, it is not clear whether the apparent response to treatment will be durable over years, or if the patient will relapse. This should be more clearly noted.
- We had explained the effect of treatment withdrawal on our child as mentioned above.

--3. The statement that this is the first case of primary EM presenting at age 3 or earlier is not true. The following cases or families include onset at age 3 or less, and should be cited:

We revised and mentioned that the age of presentation of our case at the age of 3 is not the only case as reported by other families and we addressed the references of this as the reviewer indicates.


We already cited and mentioned all references reported by the reviewers in its context and references list as the reviewer indicates.

-4. Many more Nav1.7 mutations than described in this paper as submitted have been linked to EM. The authors can go the literature and describe them all, or cite this review which lists all of them:


We cited the mentioned reference as the reviewer indicates.

-5. The discussion should point out that some rare pts with EM respond well to treatment with carbamazepine, and their mutations have been shown the sensitive the Nav1.7 channel to this drug (Fischer, T.Z., Gilmore, E.S., Estacion, M, Eastman, E, Taylor, S, Melanson, M, Dib-Hajj, S, Waxman, S.G., A novel Nav1.7 mutation producing carbamazepine-responsive erythromelalgia. Ann Neurol, 65:733-741, 2009).

In the discussion we pointed out that some patients respond well to treatment with carbamazepine, and their mutations have been shown the sensitive the Nav1.7 channel to this drug and we had cited the reference mentioned above as the reviewer indicates.

Recent studies have indicated that it is possible to predict the response of patients with EM to treatment with sodium channel blockers on the basis of atomic-level structural modeling (Yang, Y., Dib-Hajj, S.D., Zhang, J.,
Zhang, Y., Tyrrell, L., Estacion, M., and Waxman, S.G. Structural modeling and mutant cycle analysis predict pharmacoresponsiveness of a NaV1.7 mutant channel, Nature Comm., 3: 1186, 2012), raising the possibility that, in the future, it may be possible to genotype patients with EM, and prospectively predict the response to various drugs via pharmacogenomics.

- We addressed that recent studies have indicated that it is possible to predict the response of patients with EM to treatment with sodium channel blockers on the basis of atomic-level structural modeling and we mentioned the above reference as the reviewer indicates.

**Quality of written English:** Acceptable  
**Declaration of competing interests:**  
I declare that I have no competing interests

**Reviewer's report**  
**Title:** Case report Erythromelalgia: An Egyptian case report with a new line of treatment and literature review  
**Version:** 3 **Date:** 15 September 2013  
**Reviewer:** Sudip Kumar Ghosh  
Which of the following best describes what type of case report this is?: None  
Has the case been reported coherently?: Yes  
Is the case report authentic?: Yes  
Is the case report ethical?: Yes  
Is there any missing information that you think must be added before publication?: Yes  
Is this case worth reporting?: Yes  
Is the case report persuasive?: Yes  
Does the case report have explanatory value?: Yes  
Does the case report have diagnostic value?: Yes  
Will the case report make a difference to clinical practice?: Yes  
Is the anonymity of the patient protected?: Yes

**Comments to authors:**  
1) Abstract section:  
a."We present a case of an Egyptian child with primary erythromelalgia manifested at very early onset of age and showed partial response to unusual therapy.”
We present a case of an Egyptian child with primary erythromelalgia manifested at an early age and showed partial response to therapy with cetirizine.

- We changed (very early onset of age) to (early age) in the Abstract and main text sections as the reviewer indicates.

b. Case presentation last paragraph: correct the spelling of ‘citizine’
- citizine corrected to citirizine.

c. “This is a case report of a 34-month-old Egyptian child with primary erythromelalgia manifested at very early onset of age.”
Comments:
Repetition of the introduction. Replace with: “This is a case report of a 34-month-old Egyptian child with primary erythromelalgia manifested at an early age”
- We changed (very early onset of age) to (early age) in the Abstract and main text sections.

2. Description of skin biopsy should be a part of the 'case report' section
- We described the skin biopsy in the 'case report' section as the reviewer indicates and became as follow: Skin biopsy was performed, showing nonspecific changes and this was consistent with the diagnosis of primary EM (Figs.3,4) in the form of numerous telangectatic blood vessels in the capillary dermis associated with sparse perivascular mononuclear cell infiltrate, some vessels show swelling of endothelial lining.

3. “This may lead us to think about a new theory of chronic long standing local allergic reaction which enlighten response to cetirizine in our case in spite of normal serum IgE titre”
It is not clear what is meant by allergic reaction?
Variable response of erythromelalgia to antihistamines makes this conclusion less tenable. Please comment.
- Our comments may be more obvious on the basis of atomic-level structural modeling as prescribed by Yang et al as regards pharmacoresponsiveness of a NaV1.7 mutant channel to different drugs.

4. “We believe that it is the first report for this presentation at this age and also we believe it is the first Egyptian report of this kind in the literature.” Please clarify how the authors came to this conclusion.
Quality of written English: Needs some language corrections before being published

Declaration of competing interests:
'I declare that I have no competing interests

Reviewer's report
Title: Case report Erythromelalgia: An Egyptian case report with a new line of treatment and literature review
Version: 3 Date: 17 September 2013
Reviewer: Waseem Bakkour

Which of the following following best describes what type of case report this is?: Other
If other, please specify:
Possible new treatment approach for erythromelalgia

Has the case been reported coherently?: Yes
Is the case report authentic?: No
Is the case report ethical?: Yes
Is there any missing information that you think must be added before publication?: Yes
Is this case worth reporting?: No
Is the case report persuasive?: No
Does the case report have explanatory value?: No
Does the case report have diagnostic value?: No
Will the case report make a difference to clinical practice?: No
Is the anonymity of the patient protected?: Yes

Comments to authors:
Although a report of primary erythromelalgia in a 2 year old would have been interesting I feel that genetic testing is a must here. The response to antihistamines was not qualified and there is very little discussion about the mechanism of this response. The literature review lacks clear message and structure and very difficult to follow.
As regards the (genetic testing) we could not do it as it is expensive and we depended upon the clear history and clinical picture of the case in the diagnosis, adding that the genetic study may be more valuable in studies dealing with pharmacological response to different drugs on a large scale.

The response of our child to cimitirizine hydrochloride may be understood on the basis of atomic-level structural modeling as mentioned by Yang et al and this was mentioned in the discussion section.

Quality of written English: Not suitable for publication unless extensively edited
We extensively edited the manuscript to be suitable for publication.

Declaration of competing interests:
I declare that I have no competing interests