Author's response to reviews

Title: Erythromelalgia, a rare condition: a case report and review of the literature.

Authors:

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Author's response to reviews:

Dear Editor,

Dr. Thomas Koroscil and I would like to resubmit our case report titled "Erythromelalgia: A rare condition" after making changes in response to questions and comments made by peer reviewers. The manuscript ID is 1003236891243632, originally submitted on December 22, 2008.

Thank you for getting the case report peer reviewed and providing me an opportunity to resubmit the manuscript.

We would like to express my gratitude to the reviewers – Drs Waxman and Drenth, for their questions and insightful comments. Their suggestions have certainly helped refine the case report. Their questions and comments have been addressed in the sections below and the manuscript has been modified accordingly.

As mentioned earlier, Erythromelalgia is a rare disorder and the diagnosis can be easily missed by physicians. We hope that this article will help the medical community learn more about this disorder, especially to those who have not seen this disease before. In addition, the premature ovarian failure resulting from the patient’s acquired hypothermia is a condition previously unreported.

Below is a point-to-point response to the reviewers’ comments, including details of changes made to the manuscript where needed.

Response to comments by Dr. Waxman:

1. "Family history should be specified, since about 10-15% of cases of EM are familial."

Response: We have specified that our patient denied any similar symptoms within family members. She has no family history of EM, myeloproliferative or autoimmune disorders.

2. "The text states that Cummins et al (2004) "suggested" that mutations producing familial EM shift activation of Nav1.7 in a hyperpolarizing direction. They did not suggest this, but rather showed it, in a definitive manner, using
patch clamp to examine the voltage-dependence and kinetics of activation and inactivation in the mutated channels."

Response: In the Discussion section, the text has been reworded from "suggested" to "demonstrated".

3. "The text similarly states that Dib-Hajj et al (2005) "suggested" another mutation in Nav1.7 as causing EM in another kindred. Again, Dib-Hajj et al did not suggest this, but rather demonstrated it, via sequencing and then functional analysis of the mutant channel. In this case, the kindred was a large one, containing more than a dozen subjects with EM, and the mutation segregated precisely with phenotype."

Response: In the Discussion section, the statement has been reworded from "suggested" to "demonstrated".


Response: We have amended and cited these reviews under the Discussion section.


Response: As suggested, the following text was added to the Discussion Section: "the cause of sporadic EM remains unknown, however some juvenile cases reported were thought to be the result of spontaneous "founder" mutations."

Response to comments by Dr. J P Drenth:

1. Comment: Dr. Drenth commented on premature ovarian failure. "How should this fit with the pathogenesis of erythermalgia? If there is a connection how to follow that up? Any clinical implications?"
Response: We did not suggest that there is a relationship between premature ovarian failure and pathogenesis of erythermalgia. Pathogenesis of EM remains unclear. Our patient first developed symptoms of EM and started using cooling measures to reduce the severity of symptoms. Then around 2 years later, she developed premature ovarian failure. We are suggesting that the patient’s premature ovarian failure was a consequence of her acquired hypothermia, not from EM.

2. Comment: "Was poikilothermia excluded?"

Response: Poikilothermia is a body temperature dysregulation syndrome. Usually patients with hypothalamic problems or spinal cord injuries can develop poikilothermia. Our patient had a normal MRI of the brain without any hypothalamic lesion. She has not suffered any form of trauma, nor had any other neurological symptoms reported. She never had a prior history of body-temperature dysregulation.

3. Comment: "The authors indicate that genetic testing of SCN9a is feasible. Did they perform that for this patient?"

Response: Genetic testing for this condition is available but is not a confirmatory laboratory test. The patient was offered genetic testing but she refused.

4. Comment: "The authors cite the effect of mexiletine, and indeed several reports suggest a positive effect. Was it tried in their patient?"

Response: When we started writing this case report, that time patient was considering trying mexiletine therapy. Most recently, she received this therapy and did not benefit from it. This has been added to our updated manuscript.

Feedback from peer reviewers is appreciated and we will be glad to answer any questions.

Sincerely,
Shobhana Gaur