Reviewer’s report

Title: A rare case of pediatric recurrent rhabdomyolysis with compound heterogenous variants in the LPIN1

Version: 0 Date: 28 Apr 2020

Reviewer: Mark Tarnopolsky

Reviewer's report:

The authors describe a child with 2 documented cases of rhabdomyolysis who was found to have bi-allelic variants in LIPN1. The variants appear to be likely pathogenic.

General comments:

1. As the authors indicate, LIPN1 mutations have been well described in the past, albeit, usually in the Caucasian population. Thus, the novel aspects of the paper include the variants themselves and the ethnicity of the proband. The authors indicate that the limitation is the absence of functional studies or multiple cases to establish a phenotype-genotype correlation, but the variants do appear to be pathological and fit the phenotype. What were the parts of the ACMG criteria that were met - more details would help.

2. I may have missed it but I did not see acyl-carnitine profiling in this patient to rule out a FAOD?

3. Lactate and cytokines go up roughly in parallel in response to acute exercise and are somewhat proportionate (i.e., higher intensity exercise and longer duration leads to higher IL-6 concentrations and this parallel the lactate). Are the authors implying that cytokines per se are causing rhabdomyolysis? Muscles release cytokines directly (myokines) such as IL-6 and very high levels can be achieved in top sport athletes pushing to a very high level with a very low risk of rhabdomyolysis (it is much more common in the untrained). The increase in cytokines during exercise (myokine release) is trivial compared to the massive release that occurs from the WBCs at 24 - 48 h after a bout of rhabdomyolysis (when neutrophils and macrophages in the necrotic muscle are at their peak). Thus, it is almost certainly not the acute myokine release of cytokines that drives rhabdomyolysis but their appearance merely reflects the body's response to the necrosis of the muscle from whatever the specific trigger is (? phospholipid alterations of the membrane leading to high calcium influx and activation of calpains, ER stress, SR damage, oxidative stress, etc.).

4. I am not familiar with the river prawn issue as I suspect many readers will not. Can you please add more to this - does this often lead to rhabdomyolysis or fever or ?

5. It is important to know more about the type of exercise that triggered the one event. I am not sure what "the solid ball" is - was this a weighted medicine ball or just throwing a baseball around? The child seems a bit young to be doing weight training in the traditional sense. How long had he fasted for you indicate that he missed dinner - how long was the fast? Given that he appears to be otherwise active it appears that fasting is the more important trigger. Also, what was the temperature of the day when he got ill for if it was very hot and he became dehydrated then this may also be a triggering factor.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

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

Yes

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

Yes

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Not relevant to this manuscript

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