Author’s response to reviews

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

Authors:
Ruochen Che (cheruochen@163.com)
Chunli Wang (chunliwang1@126.com)
Bixia Zheng (zbx_88117@163.com)
Xuejuan Zhang (15895908376@163.com)
Guixia Ding (bhgyuan@163.com)
Fei Zhao (zhaofei@njmu.edu.cn)
Zhanjun Jia (jiazj72@hotmail.com)
Aihua Zhang (bszah@163.com)
Songming Huang (smhuang@njmu.edu.cn)
Quancheng Feng (williamvon@126.com)

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Author’s response to reviews:

Dear editor and reviewers:

Thank you for your comments. We’ve revised the manuscript according to your advices.

Reviewer 1
1. All the LPIN1 in the abstract and text have been changed into italic type.
2. ‘Myoglobinuria’ has been revised into ‘cola-colored urine’.
3. The age for the two episodes of rhabdomyolysis and the level of blood CK were specified in the abstract.
4. Haff disease has been briefly introduced.
5. In the article ‘Cardiac function and exercise adaptation in 8 children with LPIN1 mutations’ by Dr Antoine Legendre (PMID: 29325813), they mentioned about several basic research results:’ At high levels, cytokines are known to act as myotoxins that induce muscle proteolysis, which is responsive to rhabdomyolysis. Cytokines are also secreted by skeletal muscle during prolonged exercise, which is another trigger of the disease, potentially amplifying the immune response. However if plasma lactate levels remained normal during effort, cytokines have not been dosed during exercise’. The last sentence did not give any reference which we believed it’s the conclusion or experiences of the authors themselves.
Therefore, we quoted the sentence to give the speculation that short high intensity exercise would be tolerable in the absence of fever. We have further illustrated the saying in the manuscript to make it clear.
6. We’ve added the sentences in the conclusion part.
7. We’ve further improved the quality of the figures, which meet the commands of the journal. But when I open the proof, the figure still appear a little blurred maybe because the file we are viewing is in a low resolution.

Reviewer 2
1. We’ve added the detail information of the variant classification into the manuscript.
2. The parents have told us that they’ve done acyl-carnitine profiling using tandem mass spectrometry years ago in another hospital and the result was negative. But we did not see the report. Therefore, we did not mention it in the article. We’ve added the explanation into the manuscript.
3. We could totally understand your point. Actually, we are not the expert in the basic research of myopathy. We just try to explain why the boy could tolerate some short-term but even high-intensity exercises in daily life when there’s no infectious trigger. According to the article ‘Cardiac function and exercise adaptation in 8 children with LPIN1 mutations’ by Dr Antoine Legendre (PMID: 29325813), several basic research results were mentioned:’ At high levels, cytokines are known to act as myotoxins that induce muscle proteolysis, which is responsive to rhabdomyolysis. Cytokines are also secreted by skeletal muscle during prolonged exercise, which is another trigger of the disease, potentially amplifying the immune response. However if plasma lactate levels remained normal during effort, cytokines have not been dosed during exercise’.
However, the detailed comments from you raised the awareness that it remains controversial. Increased cytokines should be secondary to the myolysis, but is there any possibility that cytokines and myolysis are crosstalked? Myolysis triggered the cytokines increase, and overwhelming cytokines could be the second strike to the injury. Therefore, we did some changes in the manuscript. If that’s still improper, the part can be deleted.
4. We’ve added some detailed information about ‘Haif Disease’.
5. The solid ball is a 1kg-2.5kg rubber ball with sands inside. Solid ball is a little different from medicine ball, since it can be threwed far away and in low elasticity. Throwing solid ball is one of the physical evaluation tests that most Chinese students from primary schools and middle schools should take. The further you throw, the higher score you get. The day that he practised throwing solid ball is in autumn, warm but not so hot. He’ve missed the supper and directly went to bed. Therefore, we speculated that he had been in fast for at least 12 hours. We’ve given more detail about the possible trigger.

We appreciate the efforts of reviewers and editors to revise the manuscript. And if there’s any further question, do not hesitate to contact us.

Best wishes

Quancheng Feng
Children’s Hospital of Nanjing Medical University