Correspondence

Response to Finsterer and Zarrouk-Mahjoub

To the Editor,

We thank Drs. J. Finsterer and S. Zarrouk-Mahjoub for their thoughtful comments [1] to our manuscript [2]. The clinical presentation of rhabdomyolysis including exertional rhabdomyolysis is highly variable. In addition, there is currently no universally agreed upon definition of exertional rhabdomyolysis. Nonetheless, characteristic clinical features of rhabdomyolysis are muscle pain, weakness, and/or muscle swelling with transient elevation of serum creatine kinase with or without myoglobinuria [3,4]. Our data and published reports showed that muscle pain is the most common presenting symptom of rhabdomyolysis [3]. In our case series, R465 was the only patient who did not complain of muscle pain.

We agree the language concerning the electromyographic results is not clear: we intended the term to encompass the totality of electrodiagnostic data (e.g., nerve conduction studies, needle electromyographic studies). It is our practice that patients referred for electrodiagnostic evaluation of possible muscle disease undergo screening nerve conduction studies for large fiber neuropathy, including upper and lower extremity studies, prior to needle examination. Save for the subject whose only abnormality was the noted superficial peroneal sensory potential (see our presumptive explanation in the text), no other abnormalities were noted.

We also agree that mutations in mitochondrial (mt)DNA have been implicated in rhabdomyolysis and exercise intolerance, and whole exome sequencing (WES) will not cover mtDNA. Patients with mtDNA mutations usually present with multigorgan involvement and typical histopathological features such as ragged red fibers in muscle biopsy [5]. None of these features were seen in our case series. Furthermore, none of patients had a family history suggestive of maternal inheritance. These evidence indicate that the contributions of mtDNA mutations are highly unlikely which allowed us to use whole exome sequencing in the study.

The methods section of the manuscript provides a brief description of genetic analysis: the use of American College of Medical Genetics (ACMG) guidelines [6] for a variant’s classification and Sanger sequencing for a variant validation of WES results [2]. Published ACMG guidelines include a total of 28 different criteria that address variant prevalence in the population, literature and locus specific databases, functional data, segregation data, de novo occurrence, and computational predictions [6]. The use of these criteria is open to modifications and interpretations. We have tried to use all ACMG criteria whenever it was possible. However, depending on data availability, and disease or gene specific characteristics, some criteria including functional data, co-segregation data and de novo occurrence were not applicable for the majority of variants. Given wide use of ACMG guidelines, we omitted a lengthy explanation of criteria modification for multiple genes and variants found in our study.

We appreciate comments regarding segregation analysis, functional data and multisystem manifestation of metabolic myopathies. Family members were unavailable (R410 was adopted) or declined to enroll in the study, often due to lack of family history of muscle diseases or phenotypes seen in index case. The predominant features reported by patients in our study were muscle symptoms including muscle pain, fatigue and weakness. Chest pain suggestive of cardiac involvement was reported in one subject. No abnormalities of the acyl-carnitine profile were detected in any of studied cases except R469. Finally, we addressed study limitations including lack of functional studies in the discussion. This was an exploratory study to address the complexity of genetics in recurrent exertional rhabdomyolysis.

References

[1] J. Finsterer, S. Zarrouk-Mahjoub, Whole exome sequencing may be insufficient to cover the causality spectrum of rhabdomyolysis, Mol. Genet. Metab. Rep. (2018).
[2] N. Sambuughin, et al., Pathogenic and rare deleterious variants in multiple genes suggest oligogenic inheritance in recurrent exertional rhabdomyolysis, Mol. Genet. Metab. Rep. 16 (2018) 76–81.
[3] J.R. Nance, A.L. Mammen, Diagnostic evaluation of rhabdomyolysis, Muscle Nerve 51 (6) (2015) 793–810.
[4] R.S. Scalco, et al., Exertional rhabdomyolysis: physiological response or manifestation of an underlying myopathy? BMJ Open Sport Exerc. Med. 2 (1) (2016) e000151.
[5] E.A. Schon, S. Dimauro, M. Hirano, Human mitochondrial DNA: roles of inherited and somatic mutations, Nat. Rev. Genet. 13 (12) (2012) 878–890.
[6] S. Richards, et al., Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, Genet. Med. 17 (5) (2015) 405–424.

Nyamkhishig Sambuughin⁎, Jonathan Smith⁎, Francis O’Connor⁎, Patricia Deuster⁎

⁎ Corresponding author.

a Consortium for Health and Military Performance, Department of Military and Emergency Medicine, Hébert School of Medicine, Uniformed Services University, Bethesda, MD, USA
b Department of Neurology, Walter Read National Military Medical Center, Bethesda, MD, USA

E-mail address: nyamkhishig.sambuughin.ctr@usuhs.edu (N. Sambuughin)

https://doi.org/10.1016/j.ymgmr.2018.08.004

Received 24 August 2018; Received in revised form 24 August 2018; Accepted 25 August 2018

2214-4269/ © 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).