Congenital myasthenia causes a chronic impairment of aerobic and strength performance and exercise-induced hyperglycemia in female mice

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Introduction: Congenital Myasthenic Syndromes (CMSs) comprise rare and diverse hereditary genetic disorders in neuromuscular junction proteins, leading to progressive muscle weakness and impairing the quality of life of these individuals. Among these proteins, those involved in the synthesis (ChAT) and storage (VAChT) of acetylcholine have been shown to be critical to muscle function and homeostasis. Previous studies using VAChT knockdown mice (VKD) expressing ~30% of this protein have demonstrated an impairment in physical performance in male mice. However, it is unknown whether females are also compromised in this CMS model and what age the alterations in performance may occur. **Objective:** To evaluate aerobic and strength performance and metabolism in female VKD mice from 2 to 6 months of age. **Methods:** Muscle strength (peak force) was measured monthly by grip strength meter.Aerobic performance (i.e., peak oxygen consumption (VO2peak), time to fatigue

(TTF), distance and maximum running speed (Smax)) was also evaluated monthly by incremental load test (ILT) in treadmill in both wildtype (WT) and VKD female mice (2- to 6-month-old; ~22g). Blood glucose and lactate were also assessed after 5 minutes of ILT. All experiments and protocols were approved by The Ethics Committee on Animal Use from UFMG. **Results:** Muscle strength was impaired (≈ 30%, $P<0.05$) in VKD mice from 4 to 6 months of age. The aerobic performance evaluated by VO2peak (≈ 45%, $P<0.05$), TTF (≈ 85%, $P<0.05$), running distance (≈ 90%, $P<0.05$) and Smax (≈ 70%, $P<0.05$) were significantly reduced and an increase in blood glucose was observed post-ILT (≈ 30%, $P<0.05$) in VKD compared to WT in all analyzed time points. However, no significant difference was found in blood lactate in any group ($P>0.05$). **Conclusion:** Our findings show that female VKD mice also present a marked decline in both aerobic and strength performance and an unexpected hyperglycemic response to exercise. Next, the cellular and molecular adaptations in skeletal muscle will be analyzed. We also intend to investigate the effects of non-pharmacological treatments, e.g., exercise training and nutrition, to improve physical performance and slow down the progression of CMS model.

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