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Kinematic Gait Analysis Is a Non-Invasive, More Objective and Earlier Measurement of Impairment in the Mdx Mouse Model of Duchenne Muscular Dystrophy

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Abstract : Duchenne muscular dystrophy (DMD) is caused by an X linked mutation in the dystrophin gene; lack of dystrophin causes a progressive muscle necrosis which leads to a progressive decrease in mobility in those suffering from the disease. The MDX mouse, a mutant mouse model which displays a frank dystrophinopathy, is currently widely employed in pre clinical efficacy models for treatments and therapies aimed at DMD. In general the end-points examined within this model have been based on invasive histopathology of muscles and serum biochemical measures like measurement of serum creatine kinase (sCK). It is established that a “critical period” between 4 and 6 weeks exists in the MDX mouse when there is extensive muscle damage that is largely sub clinical but evident with sCK measurements and histopathological staining. However, a full characterization of the MDX model remains largely incomplete especially with respect to the ability to aggravate of the muscle damage beyond the critical period. The purpose of this study was to attempt to aggravate the muscle damage in the MDX mouse and to create a wider, more readily translatable and discernible, therapeutic window for the testing of potential therapies for DMD. The study consisted of subjecting 15 male mutant MDX mice and 15 male wild-type mice to an intense chronic exercise regime that consisted of bi-weekly (two times per week) treadmill sessions over a 12 month period. Each session was 30 minutes in duration and the treadmill speed was gradually built up to 14m/min for the entire session. Baseline plasma creatine kinase (pCK), treadmill training performance and locomotor activity were measured after the “critical period” at around 10 weeks of age and again at 14 weeks of age, 6 months, 9 months and 12 months of age. In addition, kinematic gait analysis was employed using a novel analysis algorithm in order to compare changes in gait and fine motor skills in diseased exercised MDX mice compared to exercised wild type mice and non exercised MDX mice. In addition, a morphological and metabolic profile (including lipid profile), from the muscles most severely affected, the gastrocnemius muscle and the tibialis anterior muscle, was also measured at the same time intervals. Results indicate that by aggravating or exacerbating the underlying muscle damage in the MDX mouse by exercise a more pronounced and severe phenotype in comes to light and this can be picked up earlier by kinematic gait analysis. A reduction in mobility as measured by open field is not apparent at younger ages nor during the critical period, but changes in gait are apparent in the mutant MDX mice. These gait changes coincide with pronounced morphological and metabolic changes by non-invasive anatomical MRI and proton spectroscopy (1H-MRS) we have reported elsewhere. Evidence of a progressive asymmetric pathology in imaging parameters as well as in the kinematic gait analysis was found. Taken together, the data show that chronic exercise regime exacerbates the muscle damage beyond the critical period and the ability to measure through non-invasive means are important factors to consider when performing preclinical efficacy studies in the MDX mouse.

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