Title: Modelling inflammatory brain-heart interaction in Duchenne Muscular Dystrophy

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Structured Abstract:

Introduction: Duchenne muscular dystrophy (DMD) is a neuromuscular degenerative disorder caused by dystrophin protein loss in various tissues—notably skeletal muscles and the brain. DMD is characterized by progressive skeletal muscle, cardiac, and cognitive degeneration, accompanied by chronic inflammation, and eventual death by cardiac or respiratory failure. While endogenous and systemic inflammation are known to be associated with DMD skeletal and cardiac muscle degeneration, little is known about systemic inflammation's impact on the brain and even less about neuroinflammation in DMD—despite it being a prime proponent of other neurodegenerative diseases (e.g. Alzheimer's). Recent studies have shown that inflammatory responses to local myocardial damage systemically trigger cerebral microglial activation—a hallmark of neuroinflammation. This study aims to both delineate the inflammatory interaction between the heart and brain using an in-vivo whole-body DMD model, and to establish an imaging protocol to non-invasively model DMD progression.

Methods: Transgenic murine models of moderate DMD severity (8 week old) and age-matched wild-types (WT) were imaged via 60 min dynamic positron emission tomography (PET), and associated biodistribution and autoradiography analyses using 18F-FEPPA—a tracer targeting translocator proteins (TSPO), which are overexpressed on both microglial and macrophages. Mean Standardized Uptake Values (SUVm) were generated from PET time-activity curves at 30-60mins for both whole brain and myocardium. Each mouse's brain, and heart were collected for quantification and colocalization of TSPO with known inflammatory biomarker (e.g. IL6) via immunohistochemistry.

Results: Moderately severe DMD mice showed global elevation in TSPO PET binding in the heart, brain, and skeletal muscles, which co-localized with increased tracer uptake and fluorescence intensity in autoradiography and immunohistochemistry findings respectively (n=3). Increased heart:lung SUV ratio and SUVBrain were seen for DMD heart and brain respectively compared to WT. Further immunohistochemistry findings of heart and brain sampled from mice models of increasing DMD severity also showed progressively increasing levels of TSPO expression. Biodistribution data also showed heightened uptake of 18F-FEPPA across different tissue types—particularly in the heart and brain.

Conclusion: These data are the first to demonstrate the presence of inflammatory biomarkers in the brain during DMD, and model in-vivo the suspected link between cardiac and neurodegeneration using inflammation in a dystrophic disease. Current gold-standard for DMD prognosis are muscle biopsies which are localized to specific muscle segment despite DMD being a systemic ailment. This method highlights the advantage of using 18F-FEPPA PET to non-invasively detect DMD progression—increasing the possibility to propose early intervention prior to severe muscular or neurological damage.