RESEARCH PROGRESS REPORT SUMMARY

Grant 02165-MOU: Identification of Biomarkers and Therapeutic Targets for Canine Degenerative Myelopathy: The Search for A Cure

Principal Investigator: Joan Coates, DVM
Research Institution: University of Missouri, Columbia
Grant Amount: $154,077.00
Start Date: 1/1/2015 End Date: 12/31/2018
Progress Report: Mid-Year 4
Report Due: 6/30/2018 Report Received: 7/16/2018

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Original Project Description:

Degenerative myelopathy (DM) is an adult onset disease of the spinal cord causing progressive weakness and paralysis of the hind limbs and eventually all limbs. Mutations in an enzyme that converts superoxide to water and hydrogen peroxide, superoxide dismutase 1 (SOD1), have been linked to DM and amyotrophic lateral sclerosis (ALS-Lou Gehrig's disease). DM is associated with degenerative loss of axons, which transmit signals from the brain and spinal cord to their targets (muscle). Currently no diagnostic test exists that would allow for repeated measurements with minimal invasiveness. Dr. Coates is proposing to develop a test that would assay the blood and cerebrospinal fluid (CSF) for proteins that are exclusively found in axons under non-disease conditions, referred to as neurofilament proteins. They will correlate the concentrations of neurofilament proteins in CSF and blood with disease stage, and anticipate that neurofilament protein concentration in blood and CSF will increase as disease progresses. Such a test will allow for minimally invasive monitoring of disease. Furthermore, such a diagnostic test could be used to measure the success of therapy, which may be underway in a cohort of DM-affected dogs [Boxers and Pembroke Welsh Corgis (PWC)] (funded by NIH/NINDS). They will complement the test for neurofilament proteins with other studies that measure disease progression such as specific MRI techniques to evaluate the brain and spinal cord and electrical testing of the muscle and nerves. These are functional disease markers that are also being studied in ALS patients.

Funding for the research is provided through the efforts and generosity of the American Boxer Charitable Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee administration of funds and scientific progress reports.
Publications:


Abstract


Presentations:


2. Melissa J. Lewis, James Holland, Jeremy L. Shomper, Baye G. Williamson, Daniella Vansteenkiste, Katherine F. Bibi, Stefanie Lim, Janice Robertson, Joan R. Coates. Diffusion tensor imaging detects brain pathology in canine degenerative myelopathy. 29th International Symposium on ALS/MND. December 7-9, 2018; Glasgow Scotland, UK. Abstract submitted


4. Coates JR, Sah D. A gene therapy approach targeting SOD1 in a canine disease model of ALS. Workshop Translational Approaches for SOD1-ALS. December 7, 2017; Boston MA, USA.


7. Coates JR. 2016 Georgia Veterinary Medical Association Fall Convention. Diagnosis and treatment of canine degenerative myelopathy. Westin Atlanta Perimeter North, Atlanta, GA, November 4-6, 2016. (1 h)


11. Coates JR. Canine degenerative myelopathy. Brain Camp 2016 – Noteset. ACVIM/The Ohio State University, July 29, 2016. 1 h


15. Christine M. Sibigtroth, Maria R. Jones, Virginia B. Garcia, Joan R. Coates, Gayle C. Johnson, Eric L. Villalón and Michael L. Garcia. Lumbar spinal cord neuroprotective microglia and fractalkine are increased with disease progression in canine degenerative myelopathy. 2016 American College of Veterinary Internal Medicine Annual Forum. Denver, CO June 9, 2016. Accepted Oral Presentation. Won the ACVIM neurology resident research abstract award.


18. Christine M. Sibigtroth, Virginia B. Garcia, Gerry P.J. Shaw, Joan R. Coates, Michael L. Garcia. Increased phosphorylated neurofilament heavy (pNF-H) in CSF as a potential disease marker of canine degenerative myelopathy. 26th International Symposium on ALS/MND; December 11-13, 2015; Orlando FL, USA. Submitted 5/30/2015. Accepted: Poster Presentation (SW9; online page 8)


22. Coates JR. The Linus Pauling Institute (Dr. Joe Beckman) and Small Animal Rehabilitation Foundation (Dr. Wendy Baltzer), Oregon State University College of Veterinary Medicine. Canine degenerative myelopathy: A disease model of amyotrophic lateral sclerosis (Lou Gehrig’s disease). April 9, 2015. (1h)

Report to Grant Sponsor from Investigator:

Degenerative myelopathy (DM) is an adult onset disease of the spinal cord causing progressive weakness and paralysis of the hind limbs and eventually all limbs. Mutations in an enzyme that protects the spinal cord from oxidative stress are linked to DM and amyotrophic lateral sclerosis (ALS-Lou Gehrig’s disease). DM is associated with degenerative loss of axons, which transmit signals from the brain and spinal cord to their targets (muscle). Monitoring the progression of disease is critical for development of effective therapies, but currently no diagnostic test exists that would allow for repeated measurements with minimal invasiveness. We have developed a test that would assay the blood and cerebrospinal fluid (CSF) for proteins exclusively found in axons under non-disease conditions, referred to as neurofilament proteins. Preliminary data suggest that measuring
neurofilament proteins in CSF is a diagnostic marker for DM but we need to establish specificity data to distinguish between other central axonopathies. We have shown that neurofilament proteins in CSF remain elevated through all 4-disease stages. We will measure neurofilament proteins in CSF and serum to measure the success of therapy in a cohort of DM-affected dogs (funded by NIH/NINDS). We are complementing the test for neurofilament proteins with other studies that measure disease progression such as specific MRI techniques to evaluate the brain and spinal cord and electrical testing of the muscle and nerves. These functional disease markers used in ALS patients. We continue to collect preliminary data from DM affected dogs using magnetic resonance spectroscopy and diffusion tensor imaging to evaluate for difference in metabolites in the brain. After evaluation of more dogs, these preliminary data suggest a significant difference in some of the metabolites and in diffusion tensor imaging between DM-affected and normal dogs. The observed differences were independent of age, sampling area and sample time point. We are in the process of recruiting cases to continue to evaluate longitudinal study of disease measures and treatment efficacy of an antisense oligonucleotide therapy.