Canine ALS Model Provides Unique Opportunity for Therapy Testing

By Richard Robinson

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A canine version of ALS may provide a useful model in which to test some of the most advanced therapies against the human form of the disease, according to Joan Coates, D.V.M., Professor of Veterinary Medicine at the University of Missouri. Dr. Coates, a specialist in veterinary neurology, spoke recently in a webinar sponsored by The ALS Association.

In dogs, the disease is called canine degenerative myelopathy (CDM), and it shares some remarkable similarities to human ALS. It is a late-onset disease, beginning between the ages of 9 and 14 years, and leads to hind limb paralysis and the inability to walk within one year. It is characterized by muscle wasting and loss of both upper and lower motor neurons, as in ALS. Difficulty breathing and swallowing define the end stage of the disease, usually within 5 years of onset. Unlike ALS, loss of sensory function is prominent from the earliest stages.

Most surprisingly, CDM is due to mutation in the SOD1 gene, the same gene responsible for about 20% of all familial ALS cases. The mutation has been found in more than two dozen dog breeds. In the normal version of the gene, the DNA code causes the amino acid glutamate to be added to the SOD1 protein in a specific place. In the CDM-causing mutation, a lysine amino acid is encoded instead. As in the human version, the mutation causes the protein to aggregate, or clump together, which is believed to contribute to the disease process.

All these factors contribute to the potential utility of the canine disease as a model for ALS. In addition, dogs are much closer in size to humans than are mice, Dr. Coates pointed out, and have a more complex nervous system, meaning that results of treatment in the dog may better predict results in humans than the same treatment in mice.

With funding from The ALS Association, Dr. Coates is currently collaborating with two leading ALS researchers to determine how the dog model can best be used for testing therapies. With Dr. Tim Miller at Washington University in Saint Louis, she is exploring the use of antisense molecules against the SOD1 messenger RNA, similar to the recent safety trial of antisense in people with the SOD1 mutation. The goal of the treatment is to prevent formation of the protein. A major focus of that work is to develop biomarkers for future clinical trials of
antisense therapy. For instance, the large size of the dog limb muscle makes it amenable to the same electromyography measurements used in humans, she noted.

With Dr. Janice Robertson of the University of Toronto, she is beginning a trial of an immunization treatment against the misfolded SOD1 protein. Here, the goal is to provoke the immune system to remove and degrade the protein before it aggregates or otherwise causes harm. The goal of the trial is to determine whether treatment can delay loss of ambulation, as well as to test biomarkers that could be used in human trials.

Dr. Coates is also collaborating with The Broad Institute, a major genomic discovery laboratory, to look for other genes that influence the onset and progression of the disease. These may provide clues about similar genes in humans, which could in turn suggest new avenues for treatment.

“These studies highlight the importance of having diverse model systems,” said Lucie Bruijn, Ph.D., M.B.A., Chief Scientist for The Association. “They also point out the incredible value that can come from collaborations among researchers in different fields. It is great to see such talent and collaboration coming together.”

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