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COGNITIVE DECLINE IN A DOG MODEL FOR AN INHERITED NEURODEGENERATIVE DISEASE USING T-MAZE PERFORMANCE

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Neuronal ceroid lipofuscinosis is a heritable neurodegenerative disease characterized by accumulation of autofluorescent lysosomal storage granules in neural tissues accompanied by cognitive decline, seizures, and locomotor deficits. Our laboratory identified a mutation, occurring in Dachshunds, of tripeptidyl peptidase I (*TPPI*), the canine ortholog of human *CLN2* (Awano et al., 2006). In order to establish biomarkers for evaluating experimental therapies in this model, we characterized phenotypic changes in seven age-matched dogs over an 8 month period.

Genotyping indicated that 2 puppies were homozygous for the mutant allele and 5 were homozygous normal. All dogs had regular physical and neurologic examinations. Funduscopy, electroretinography and cognitive function testing were performed at regular intervals. Cognitive function was assessed with the CanCog T-maze apparatus.

Physical examination remained normal for all dogs. In affected dogs, changes in funduscopy, ERG and pupillary light reflexes presented between 5.5 and 6 months of age. By 7 months, mild intention tremor and cerebellar ataxia were observed. Affected dogs were still visual at 8 months. MRI revealed diffuse cerebral and cerebellar atrophy and brain weights were reduced by 15% when compared to normal dogs of similar size.

There were pronounced differences in performance between affected and normal dogs in the T-maze learning task. A cognitive deficit in the affected dogs was clearly present at 4 months of age and progressively worsened at each subsequent time point. We conclude that

the reversal learning task is a sensitive, early measure of disease progression which could serve as a useful biomarker for evaluation of treatment strategies.

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