PUPILLARY LIGHT REFLEX DEFICITS IN A CANINE MODEL OF NEURONAL CEROID LIPOFUSCINOSIS AND THE EFFECTS OF ENZYME REPLACEMENT THERAPY

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ABSTRACT

The pupillary light reflex (PLR) is a change in pupil size that occurs in response to light entering the eye and requires functional integrity of the retina and specific neural pathways in the central nervous system (CNS). Pupillography or quantitative analysis of the PLR allows its use as a biomarker for monitoring disease progression in neurological disorders that affect these pathways. A late-infantile form of neuronal ceroid lipofuscinosis (CLN2) results from a lack of the lysosomal enzyme TPP1. Dogs affected by CLN2 present with progressive ataxia, cognitive and behavioral changes, myoclonic seizures and vision loss accompanied by progressive brain atrophy. A strong resemblance to human CLN2 makes these dogs an excellent model in which to test possible treatments prior to beginning human clinical trials.

Using equipment and methodology we developed, the PLR was evaluated in response to white light stimuli of various intensities in normal and CLN2-affected dogs. CLN2-affected dogs exhibit PLR deficits that progress with age and likely result from a decline in retinal function and neurodegeneration in areas of the CNS involved in modulating the PLR. Studies were undertaken to determine if TPP1 enzyme replacement therapy (ERT) to the CNS could ameliorate PLR deficits associated with CLN2. Some dogs treated with ERT exhibited a substantial delay in the appearance of PLR deficits compared with untreated affected dogs without a preservation of retinal function. It is likely that ERT normalized the PLR by preventing degeneration in areas of the central nervous system involved in modulating the PLR.

The characterization of disease-related alterations to the PLR contributes to our understanding of the pathology underlying CLN2. Preventing development of PLR deficits can be used to objectively assess the efficacy of therapeutic interventions for CLN2 that are currently being evaluated.