OBJECTIVES

To investigate the effect of genetic and environmental factors on neuropathological and behavioural changes in an established mouse model of juvenile onset amyotrophic lateral sclerosis (ALS2).

INTRODUCTION

The ALS2 gene encodes alsin, a protein with guanine nucleotide exchange factor (GEF) activity and a role in the development and maintenance of the actin cytoskeleton. Null and conditional mutations in ALS2 are characterized by juvenile onset, slow progression, and heterogeneous clinical phenotypes including juvenile onset primary lateral sclerosis (JPLS), infantile onset ascending hereditary spastic paraparesis (IHASP), and juvenile onset ALS (ALS2)1. However, Als2 deficient mouse models have failed to reproduce the classical hallmark symptoms of motor neuron disease or ALS2. Therefore, we investigated the possibility that ALS2-linked pathologies arise from the combinatorial effects of genetic predisposition and neurotoxins in the diet. In particular, we examined the effect of exposure to neurotoxic dietary sterol glucosides (SG) on the onset and progression of an ALS2 motor phenotype in both Als2 knockout (KO) and their wild-type littermates. We hypothesize that Als2 mice were more susceptible to neuropathological changes when exposed to neurotoxins.

METHODS

We have established a colony of Als2-/- mice started from mice produced by Devon et al2. The colony was maintained by breeding homozygotes to produce Als2+/- offspring (N=33) and breeding homozygotes to yield Als2-/- (N=9). Wild type littermates of the same strain (n=20) were obtained from Jackson Laboratories. Starting at 10 weeks of age, a total of 23 mutant mice received daily dietary mouse chow pellets containing SG at 42mg SG/kg body weight (to a total weight of 1.5g per pellet). At the same time, 19 age-matched mutants also received SG-containing pellets. Both treated and control mice were provided with a daily total food intake of 2.5g. Animals were assessed monthly for motor dysfunction by measuring grip strength, motor coordination, and clasp reflex. Assessments for gait disturbances were administered at 5, 7, 9, and 12 months of age. Upon reaching 15 months of age, animals were euthanized and perfused intracardially. Spinal cord and brain were collected and processed for histology.

CONCLUSION

Als2-deficient mice demonstrate significant differences in muscle strength and motor function compared to wild type counterparts, including superior overall performance on the Rotarod and grip strength tests. SG-treated mice demonstrated significant gait disturbances compared to controls while walking on a treadmill. Exposure to sterol glucosides in combination with genetic predisposition produces the greatest motor deficits than either stressor alone.

REFERENCES


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