Early Detection and Characterization of Neurological Function in SOD1 G93A mice

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INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease, which to date lacks effective treatment options. In an attempt to support drug discovery efforts in this therapeutic area, we have initiated a panel of preclinical behavioral tests in a common mouse model of ALS. These transgenic mice over-express human SOD1-G93A and are commonly employed as an animal model of familial ALS [1,2]. The present study was aimed at identifying behavioral tests that are most sensitive to the emergence of behavioral/neurological deficits in male and female SOD1 G93A mice (SOD1) compared to wild-type (WT) controls. Specifically, the test battery consisted of commonly used metrics such as fore- and hind-limb grip strength, rotarod, open field and more complex proprietary algorithm-based behavioral platforms such as NeuroCube ® and SmartCube ® Systems.

METHODS

ANIMALS

➢Male and female mice transgenic for human *SOD1 G93A [B6SJL-TgN(SOD1-G93A)1 GUR]* **(SOD1)** were used in this study starting at an age of 7 weeks (Jackson Laboratories, Bar Harbor, ME).

BEHAVIOR ANALYSIS

➢**Grip Strength:** Grip strength was measured using a push-pull gauge (Chatillion Force Gauge, San Diego Instruments, San Diego, CA) with a mesh grip piece attached. The fore- and hind limb grip force was recorded on the strain gauge.

➢**Rotarod:** Motor coordination was assessed by Rotarod. Mice were placed on an accelerating rotarod and the latency to fall was recorded. The mice were given three accelerating trials of 3 minutes (4-28 rpm).

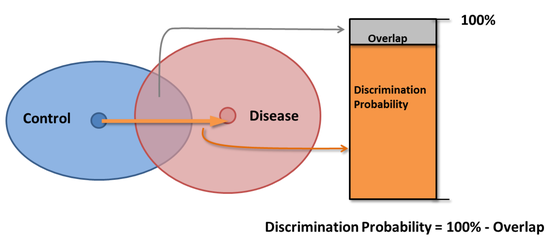
➢**Open Field:** The open field test was run in test arenas measuring 10.75” x 10.75” x 8”H, with horizontal and vertical infra-red (I/R) beams to capture activity (model ENV 510; Med Associates, St. Albans, VT). Data were captured via acquisition and analysis software (Activity 4.30; Med Associates, St. Albans, VT).

➢**SmartCube® System:** This proprietary platform uses computer vision to automatically capture and score changes in activity, spatial patterns, spontaneous behavior, reactive behavior, gait, and other measures in mice.

➢**NeuroCube® System:** This proprietary platform uses computer vision to automatically capture and score changes in gait (geometry and dynamics), paw pressure, paw imaging, body positioning, and other measures in mice or rats.

➢**Feature Analysis:** Phenotypic data are typically presented by two classes, Control and Disease (SOD-1). The original feature set is transformed to the non-redundant de-correlated ranked features space. The Control and Disease data are then plotted in the coordinate system formed by the two highest-ranked (best-discriminating between the two group’s new features). The quality measure of disease model = Overlap between the Control and Disease groups (*Discrimination Probability* = 100% - Overlap)

➢**Statistical Analyses:** Survival data, where loss of righting reflex was used as a surrogate measure, were analyzed with a Kaplan-Meier analysis. Data obtained in grip strength, rotarod and open field tests were analyzed using multi-factorial analyses of variance (ANOVA). For each group 13-15 mice were used.



RESULTS

Figure 1: Decline in Body Weight and Survival of SOD1 Compared to Wild-type Mice

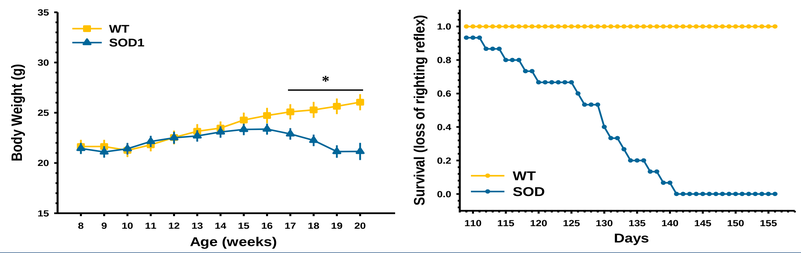


Figure 2: Decline in Motor Coordination, Muscle Strength and Open Field Activity with Disease Progression in SOD1 Compared to Wild-type Mice

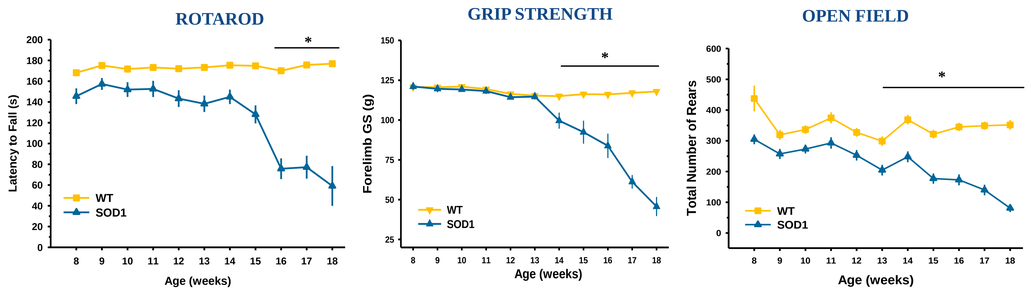
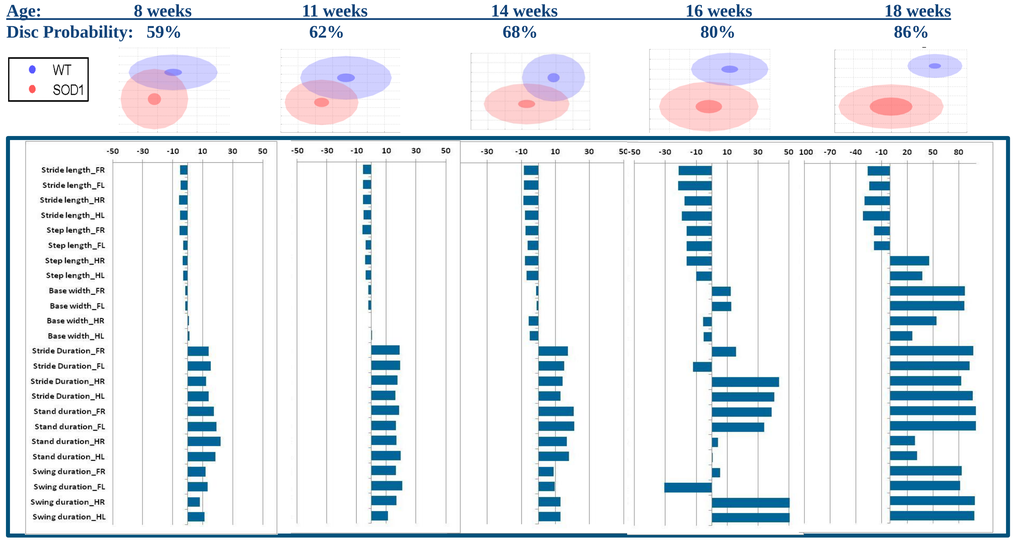


Figure 3: Disease Progression of Gait Feature Using NeuroCube ® Technology in SOD1 Compared to Wild-type Mice



ABREVIATIONS: HL (Hind Limb); FL (Fore Limb), X axis represents discrimination probability as a % of WT mice.

Figure 4: Gait Deficits at 16 Weeks of Age in SOD1 Compared to Wild-type Mice Using NeuroCube Technology ®

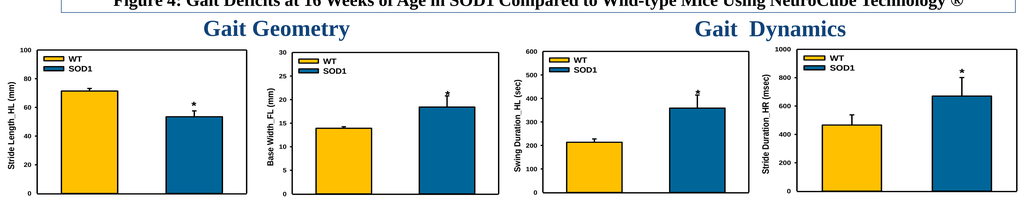


Figure 5: Disease Progression with Age Using SmartCube ® Technology in SOD1 Compared to Wild-type Mice

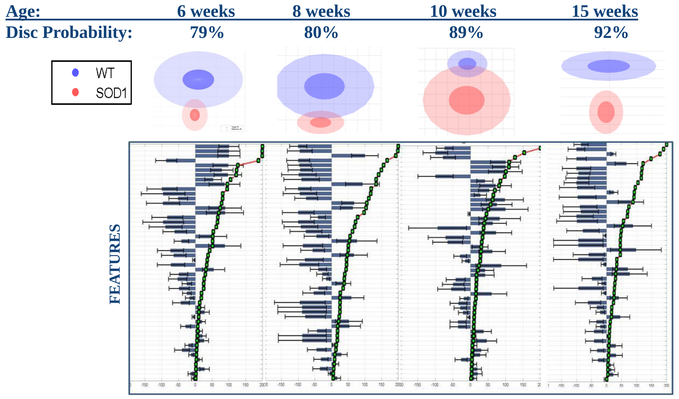
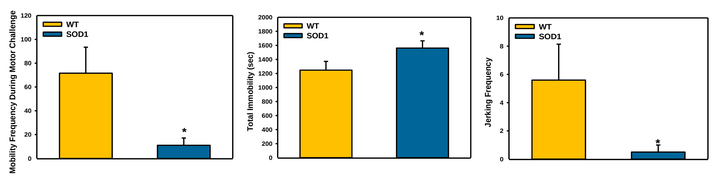


Figure 6: Motor Deficits at 15 Weeks of Age in SOD1 Compared to Wild-type Mice Using SmartCube Technology ®



DISCUSSION

➢The platform of behavioral tests employed here demonstrate that routine behavioral paradigms such as rotarod, grip strength and open field are able to detect neurological and motor function deficits in SOD1 versus WT mice as early as 13-15 weeks of age.

➢ Interestingly, more advanced computer vision systems are able to identify distinctive behavioral patterns and discriminate the disease phenotype as early as 6-8 weeks of age.

➢Specifically, by using the NeuroCube ® system to measure gait deficits, we found that SOD-1 mice showed a reduction in both gait geometry and gait dynamic features which was evident as early as 8 weeks and progressed with age.

➢Similarly, by using our SmartCube® technology that measures whole animal behavior, we identified behavioral changes in motor-related features and as early as 6-8 weeks of age in the SOD-1 mice.

➢This earlier period of disease identification presents a valuable model in which to explore and improve future assessment of potential therapeutic approaches for ALS.

ACKNOWLEDGEMENTS

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REFERENCES

➢1. Kafkafi et al., Behavioral Neuroscience (2008)

➢2. Ramsden et al., J Clin Pathol: Molecular Pathol (2001)