Spinocerebellar ataxia 1 (SCA1) is a neurodegenerative disease with onset in the third or fourth decade of life. The condition is characterized by progressive problems with movement. Initial signs include issues with coordination and balance. The disease is caused by the expansion of a CAG repeat in the gene encoding protein ataxin-1 (Orr et al., 1993). The longer the expansion, the earlier the onset and worse trajectory of the disease course. Further studies into the molecular mechanism of the disease is on-going, and little is known about the regional-specific brain volumetric changes that may accompany the onset of SCA1. In Huntington’s disease, decreases in striatal volume are accompanied by increases in cerebellar volume (Niccolini & Politis). We hypothesize the inverse may occur in SCA1.

The purpose of this research was to investigate the extent to which brain volumetric changes correlate with the development of motor impairments in SCA1. Because changes in proportional cerebellum and striatal volume in addition to just the cerebellum in humans with SCA1 are warranted.

Methods

Research Objectives

Methods

Introduction

The purpose of this research was to investigate the extent to which brain volumetric changes correlate with the development of motor impairments in SCA1.

We tested the hypothesis that cerebellar abnormalities in SCA1 mice may be detectable at an early age, may predict motor impairments, and that changes in striatal volume may compensate for dysfunctional cerebellum.

Methods

The SCA1144Q/2Q mouse has double the number of glutamine residues typically found in the human population. A larger sample size and observations in a longer disease course are needed to fully understand the relationship between volumetric changes in the cerebellum and striatum.

Presenting data from the SCA1144Q/2Q mouse model adds insight into the developmental trajectory of SCA1 and provides an earlier window of time to assess symptoms in human patients.

Future Directions

Deviations from this study included the use of an MRI scanner for imaging, which allowed for a more accurate assessment of brain volume changes.

Limitations

Acknowledgements

I would like to thank the entire team in the Parker Lab, the Iowa Neuroscience Institute, the Belin-Blank Center, and the entire faculty of SSTP for providing me with this research opportunity.

References


Conclusions

The early cerebellar overgrowth observed in the SCA1144Q/2Q mice should be investigated. This can potentially be done using histological analyses of neurons within the cerebellum, especially Purkinje cells, during the early stages of the disease.

We hypothesize the inverse may occur in SCA1.

Future studies investigating volumetric changes in humans with SCA1 are warranted.


**Developmental characterization of motor impairments in mice with spinocerebellar ataxia1**

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**Introduction**

- Spinocerebellar ataxia 1 (SCA1) is a neurodegenerative disease with onset in the third or fourth decade of life.
- The condition is characterized by progressive problems with movement. Initial signs include issues with coordination and balance.
- The disease is caused by the expansion of a CAG repeat in the gene encoding protein ataxin-1 (Orr et al., 1993). The longer the expansion, the earlier the onset and worse trajectory of the disease course.
- Further studies into the molecular mechanism of the disease is on-going, and little is known about the regional-specific brain volumetric changes that may accompany the onset of SCA1.
- In Huntington’s disease, decreases in striatal volume are accompanied by increases in cerebellar volume (Niccolini & Politis). We hypothesize the inverse may occur in SCA1.

**Research Objectives**

- The purpose of this research was to investigate the extent to which brain volumetric changes correlate with the development of motor impairments in SCA1.
- We tested the hypothesis that cerebellar abnormalities in SCA1 mice may be detectable at an early age, may predict motor impairments, and that changes in striatal volume may compensate for dysfunctional cerebellum.

**Methods**

- Righting Reflex: Mice were placed on their backs and time to replant all four paws on the surface of the table was recorded.
- Rotarod: Mice were placed on a rotating rod that accelerates from 4 rpm to 60 rpm over the course of five minutes. The time mice remained on the rod before falling off or the first passive rotation was recorded.
- Balance Beam: Mice were placed on a balance beam and the travel time from the start line to the finish line was recorded.
- Open Field: Mice were placed in a 43 cm x 43 cm open field chamber and movements were tracked using Plexon Cineplex Studio software (10 mins).

**Erasmus Ladder**

- An additional cohort of WT and SCA1 mice was tested for motor and motor learning impairments on the Erasmus Ladder where the steps and missteps of the mice are detected. Trials involving motor learning include a warning beep to indicate a raised barrier which the animal learns to jump as an indication of motor learning.

**Neural Imaging**

- **MRI Scan of Mouse Brain**
- Representative Rodent MRI: Horizontal (A), sagittal (B), and coronal (C).

**Results**

- **Righting Reflex, Rotarod, & Balance Beam**
- **Open Field**
- **Erasmus Ladder**
- **Neural Imaging**

**Conclusions**

- The emergence of motor impairments around week 5 in the SCA1144Q/2Q mouse model adds insight into the developmental trajectory of SCA1 and provides an earlier window of time to assess symptoms in human patients.
- Because changes in proportional cerebellum and striatal volumes coincided with motor deficits, new therapies may be developed to target these brain structures.

**Future Directions**

- The early cerebellar overgrowth observed in the SCA1144Q/2Q mice should be investigated. This can potentially be done using histological analyses of neurons within the cerebellum, especially Purkinje cells, during the early stages of the disease.
- This work also motivates future studies focusing on behavioral impairments correlated to striatal volume in addition to just the cerebellum in SCA1.
- Future studies investigating volumetric changes in humans with SCA1 are warranted.

**Limitations**

- The SCA1144Q/2Q mouse has double the number of glutamine residues typically found in the human population.
- A larger sample size and observations in a longer disease course are needed to fully understand the relationship between volumetric changes in the cerebellum and striatum.

**Acknowledgements**

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**References**
