Umeå University Medical Dissertations, New Series No 1854

Extraocular Muscles in Amyotrophic Lateral Sclerosis

Anton Tjust

Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt försvar i sal N320, vån 3, Naturvetarhuset, fredagen den 27 januari, kl. 09:00. Avhandlingen kommer att försvaras på engelska.

Fakultetsopponent: Docent Eva Hedlund
Institutionen för neurovetenskap, Karolinska Institutet Stockholm, Sverige.

Institutionen för Integrativ Medicinsk Biologi
Institutionen för Klinisk vetenskap, Oftalmologi
Umeå universitet
Umeå 2017

Organization
Umeå University

Document type
Doctoral thesis

Date of publication
9 January 2017

Department of Integrative Medical Biology
Department of Clinical Sciences, Ophthalmology

Author
Anton Tjust

Title
Extraocular Muscles in Amyotrophic Lateral Sclerosis

Abstract

Amyotrophic lateral sclerosis (ALS) is an incurable neurodegenerative disease of motor neurons characterized by muscle paralysis and death within 3-5 years of onset. However, due to unknown mechanisms, the extraocular muscles (EOMs) remain remarkably unaffected. The EOMs are highly specialized muscles that differ from other muscles in many respects, including innervation and satellite cells (SCs). Understanding whether these factors play a role in the relative sparing of EOMs in ALS could provide useful clues on how to slow down the progression of ALS in other muscles.

The EOMs and limb muscles from terminal ALS patients and age-matched controls as well as the commonly used $SOD1^{G93A}$ ALS mouse model were studied with immunofluorescence. Antibodies against neurofilament and synaptophysin were used to identify nerves and neuromuscular junctions (NMJs); against Pax7, NCAM, MyoD, myogenin, Ki-67, dystrophin and laminin, to identify SCs and their progeny in EOMs and limb muscles. The proportion and fiber size of myofibers containing myosin heavy chain (MyHC) slow tonic and MyHC slow twitch were also determined in human EOMs.

The abundance of SCs differed extensively along the length of control human EOMs, being twice as abundant in the anterior portion. Pax7-positive cells were also detected in non-traditional SC positions. EOMs from terminal ALS patients showed similar numbers of resting and activated SCs as the controls. In limb muscles of ALS patients, the number of resting and activated SCs ranged from low (similar to normal aged, sedentary individuals) to high numbers, especially in muscles with long duration of disease and varied between the upper and lower limbs. The EOMs maintained a high degree of innervation compared to hindlimb muscles of symptomatic $SOD1^{G93A}$ mice. MyHC slow tonic fibers were less abundant in ALS patients than in controls. The change seemed more pronounced in bulbar onset patients, and in this group of subjects only, there was a strong association between decline in MyHC slow tonic fibers and age of death. Notably, the decline in MyHC slow tonic fibers was unrelated to disease duration.

Our data suggested that SCs play a minor role in the progression of ALS in general and in the sparing of the EOMs in particular. The generally preserved innervation in the EOMs of G93A mice may reflect distinct intrinsic properties relevant for sparing of the oculomotor system. Even though the EOMs are relatively spared in ALS, MyHC slow tonic myofibers were selectively affected and this may reflect differences in innervation, as these fibers are multiply innervated.

Keywords
ALS, EOM, Satellite cells, innervation, neuromuscular disease, neurodegenerative disease, immunofluorescence.

Language
English

ISBN
978-91-7601-618-3

ISSN
0346-6612

Number of pages
56 + 4 papers