IJAE
Vol. 117, n. 2 (Supplement): 22, 2012
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Time course and mechanisms of motoneuron death in a type II spinal muscular atrophy mouse model

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Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease leading to motor impairment, muscle atrophy and premature death caused by motoneuron degeneration. It is caused by the deletion/mutation of the telomeric survival motoneuron gene (SMN1), whereas the number of copies of the centromeric gene SMN2, which produces reduced levels of functional protein, is inversely proportional to the severity of disease (from severe to mild). However, the causes of selective motoneuron death still remain elusive. To clarify the time course and the mechanisms of motoneuron (MN) death, we investigated the SMNdelta7 murine model of SMA II (the intermediate SMA form), in which motor dysfunction leads to death at P13.

We collected brains and spinal cords from SMA II and wild type embryos/pups at E19, P4, P9 and P13 for neuron counts and immunohistochemistry. Newborns underwent a battery of motor tasks and were assessed daily for body weight and survival.

In ChAT-immunoreacted and Nissl-stained spinal sections, stereological counts reported a dramatic reduction in the number of lower (cervical) MNs (almost 40% at P13) in the SMA II mice; in particular MNs innervating proximal muscles seemed the most affected. In addition, we noticed an increased ChAT expression through time, making ChAT-MN count less reliable than Nissl-ones.

Moreover, even though most studies mainly report death of lower motoneurons, stereological counts in the motor cortex revealed a specific decrease of layer V cortical pyramidal neurons in SMA II mice compared to WT. Also the corpus callosum thickness appeared halved in the P9 SMA II mice.

Finally, immunohistochemistry against cleaved Caspase-3 and LC-3 suggested an involvement of the apoptotic and autophagic modes of cell death, respectively.

Therefore, at least in the animal model, SMA affects both upper and lower motoneurons, and SMN1 role in neuronal development and survival should be further investigated. Targeting apoptotic and autophagic pathways can delay the disease progression, as we are currently showing in other studies.

Keywords: Stereological count, motor cortex, apoptosis, autophagy.