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Morphological characterization of a single knock out double transgenic mouse model of spinal muscle atrophy

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Spinal muscular atrophy (SMA) is a neurogenetic autosomal recessive disorder characterized by degeneration of lower motor neurons associated with muscle atrophy and paralysis. Due to a lack of an in depth knowledge on the molecular mechanisms and fine neuropathology of SMA, validation of appropriate animal models is key in fostering SMA research.

Recent studies set up an animal model showing long survival and slow disease progression. This model is knocked out for mouse SMN (Smn−/−) gene and carries a human mutation of the SMN1 gene (SMN1A2G), along with human SMN2 gene.

In the present study we used this knockout double transgenic mouse as a SMA III model, to characterize the spinal cord pathology along with motor deficit at prolonged survival times (18 months). This long time interval (i.e. up to 535 days) was never analyzed before especially concerning specific motor tasks.

We found that the delayed disease progression was likely to maintain fair motor activity despite a dramatic loss of large motor neurons (44.77%). At this stage, spared motor neurons showed significant cell body enlargement. Moreover, similar to what was described in patients affected by SMA we found neuronal heterotopy in the anterior white matter. Motor neuron degeneration was accompanied by the loss of SMN protein in the spinal cord.

In summary, the present study validates over a long time period a SMA III mouse model showing neuropathology reminiscent of human patients and provide a useful experimental model to probe novel therapeutic strategies.

Keywords: Spinal muscle atrophy, mouse model, motor neurons, neurodegeneration.