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- ACID SPHINGOMYELINASE KNOCKOUT MICE: PERIPHERAL NERVOUS SYSTEM ALTERATIONS -

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INTRODUCTION: Glicolipid metabolism disorders with anomalous turnover of cell membranes are the pathological basis of Niemann-Pick Disorders (NPD). NPD type A is an infantile neurodegenerative disease, with progressive psychomotor retardation, visceromegaly and death by 3-4 years. On molecular basis, NPD type A is characterized by lysosomal storage of sphingomyelin (SM), a constituent of the external eukaryotic plasma membranes. SM storage derives from loss or low activity of acid sphingomyelinase (ASM), a lysosomal enzyme that degrades SM in sphingosine and ceramide, two second messengers involved in receptor-signal transduction processes that lead to apoptosis, differentiation and proliferation of cells.
In this study we examined the pathological effects of NPD type A on the peripheral nervous system (PNS) in a mouse model, considering earlier times of development in comparison to the data previously reported in literature.
MATERIAL AND METHODS: Three-month-old acid sphingomyelinase knockout (ASMKO) and wild-type mice were used to characterize morphological and ultrastructural changes in PNS. Dorsal root ganglia (DRG) and sciatic nerves were processed for light and electron microscopy using standard methods.
RESULTS: Light microscopy morphological analysis on toluidine blue-stained sections revealed no alteration of DRG neurons shape, but the occurrence of two types of large vacuolar inclusions in the cytoplasm of neurons and satellite cells was observed in ASMKO mice: dark vesicular aggregates, and clear vacuoles. These pathological aspects were also present in the cytoplasm of Schwann cells in peripheral nerves. Axons were normal and no active myelin breakdown was observed on transverse sections, although some myelinated fibres had a reduction in myelin thickness in comparison with axon diameter. On electron microscopy evaluation, osmiophilic inclusions in DRG neurons were mostly multilamellar bodies, while satellite cells had large and dense intracytoplasmatic vesicles with rounded shape. The axons and microtubular organization in peripheral nerves appeared normal in ASMKO compared to wild type mice.
CONCLUSIONS : ASMKO is a reliable transgenic model of NPD type A, which reproduces most of the pathological changes observed in the central nervous system (especially in cerebellum), while only few information about the PNS is available. In this preliminary studies we observed the characteristic foam cells described as Niemann-Pick cells in PNS, confirming its involvement even at early stages in NPD. The absence of an evident primary demyelination and the normal structure of axons in sciatic nerves do not validate observations of a severe involvement of peripheral nerves in this model, even if the presence of myelin-like structures in vacuolar inclusions of satellite and Schwann cells is confirmed.
In agreement with previous studies performed at later development stages, ASMKO mice do not reproduce the severe myelinopathy described in some cases of human NPD type A.

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