Oligodendrocytopathy and astrocytopathy precede myelin loss and blood-brain barrier disruption in a mouse model of osmotic demyelination syndrome

Osmotic demyelination syndrome (ODS) is a non-inflammatory disorder of the CNS myelin that occurs following too rapid correction of chronic hyponatremia. The physiopathology remains unclear although hypothetical mechanisms include blood-borne myelinotoxic factors or deleterious osmotic fluctuations focally in white and gray matter-mixed rich regions. To morphologically and functionally investigate the development of ODS in vivo, we generated a novel murine model of ODS. Eriochrome and anti-MBP stainings revealed typical demyelinating lesions in the thalamus, mesencephalon, pons and subcortical regions at 48 hours post-correction in ODS mice brains. Lesions were associated with a significant decrease of APC+ and Cx47+ oligodendrocytes, starting as soon as 24 hours post-correction. Oligodendrocytopathy was temporally and spatially correlated with the loss of astrocyte markers (ALDH1L1, AQP4, S100) and both with the areas affected by demyelination. Using IgG immunostaining and Evans Blue extravasation assay, we demonstrated that blood-brain barrier disruption started at 48 hours post-correction. Following osmotic insult, Iba1+ microglial cells infiltrated the brain tissue within 12 hours post-correction, while acquiring an activated morphology, from quiescent type A to types B, C and D at latter time points. IL-1ß and LIF mRNA, known to influence myelin integrity, were both significantly upregulated in the thalamus of ODS mice. ODS mice showed inabilities to perform motor tasks (Rotarod and Grip strength) and impairments in brainstem auditory evoked potentials. In conclusion, this murine model of ODS reproduces the demyelinating lesions observed in human pathology and raise new questions about the early role played by astrocytes or microglial cells in demyelination.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.