Therapy and pathogenesis of metachromatic leukodystrophy: Studies in a mouse model.

Metachromatic leukodystrophy is a severe lysosomal storage disorder caused by the deficiency of the sulfatide degrading enzyme arylsulfatase A (ASA). In the nervous system this leads to sulfatide storage in oligodendrocytes/Schwann cells, subsets of neurons and astrocytes. Patients develop a wide variety of neurologic symptoms, which are due to progressive demyelination. In ASA deficient mice the sulfatide storage pattern is similar to that in humans. The mice do, however, not develop the widespread demyelination observed in patients.

To assess the therapeutic potential of enzyme replacement therapy (ERT), ASA knockout mice were treated by intravenous injection of recombinant human ASA. The uptake of injected enzyme was high into liver, moderate into peripheral nervous system (PNS) and kidney and very low into brain. A single injection led to a time- and dose-dependent decline of the excess sulfatide in PNS and kidney by up to 70%, but no reduction was seen in brain. Four weekly injections with 20 mg/kg body weight not only reduced storage in peripheral tissues progressively, but surprisingly also reduced sulfatide storage in brain and spinal cord. Improved neuromotor coordination capabilities and normalized peripheral compound motor action potential demonstrate the benefits of ERT on the nervous system function.

Since ASA deficient mice lack demyelination which is the pathological hallmark of MLD we attempted to aggravate the phenotype of ASA deficient mice. For that purpose we generated transgenic mice, which overexpress the sulfatide synthesizing enzyme galactosylceramide-sulfotransferase (CST) under the control of the PLP promoter in oligodendrocytes or the UDP-galactose:ceramide galactosyltransferase (CGT) under the control of the Thy1.2 promoter in neurons. The transgenic mice were crossed with ASA deficient mice. The rationale behind this approach is that the transgenes should cause an enhanced synthesis of sulfatide, which on the background of ASA deficient mice should enhance sulfatide storage and thus the phenotype.

PLP- CST transgenic/ASA deficient mice store about twice as much sulfatide as ASA deficient mice. In contrast to the ASA deficient mice, they also develop severe motor coordination deficits at the age of about 12 months. Histological examination demonstrates demyelination in the peripheral and central nervous system. This shows that the enhancement of sulfatide synthesis by the transgene causes an aggravation of the myelin pathology compared to the mice which are ASA deficient only. Thy1.2-CGT transgenic/ASA deficient mice showed an enhanced accumulation of C18:0 fatty acid containing sulfatide in the cortex and storage material could be detected histochemically in neurons of spinal cord and forebrain. Animals develop severe motor deficits at the age of 2 months and there life span is reduced to 6 to 11 months. Ultrastructural examination revealed axonal degeneration. This suggests, that neuronal storage contributes to the neurologic deficits occuring in metachromatic leukodystrophy.