Lysosomal storage disorders (LSDs) are caused by the defective activity of lysosomal pro tease, which results in intracellular accumulation of undegraded metabolites. Sphingolipid (SL) storage disorders are a sub-group of LSDs, in which unmetabolized SLs and glycosphingolipids accumulate. Research over the past few years has demonstrated that SL storage can result in multiple direct or indirect effects on various cellular compartments and on biochemical pathways. SL storage disorders are normally associated with devastating neurodegeneration and death at early age.

Gaucher disease (GD), the most common LSD, is caused by the defective activity of glucocerebrosidase (GlcCerase), the lysosomal hydrolase responsible for glucocerebroside (GlcCer) degradation. As a result of this autosomal, recessive genetic defect, the glucosphingolipids, GlcCer and glucosylsphingosine accumulate intracellularly. Tissue macrophages engorged with glucolipid-laden lysosomes (‘Gaucher cells’) are the hallmark of the disease.

Generation of animal models that faithfully recapitulate the three clinical sub-types of GD has proved to be more of a challenge than first anticipated. The first mouse to be produced died within hours after birth due to skin permeability problems, and mice with point mutations did not display symptoms correlating to human disease and also died soon after birth. Recently, conditional knockout mice (the ‘Karlsen mouse’) that mimic some features of the human disease have become available, and this mouse has been of huge importance for advancing our understanding of the neurological changes that occur in neurological forms of GD.

The rare neuropathic forms of GD are characterized by profound neurological impairment and neuronal cell death, but little is known about the neuropathological changes that underlie these events. We systematically examined the onset and progression of various neuropathological changes (including microglial activation, astrogliaisis and neuron loss), and documented the brain areas that are first affected, which may reflect vulnerability of these areas to GlcCerase deficiency. We have also identified neuropathological changes in several brain areas and pathways, such as the substantia nigra reticulata, reticulotegmental nucleus of the pons, olivary nucleus and the somatosensory system, which could be responsible for some of the neurological manifestations of the human disease. In addition, we have established that microglial activation and astrogliaisis are spatially and temporally correlated with selective neuron loss.

We have also delineated the role of neuroinflammation in the pathogenesis of neuropathic GD and demonstrated significant changes in levels of inflammatory mediators in the brain. Levels of mRNA expression of interleukin-1β, tumor necrosis factor-a, tumor necrosis factor-a receptor, macrophage colony-stimulating factor and transforming growth factor-β were elevated by up to ~30-fold, with the time-course of the increase correlating with the progression of disease severity. The most significant elevation was detected for the chemokines CCL2, CCL3 and CCL5. Blood-brain barrier disruption was also evident in neurodegenerative disease GD mice. Finally, extensive elevation of nitrotyrosine, a hallmark of peroxynitrite formation, was observed, consistent with oxidative damage caused by macrophage/microglia activation. Together, our results suggest a cytopathic role of activated microglia in neuropathic GD. We suggest that once a critical threshold of GlcCerase storage is reached in neurons, a signaling cascade is triggered that activates microglia, which in turn releases inflammatory cytokines that amplify the inflammatory response, contributing to neuronal death.

Finally, Parkinson’s disease is associated with mutations in the GlcCerase gene. We performed an exhaustive literature search and found that additional LSDs might be associated with Parkinson’s disease, based on case reports, the appearance of pathological features such as α-synuclein deposits in the brain, and substantia nigra pathology.

Moreover, we propose that additional genetic, epidemiological and clinical studies should be performed to check the precise incidence of mutations in genes encoding lysosomal proteins in patients displaying Parkinson’s symptoms.