# PAPER OF THE MONTH 07/2022

TRR 295 ReTune

## Age-dependent neurodegeneration and neuroinflammation in a genetic A30P/A53T double-mutated α-synuclein mouse model of Parkinson's disease.

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Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. PD is characterized by slowness of movements, stiffness and tremor. The greatest risk factor for developing PD is aging, which means that the health impact of PD is rising with the increasing longevity of the world's population. Aside from aging, brain autopsies of PD patients and findings in toxin-based animal models for PD also point towards neuroinflammation having a detrimental impact on disease pathophysiology.

Within this work, we evaluated the effect of aging and inflammation on the loss of dopaminergic cells, which is known to occur in PD alongside the emergence of inclusion bodies consisting of misfolded α-synuclein. This study was performed in the hm2α-SYN-39 mouse model, which carries two human α-synuclein mutations known to occur in hereditary PD. The phenotype as well as morphological and neurochemical changes in the basal ganglia were studied at an age of 2-3, 7-8, 11-12 and 16-17 months. The hm2α-SYN-39 mice showed a mild, age-dependent worsening of motor performance in the cylinder test and rotarod performance test, which was not seen in age-matched wildtype littermates. A significant loss of dopaminergic cells in the substantia nigra and of dopaminergic terminals in the striatum as well as a significant reduction of striatal dopaminergic levels was found in 16-17 months hm2α-SYN-39 mice compared to 2-3 months old transgenic mice and compared to age-matched wildtype mice. Concerning neuroinflammation, we found changes in the immune system that preceded and others that accompanied the dopaminergic neurodegeneration. The loss of striatal dopaminergic terminals e.g. correlated in an age-dependent manner with a significant infiltration of CD4+ and CD8+ T cells into the striatum of hm2α-SYN-39 mice. A significant age-dependent increase of T cells, astrocytes and microglia was also observed in the substantia nigra. However, microglia cell numbers were already significantly elevated in the substantia nigra of young hm2α-SYN-39 mice before any neurodegeneration occurred.

In conclusion, we identified a mild parkinsonian phenotype, neurodegeneration as well as an increase of inflammation in the aging brain of mice carrying human, mutated α-synuclein compared to wildtype controls. These findings further solidified the role of neuroinflammation in PD pathophysiology. Contrary to toxin-based animal models for PD, the hm2α-SYN-39 mouse model allows for an age-dependent study of the disease. Aging hm2α-SYN-39 mice reproduce important aspects of the disease, which makes this model of high translational value and suitable for further studies like the trial of anti-inflammatory therapeutics and the effect of long-term experimental DBS.

**Dr. med. Lisa Rauschenberger**

Lisa Rauschenberger is a resident in the neurology department at the University hospital of Würzburg with a focus on movement disorders. Within this field, her research work focuses on unraveling the impact of environmental factors on the pathophysiology of Parkinson's disease and dystonia at the hands of rodent models. She is currently the recipient of a habilitation stipend from the Interdisciplinary Center for Clinical Research at the University of Würzburg.

**Jennifer Behnke**

Jennifer Behnke is an MD student at the Graduate School of Life Sciences and the University of Würzburg. Her research focuses on the pathophysiology of Parkinson's disease, particularly on the role of aging and neuroinflammation in disease progression.

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