Assessment of prion-like behavior of pathologic protein aggregates from ALS patients

Bernis, M.E., and Tamgüney, G.

German Center for Neurodegenerative Diseases (DZNE), Sigmund-Freud-Str. 25, Gebäude 344, 53127 Bonn, Germany. erdem@dzne.de

Research question and background

This project will assess, if aggregates of TAR DNA-binding protein (TDP-43) from brains of patients with amyotrophic lateral sclerosis (ALS) behave in a prion-like manner. The aim of our study is to better understand pathologic mechanisms in ALS, which are only poorly understood. The results of our study may lead to novel treatment options for ALS patients. ALS pathology is associated with the formation of TDP-43 aggregates. Because neuronal involvement in ALS progresses in a similar sequence in different patients it has been suggested that abnormal proteins in ALS may propagate in a prion-like manner (Braak et al., 2013; Brettschneider et al., 2013). It has been suggested that the spreading manner is consistent with the induction and dissemination of TDP-43 pathology from the cortical neuronal projections, via axonal transport, through synaptic contact to the spinal cord and other regions of the brain. Prion-like spreading in a mouse model for synucleopathies has also been shown for α-synuclein aggregates from post-mortem tissues of patients with multiple system atrophy (Watts et al., 2013).

Methods and tissues used

Post-mortem tissue from patients containing TDP-43 aggregates have been processed to give 1% tissue homogenates in phosphate buffered saline. Two cohorts of 12 transgenic mice expressing human TDP-43 have been inoculated intracerebrally with 30 µl of the respective patient tissue homogenate. Control mice have been inoculated with phosphate buffered saline. The Tg(TDP-43) mice that we use in our experiments express human TDP-43 but normally do not develop any pathology throughout their life. After inoculation the neurologic status of the mice is being monitored to assess if and when these mice will develop disease. Once the mice develop disease or after 500 days after inoculation, the animals will be sacrificed to biochemically and immunohistochemically assess the potential spread of pathologic TDP-43 aggregates.

Results and conclusion

This study is ongoing and no results or conclusions have been obtained yet.

References

Braak, H., et al. (2013). "Amyotrophic lateral sclerosis--a model of corticofugal axonal spread." Nat Rev Neurol 9(12): 708-714.

Brettschneider, J., et al. (2013). "Stages of pTDP-43 pathology in amyotrophic lateral sclerosis." Ann Neurol 74(1): 20-38.

Watts, J. C., et al. (2013). "Transmission of multiple system atrophy prions to transgenic mice." Proc Natl Acad Sci U S A.