*Seminar*

# The gap Heiko Braak left : is there a preclinical period in ALS ?

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Jean-Martin Charcots revolutionary clinicoanatomical method became the basis for neurology until today. Heiko Braak added a longitudinal view of the neuropathology and showed by developing stages of degenerative diseases that the pathogenesis follows defined anatomical pathways and rules and is initiated by preclinical phases. According to his studies Parkinson´s disease starts in the gastrointestinal tract years to decades before motor symptoms show up; early Alzheimer´s pathology can be found decades before onset in the locus coeruleus. About 10 years ago he succeeded to suggest stages for amyotrophic lateral sclerosis as well; however, he was not able to show early pTDP43 pathology which consistently preceded the motor cortex and anterior horn cell neuropathology. Therefore we are left with this gap of his work: is there a preclinical stage of ALS and where can we find it ?
Biomarker studies do not reveal consistent results. There are many candidate mechanisms for the initiation of the process; among them the hypothalamus plays an important role. Recently, it has been reported that in asymptomatic controls without any signs of ALS pTDP43 can be detected in the gut and the skin. A fourth candidate is the suggestion that preclinical micro RNAs which translate into fragile X proteins could be the first pathogenetic step leading to clinical ALS. Case reports for major brain trauma preceding ALS remain anecdotes before a mechanistic link can be shown. Stephan Lewandowskis recent finding that an impaired blood-brain-barrier in the preclinical period might be a risk factor for ALS could be complementary to these thoughts.
However, all these hypotheses and speculations have one provocative thought in common: that ALS may be initially a systemic, not a brain disease.