Early tau abnormalities mature into robust tauopathy in context of late onset amyloidosis

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In Alzheimer's disease (AD), neurofibrillary tangles and amyloid plaques are key pathological features. Tangles, largely composed of Tau protein, can be detected as early as the second decade of life, while amyloid plaques typically appear around the fifth decade. Abnormalities in Tau during early life may stem from factors like head trauma, but it remains unclear whether these abnormalities are transient or evolve into pathology that progresses alongside amyloid plaque accumulation in AD. To investigate the effects of early tauopathy in the context of amyloid plaque development, the rTg4510 model was crossed with the L85 model, producing rTg4510/L85 mice. The rTg4510 mice express a regulatable tau transgene and begin developing tangles at around 2.5 months, while L85 mice develop plaques at approximately 6 months. In rTg4510/L85 mice, both tangles and plaques develop concurrently, with tau expression being regulatable. In the experimental setup, rTg4510/L85dox and rTg4510dox mice were given doxycycline starting at 1.5 months to restrict tau expression until necropsy at 12 months. Western blotting was used to compare tau levels in control and experimental groups. Preliminary immunohistochemical data show that rTg4510dox mice exhibit early tau abnormalities, but do not fully develop neurofibrillary tangles. In contrast, rTg4510/L85dox mice display significantly higher levels of phosphorylated and misfolded tau, as well as increased neurofibrillary tangles at 12 months. These findings suggest that early tau changes are progressive, with amyloid plaques potentially exacerbating tau pathology. This work could have implications for understanding tau-related risks in individuals with genetic vulnerabilities to AD and other tauopathies.

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