Acceleration of amyloidosis by inflammation in the amyloid-beta Marmoset monkey model of Alzheimer's disease

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Research question and background

Alzheimer's disease (AD) is a highly prevalent age-associated neurodegenerative disorder causing 50-80% of all cases of dementia. The actual cause of AD is still unknown, but the etiology seems to be woven by aggregation and deposition of microscopically visible abnormally folded proteins that are causally linked to cellular stress and inflammation in the brain. Inflammation is a pathogenic process involved in AD as well as in vascular dementia, which is presumably the result of transient ischemic events. This is corroborated by several observations described in literature that anti-inflammatory medication reduces the risk of developing AD. Indeed, a pro-inflammatory state is increasingly associated and mentioned as potential target for treatment of amyloidopathy that characterizes AD pathogenesis. The marmoset monkey has potential as an AD model due to its natural occurring amyloidosis. Moreover, its human-like immune system and aging phenotype, which is partly due to exposure to environmental pathogens causing transient or chronic latent infections, creates a robust more human-like immune system than that of the SPF animals.

Aim: To investigate the effect of local and/or systemic inflammation on amyloidopathy in the common marmoset AD model.

Methods and tissues used

Four middle aged (5-8y) and two old (13-14y) common marmoset monkeys (*Callithrix jacchus*) of both sexes were stereotactically injected intracranially with amyloid-beta (Aβ) fibrils at three cortical locations in the right hemisphere (frontal, parietal, and sensorimotor cortices) and both hemispheres were injected with PBS (n=3) or LPS (n=3). The effect of inflammation on amyloidopathy was also investigated in an animal that died due to a systemic inflammatory condition, marmoset wasting syndrome (MWS), which is associated with chronic colitis. The pro-inflammatory effect of LPS and Aβ was also tested in an ex vitro blood analysis (flow cytometry) for specific immune cell blood biomarkers (CD45RA and CD95). Campbell-Switzer silver staining and IHC analyses (Aβ, Aβ42, Aβ43, Iba1, and GFAP antibodies) were used on mirror sections to assess amyloidopathy, and immune reaction.

Results and conclusion

The MWS monkey and two LPS+Aβ monkeys developed plaques, of which the older LPS+Aβ animal developed severe amyloidopathy specifically in the right hemisphere surrounding the middle injection site. Furthermore, the LPS+Aβ animals had an early-AD immune blood cell expression profile as seen in human AD patients.

In conclusion, a pro-inflammatory condition accelerates (transmissible) amyloidopathy in the marmoset monkey, which indicates the possible importance of immune modulation to decrease the susceptibility for AD.