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Development of new models and analysis methods/seeding and spreading of proteinopathies

Iatrogenic transmission of Alzheimer's disease: Evidence based on experimental inoculation of Alzheimer's brains into a primate

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Abstract

Background: Epidemiologic data suggest that, in humans, iatrogenic administration of compounds (cadaver-sourced human growth hormone, dura mater graft) or cerebral surgeries with tools contaminated with A β and tau induce aggregated A β and possibly tau lesions. A β and tau lesions could thus be iatrogenically transmitted to humans. Several studies in mice have shown that experimental inoculation of amyloid and/or tau-positive brain samples into transgenic (tg) mouse models overexpressing A β or tau promotes either A β or tau aggregation in the brain of the recipient animal. Unlike rodents, primates naturally express A β or tau under normal conditions and they have a biochemical and physical cerebral environment that is closer to that of humans than that of mice. The aim of this work was to evaluate the impact of human brain samples inoculations in the mouse lemur primates.

Method: 12 adult mouse lemurs, aged from 3 to 4 years old, were included in this study. Human brain homogenates from AD patients or control (CTRL) age-matched subject were bilaterally inoculated in the hippocampus and subjacent cortex (n = 6/group). We performed longitudinal cognitive, electroencephalography (EEG) and morphological MRI studies up to 18 months post-inoculation followed by immunohistopathological examination of brain tissues.

Result: Mouse lemurs inoculated with Alzheimer brain homogenates displayed progressive cognitive impairments (clinical tests assessing cognitive and motor functions), modifications of neuronal activity (detected by electroencephalography), widespread and progressive cerebral atrophy (in vivo MRI assessing cerebral volume loss using automated voxel-based analysis), neuronal loss in the hippocampus and entorhinal

cortex (post mortem stereology). They displayed parenchymal and vascular A β depositions and tau lesions for some of them, in regions close to the inoculation sites.

Conclusion: This study is the first one to highlight neuronal and clinical dysfunction following inoculation of Alzheimer's disease brain homogenates in a primate. Based on controlled experiments, it suggests the possible iatrogen transmission of Alzheimer pathology. **Acknowledgments:** We thank the "GIE NeuroCEB" Brain Bank, the France-Alzheimer Association, the Fondation Plan Alzheimer, and the CEA Bottom-Up program.