Title: A PET, CT, and MR study: Alzheimer's Disease Interacts with Subcortical Stroke Through Inflammation and the Blood Brain Barrier

Trainee Name: Nassir Al-Khishman

Supervisor(s): Dr. Jonathan Thiessen and Dr. Shawn Whitehead

Structured Abstract:

Introduction: Subcortical stroke (SS) and Alzheimer's Disease (AD) often coexist and exacerbate one another cognitively, and we suspect they interact by disrupting inflammation and the blood-brain-barrier (BBB). Independently, SS and AD associate with inflammation that may be dichotomized into a reparative M2 phenotype and an aggressive M1 phenotype. M1 macrophages of the brain, known as M1 microglia, fight foreign bodies but also damage nearby cells including those constituting the BBB. Previously, we showed that rat comorbidity of subcortical stroke and AD enhances cognitive decline. To predict cognitive decline, we need to quantify inflammation and BBB permeability longitudinally. In this study, we hypothesized that inflammation and BBB permeability after SS are more compromised in rats genetically modified to overexpress amyloid precursor protein (Tg) than their wildtype (Wt) counterparts.

Methods: To induce subcortical stroke, the dorsal striatum was injected with the vasoconstrictor endothelin-1 or saline to yield four groups; Tg-stroke (n=5), Wt-stroke (n=5), Tg-saline (n=5), Wt-saline (n=3). We imaged at baseline then post stroke by 7-days and 28-days. Imaging included [18F]FEPPA PET to quantify inflammation, T2-weighted MRI to delineate the hyperintense infarct, and iodine contrast-enhanced CT to quantify BBB permeability surface product (BBB-PS) (Siemens Inveon, Siemens Biograph mMR, and revolution CT). We analyzed PET using uptake ratio to cerebellum (UR) and CT using the Johnson-Wilson model (CT Perfusion 4). To quantify M1 microglia at 28-days, rats were sacrificed then stained using immunohistochemistry of inducible nitric oxide synthase (iNOS). Although for simplicity only the infarct is presented, region was included as a variable in a four-way ANOVA with stroke/saline, Tg/Wt, and time (SPSS25).

Results: Compared to saline groups, stroke groups had a similarly elevated inflammation as measured by [18F]FEPPA uptake at 7-days that then dropped by 28-days. It dropped more in Tg-stroke (1.25±0.44 UR) than Wt-stroke (1.77±0.34 UR) as detected in a time-Tg/Wt interaction (F(1,21))=9.64, p <.01). Immunohistochemically, this corresponded to a lower count of the aggressive iNOS+ M1 microglia in Tg-stroke (173±92 cells/mm2) than Wt-stroke (222±232 cells/mm2), but these were not significantly different. Additionally at 28-days, BBB-PS was higher in Tg-stroke (0.27±0.26 mL/min/100g) than Wt-stroke (0.08±0.07 mL/min/100g), but the difference was not significant.

Discussion: In this study, we showed that after SS, Tg AD rats have i) less inflammation than Wt rats at 28-days, ii) specifically less M1 microglia, and iii) elevated BBB permeability. We speculate that the high BBB permeability downregulated M1 microglial response and that this combination makes the brain vulnerable to insults from the blood. This suggests that therapeutics supporting M1 microglia and the BBB after SS might benefit Tg rats and maybe eventually humans with AD.