

Cerebral vasculature, Alzheimer's disease and cerebral amyloid angiopathy: what is the connection? A mathematical model

Christina Rose Kyrtos and John S Baras, *Member, IEEE*

ALZHEIMER'S disease (AD) is the most common form of dementia, accounting for 60-80% of all dementias. AD is associated with loss of short term memory, changes in mood and sleep patterns, and loss of voluntary muscle control. Histologically, post-mortem brain sections of affected individuals show increased levels of beta amyloid ($A\beta$) deposited throughout the brain parenchyma and neurofibrillary tangles (NFTs) within neurons [1]. Elevated levels of neuroinflammatory markers and activated microglia are also present.

Another important histological finding in AD is the presence of cerebral amyloid angiopathy (CAA) in nearly 90% of AD patients [1]. This presents as the deposition and build-up of $A\beta$ within brain endothelial cells, as well as at the blood-brain barrier (BBB). The exact role of CAA in AD pathogenesis is not well understood, though it is known to increase the permeability of the BBB, increasing the transport of neurotoxins into the brain and possibly stimulating an inflammatory response or apoptosis. Conversely, if an $A\beta$ plaque deposition within the cerebral vasculature begins to occlude the vessel, ischemia and subsequent neuronal cell loss may result.

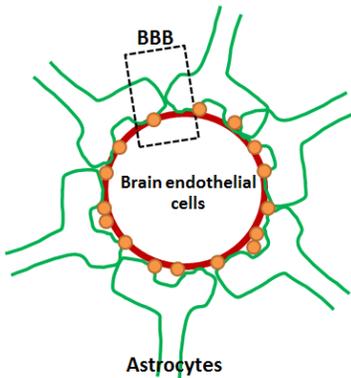
In this paper, a mathematical model studying the possible interactions between CAA and AD pathology is developed. Previous mathematical models have studied the effects of $A\beta$ transport rate on the development of CAA and looked at the effects of cerebral blood flow on AD pathology [2-4], however, no models have directly studied how CAA may be a contributory process in AD pathogenesis. The blood-brain barrier has been modeled as a single layer of endothelial cells. Transvascular transport of fluid across the BBB was defined by the Starling equation:

$$\varphi_L = \frac{L_p S}{V} [(p_L - p_I) - \sigma(\pi_L - \pi_I)]$$

where L is the lumen, I is the interstitial space, p is the hydrostatic pressure, π is the oncotic pressure, σ is the osmotic reflection coefficient, and S/V is the surface area to volume ratio. Michaelis-Menten kinetics were used to study the binding of glucose to the GLUT receptor:

$$J_s = \frac{V_{\max}[S_o]}{K_m + [S_o]}$$

where V_{\max} is the maximum velocity of solute binding, [S] is the concentration of glucose and K_m is the Michaelis constant. The model developed here specifically studies how deposition of $A\beta$ in cerebral vasculature affects BBB permeability (with subsequent neuronal cell death) and how local neuronal cell density can change as a function of the extent of $A\beta$ deposition. Figure 1 (below) demonstrates the scenarios studied by this model. Future models will study how vessel properties and the immune cells play a role in this process.



REFERENCES

- [1] Weller, Roy O., Delphine Boche, and James AR Nicoll. "Microvasculature changes and cerebral amyloid angiopathy in Alzheimer's disease and their potential impact on therapy." *Acta neuropathologica*, vol. 118(1), pp. 87-102, Feb 2009.
- [2] EK Agyare, SR Leonard, GL Curran, CC Yu, VJ Lowe, AK Paravastu, JF Poduslo, KK Kandimallaa, "Traffic jam at the blood-brain barrier promotes greater accumulation of Alzheimer's disease amyloid β proteins in the cerebral vasculature," *Mol Pharmaceutics*, 10(5), pp. 1557-1565, Dec 2012.
- [3] VZ Marmarelis, DC Shin, ME Orme, R Zhang, "Model-based quantification of cerebral hemodynamics as a physiologic marker for Alzheimer's disease," *Annals of Biomedical Engineering*, pp. 1-22, June 2013.
- [4] Spronck, Bart, et al. "A lumped parameter model of cerebral blood flow control combining cerebral autoregulation and neurovascular coupling." *American Journal of Physiology-Heart and Circulatory Physiology*, vol. 303(9), pp. H1143-H1153, Nov 2012.

This work was supported by a grant from the Hynet Center, University of Maryland.

CR Kyrtos is with the University of Maryland Institute for Systems Research and is currently studying medicine at the Pennsylvania State University, Hershey, PA 17033 USA (e-mail: ckyrtsos@hmc.psu.edu).

JS Baras is with the University of Maryland Institute for Systems Research, College Park, MD 20742 USA (e-mail: baras@umd.edu).