Neuroinflammation and Glymphatic Dysfunction in HIV-Associated Neurocognitive Disorders

ROWAN-VIRTUA School of Translational Biomedical Engineering & Sciences

Iman Hasan[1], Dianne Langford[1,2], Caitlin Tice[1,2]

[1]Department of Neuroscience, Rowan-Virtua School of Translational Biomedical Engineering and Sciences, Stratford, NJ 08084, USA

[2]Rowan-Virtua School of Osteopathic Medicine, Rowan University, Stratford, NJ 08084, USA

ROWAN-VIRTUA School of Osteopathic Medicine

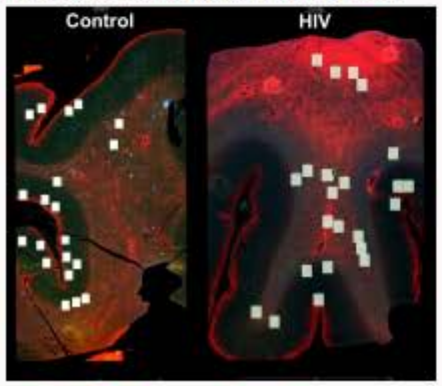
Abstract

The glymphatic system clears interstitial waste from the brain through aquaporin-4 (AQP4) water channels on astrocyte end feet. Mislocalization of AQP4 away from these perivascular domains can reduce fluid flow and promote accumulation of toxic proteins, including hyperphosphorylated Tau. Nearly 50 percent of people living with HIV (PLWH) develop HIV-associated neurocognitive disorders (HAND), and prior studies suggest that AQP4 dysfunction may play a role. A2a receptor signaling, known to drive AQP4 internalization in other neuroinflammatory conditions, may contribute to glymphatic failure in HAND.

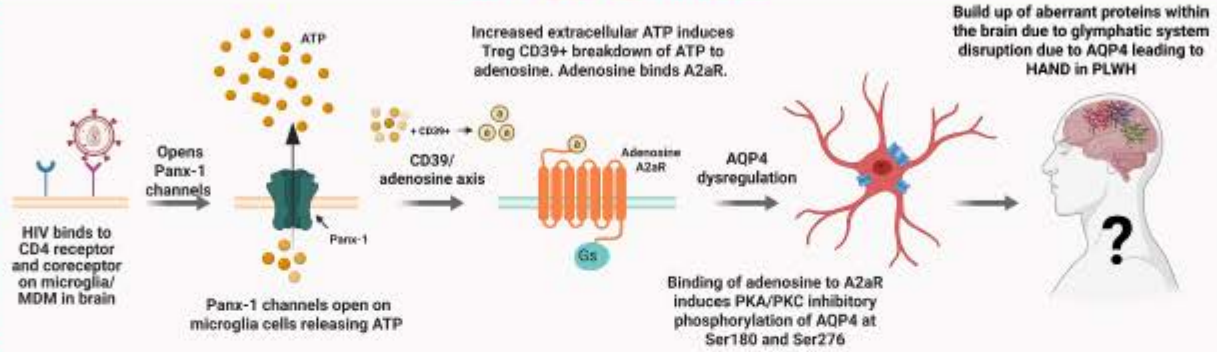
To investigate this, we profiled postmortem frontal cortex tissue from PLWH and matched controls using spatial proteomics. We observed regional increases in neuroinflammatory and neurodegenerative proteins, consistent with impaired clearance, glial activation, and proteostasis failure. These findings support a model where inflammation-driven AQP4 mislocalization contributes neurodegeneration in HAND.

Methods

Formalin-fixed, paraffin-embedded frontal cortex sections from 8 people with HIV and 8 age and sex matched controls were analyzed using the NanoString GeoMx Digital Spatial Profiler. 20 regions of interest were selected per section, covering gray matter, white matter, and sulci, guided by MAP2, GFAP, and Syto 13 morphology markers. Protein expression was profiled using the Human Neuroscience and Immune Protein Panels. UV-cleaved oligonucleotide tags from each region were hybridized to nCounter barcodes for quantification. Data were normalized to housekeeping controls and analyzed using GraphPad Prism.



Our Hypothesis



Results

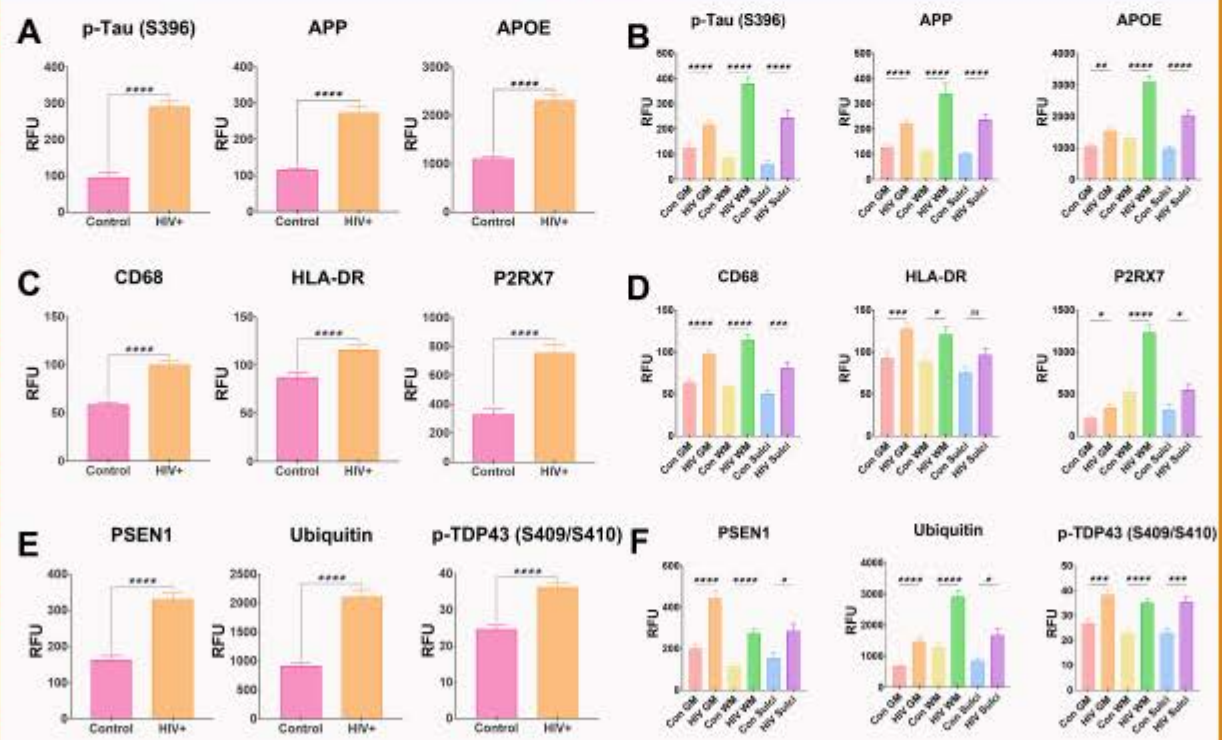


Figure 1. HIV positive brains show increased expression of proteins linked to impaired clearance and neuroinflammation Postmortem frontal cortex tissue from 8 HIV positive individuals and 8 age and sex matched controls was profiled using NanoString GeoMx Digital Spatial Profiling. **A.** Whole tissue expression of pTau S396, APP, and APOE. **B.** Regional analysis of pTau S396, APP, and APOE. **C.** Whole tissue expression of CD68, HLA DR, and P2RX7. **D.** Regional analysis of CD68, HLA DR, and P2RX7. **E.** Whole tissue expression of PSEN1, Ubiquitin, and pTDP43 S409/S410. **F.** Regional analysis of PSEN1, Ubiquitin, and pTDP43 S409/S410. Expression is shown as RFU, relative fluorescent units. Data represent mean ± SEM. Asterisks indicate significance, with *p < 0.05, **p < 0.01, ***p < 0.001, and **p < 0.0001.

Conclusions

- ***APP and APOE were significantly elevated in PLWH brains***, supporting impaired glymphatic clearance and altered lipid homeostasis, both of which may contribute to amyloid accumulation and astrocyte dysfunction in HAND.
- ***Increased pTau S396 and pTDP43 S409/S410 suggest protein aggregation and proteostasis failure***, indicating that HAND shares features with other neurodegenerative diseases.
- ***CD68 and HLA DR were upregulated, reflecting chronic microglial activation and sustained neuroinflammation***, which may exacerbate neuronal injury and interfere with glymphatic function.
- ***P2RX7 was increased in PLWH***, highlighting purinergic signaling as a potential driver of inflammasome activation and glial dysfunction in the context of HIV associated neurocognitive decline.
- ***Elevated PSEN1 and Ubiquitin levels suggest dysregulated protein processing and degradation***, autophagy and proteasomal pathways may be compromised in PLWH

Future Directions

- Assess AQP4 localization and its correlation with regional protein accumulation in PWH
- Investigate the role of P2RX7 and A2a receptor signaling in mediating glial activation and glymphatic dysfunction
- Use immunofluorescence and confocal imaging to map cell-specific expression
- Validate key findings using immunofluorescence and expand spatial profiling to include astrocyte polarity and clearance markers

Contact Information

Caitlin Tice, PhD
Instructor at Rowan University SOM

tice@rowan.edu
www.linkedin.com/caitlintice

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