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The Brodmann Area 39/40 of the Brain in Alzheimer's, Mild Cognitive Impairment, and No Cognitive Impairment Subjects at Advanced Age Demonstrate Comparable Levels of Blood-Brain Barrier Breach

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Background

- Alzheimer's disease (**AD**) is one of the most common form of dementia.
- Mild cognitive impairment (**MCI**), specifically amnestic subtype, more likely to progress to AD.
- **Pathogenesis Theories**:
  - Accumulation of amyloid-beta peptides and neurofibrillary tangles containing hyperphosphorylated neuronal tau protein.
  - Blood Brain Barrier (**BBB**) dysfunction is associated with AD pathogenesis.
- **Brodmann area 39/40**: regions of parietal cortex are responsible for language, spatial cognition, memory retrieval, attention, phonological processing, and emotional processing
- **Hypothesis:** An increased BBB permeability in Brodmann area 39/40 of AD and age-matched MCI and no cognitive impairment (**NCI**) subjects.

Methods

- **Six-micron thick sections** from the **formalin-fixed Brodmann area 39/40** were obtained from the Rush Alzheimer's Disease Center (**RADC**).
- **Immunohistochemistry: Probed** the brain sections with anti-human immunoglobulin G (**IgG**) antibodies (Vector Laboratories, CA, USA, Cat# BA-3100, dilution - 1:500)
- Since the brain parenchyma and neuropil are **immune privileged structures**, any evidence of **IgG immunoreactivity outside** of the brain vasculature is considered **a breach in BBB integrity**
- **IgG** is a **widely used biomarker for BBB breach**
- To determine the density of the leaky blood vessels in each tissue section, we
  1) Counted the blood vessels demonstrating clear IgG leak clouds.
  2) Estimated the total area of the brain section, and
  3) Determined the density of leaky blood vessels by calculating the ratio of the total number of leaky blood vessels and total area of the tissue section examined.
- Density of leaky blood vessels was used for comparison purposes

Demographics

	AD	MCI	NCI
Average age (range)	82.38 **80.3-84.3**	82.78 **79.4-86.4**	82.11 **79.0-85.3**
Males	3	5	3
Females	12	10	12

Results

Figure 1: (A-C) Blood vessels demonstrating clear IgG leaked clouds are seen in NCI, AD, and MCI. **(D)** AD Cortex probed with blocking sera and ABC (no anti-human IgG). **(C1-2)** IgG positive neurons (**red arrows**) and IgG negative neurons (**black arrows**) in IgG leak cloud of MCI subjects.

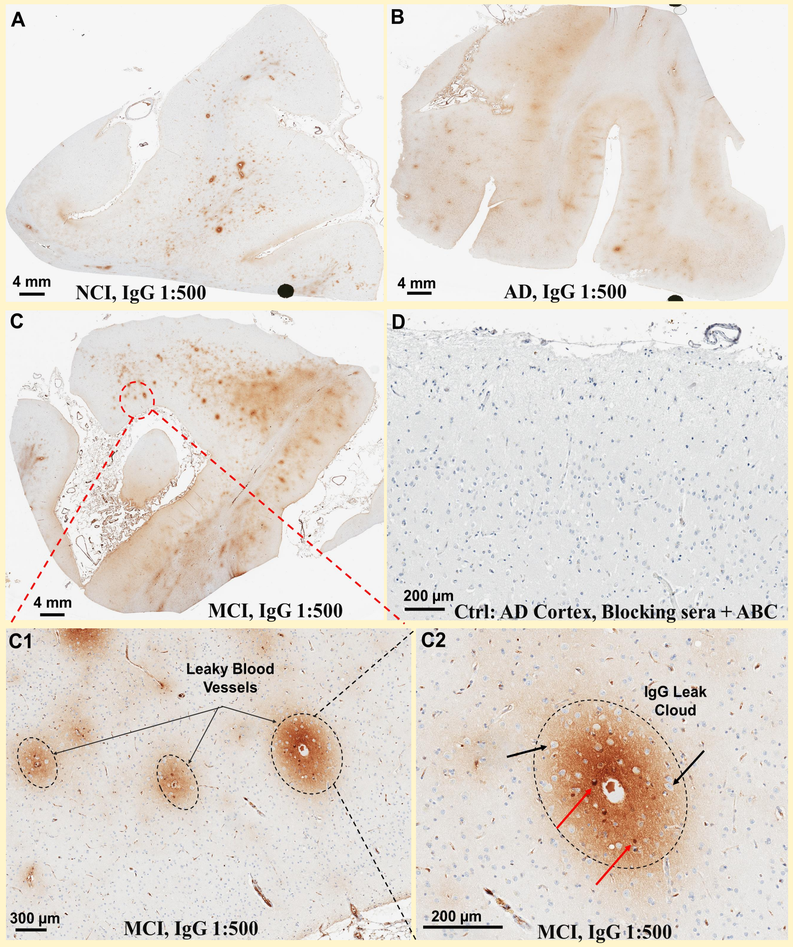


Figure 2: Density of leaky blood vessels for individual AD, MCI, and NCI subjects. *The total number of leaky blood vessels divided by the total area of cross-section.*

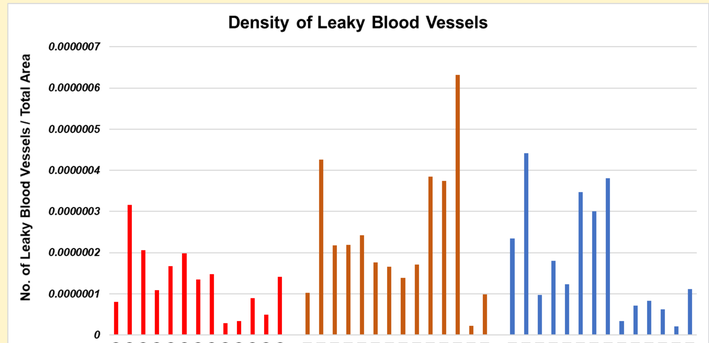
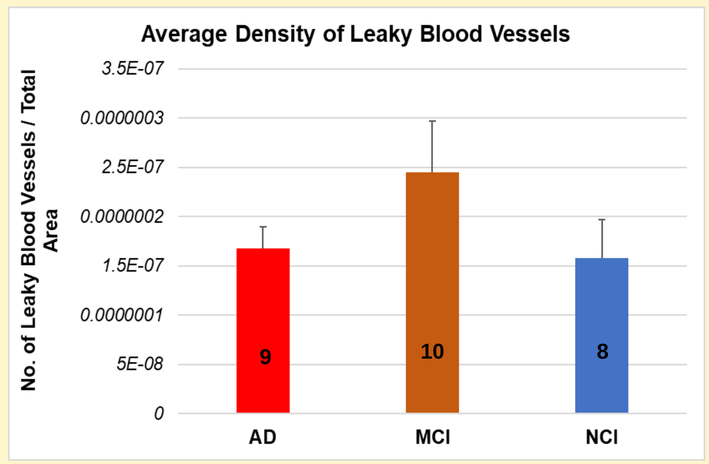


Figure 3: Average density of leaky blood vessels. *AD, MCI, and NCI, subjects showed a similar density of leaky blood vessels as we failed to see any statistical significance between these groups*



Conclusion and Future Directions

1. NCI, MCI, and AD groups demonstrated as similar density of **leaky blood vessels suggesting the loss of BBB integrity.**

2. BBB breakdown could be **one of the earliest pathophysiology changes responsible** for AD-and MCI-related cognitive and neurodegenerative changes.

A. Calculate the extent of IgG leaked (extent of BBB breach, **Ongoing**).
B. This preliminary study warrants additional investigations utilizing brain samples from younger NCI subjects **for delineating the potential role of** aging in BBB breakdown.
C. Future studies should also **utilize a larger sample size.**

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