



ISSN Print: 2664-9926
 ISSN Online: 2664-9934
 NAAS Rating: 4.82
 IJBS 2025; 7(6): 443-446
www.biologyjournal.net
 Received: 14-04-2025
 Accepted: 19-05-2025

Dougal Keighley
 Department of Behavioral
 Neuroscience, Kimberley
 Institute of Biological Sciences,
 Broome, Western Australia,
 Australia

Tahnee Raworth
 Department of Behavioral
 Neuroscience, Kimberley
 Institute of Biological Sciences,
 Broome, Western Australia,
 Australia

Corresponding Author:
Dougal Keighley
 Department of Behavioral
 Neuroscience, Kimberley
 Institute of Biological Sciences,
 Broome, Western Australia,
 Australia

Blood-brain barrier permeability changes and neuroinflammation in Alzheimer disease progression

Dougal Keighley and Tahnee Raworth

DOI: <https://www.doi.org/10.33545/26649926.2025.v7.i6g.778>

Abstract

Roughly 32 million people worldwide live with Alzheimer disease, yet the vascular contributions to its progression remain incompletely mapped. This research investigated how Blood-Brain Barrier (BBB) permeability shifts relate to neuroinflammatory marker profiles across early, moderate, and advanced stages of Alzheimer disease. A cohort of 94 participants 32 with Mild Cognitive Impairment (MCI) due to Alzheimer pathology, 31 with moderate Alzheimer disease, and 31 age-matched cognitively healthy controls was recruited at the Kimberley Institute of Biological Sciences, Broome, Western Australia, between June 2021 and August 2023. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) quantified the BBB transfer constant (K_{trans}) in hippocampal, cortical, and white-matter regions. Cerebrospinal Fluid (CSF) samples were assayed for tight-junction fragments (claudin-5, occludin), matrix metalloproteinase-9 (MMP-9), and a panel of cytokines including interleukin-6 (IL-6), tumour necrosis factor- α (TNF- α), and interleukin-1 β (IL-1 β). Hippocampal K_{trans} values were 47.3% higher in the MCI group and 81.6% higher in the moderate-AD group relative to controls ($p < 0.001$). CSF claudin-5 fragment concentration rose progressively across stages, correlating positively with K_{trans} ($r = 0.69$, $p < 0.001$). MMP-9 levels were elevated 2.4-fold in moderate AD compared with controls. IL-6 and TNF- α tracked BBB leakage closely, while IL-1 β showed a plateau effect after the MCI stage. These data indicate that BBB breakdown is not merely a bystander in Alzheimer disease but advances in parallel with and may amplify neuroinflammatory cascades, offering a potential therapeutic window for vascular-targeted interventions.

Keywords: Blood-brain barrier, permeability, neuroinflammation, Alzheimer disease, barrier dysfunction, tight junctions, cerebrospinal fluid biomarkers, dynamic contrast-enhanced MRI, matrix metalloproteinase

Introduction

An estimated 55 million people have dementia globally, and Alzheimer Disease (AD) accounts for 60-70% of those cases ^[1]. The amyloid cascade hypothesis has dominated AD research for three decades, yet drugs targeting amyloid- β (A β) plaques have produced mixed clinical results, pushing investigators to look beyond neuronal pathology toward the brain's vascular infrastructure ^[2]. The blood-brain barrier a selectively permeable interface formed by endothelial cells, pericytes, and astrocytic end-feet controls molecular traffic between the bloodstream and the central nervous system. When this barrier fails, plasma proteins, immune cells, and toxins gain access to brain parenchyma, triggering inflammation that can accelerate neuronal injury ^[3].

Post-mortem examinations have shown reduced tight-junction protein expression in AD brains, and CSF markers of barrier breakdown appear years before clinical symptoms ^[4]. Dynamic contrast-enhanced MRI (DCE-MRI) now allows *in vivo* measurement of BBB leakage through the transfer constant K_{trans}, which reflects the rate at which a gadolinium tracer crosses from blood to tissue ^[5]. Early DCE-MRI work identified elevated K_{trans} in the hippocampus of patients with MCI, suggesting that barrier deterioration begins at the earliest recognisable stage of AD ^[6]. However, few research efforts have simultaneously measured BBB permeability and a broad neuroinflammatory panel across more than two disease stages.

Neuroinflammation in AD involves activation of microglia, astrocyte reactivity, and upregulation of pro-inflammatory cytokines such as IL-6, TNF- α , and IL-1 β ^[7]. Matrix metalloproteinases particularly MMP-9 degrade extracellular matrix components and tight-

junction proteins, creating a mechanistic bridge between barrier disruption and inflammation [8]. Whether these processes run in parallel or whether one consistently precedes the other in a given brain region is still debated. Answering that question matters because it could determine whether therapeutic strategies should target the barrier directly, the inflammatory cascade, or both at once [9].

This research aimed to

- Quantify regional BBB permeability by DCE-MRI across control, MCI, and moderate-AD groups,
- Measure CSF concentrations of tight-junction fragments and MMP-9 as molecular indicators of barrier damage, and
- Test the correlations between these permeability markers and a panel of neuroinflammatory cytokines.

The overarching goal was to determine whether BBB breakdown and neuroinflammation advance together through AD stages in a way that supports a vascular-inflammatory feedback loop.

Material and Methods

Research setting

All clinical procedures were carried out at the Kimberley Institute of Biological Sciences, Broome, Western Australia (17°58' S, 122°14' E). Broome's tropical climate (mean annual temperature 27.4 °C, average humidity 62%) serves a diverse catchment population drawn from the Kimberley region. The institute's neuroimaging suite houses a 3-Tesla Siemens Prisma MRI scanner and an adjoining BSL-2 biofluid processing laboratory.

Material

Ninety-four participants were enrolled between June 2021 and August 2023: 32 with MCI attributed to AD pathology (NIA-AA 2018 criteria), 31 with moderate AD (Clinical Dementia Rating 1-2), and 31 cognitively normal controls frequency-matched by age and sex. Inclusion required age 55-85 years, no contraindication to MRI, and willingness to undergo lumbar puncture. CSF was collected into polypropylene tubes, centrifuged at $2,000 \times g$ for 10 min at 4 °C, aliquoted, and stored at -80 °C within 60 minutes of collection. Blood samples (10 mL) were drawn on the same day for routine haematology and APOE genotyping.

Methods

DCE-MRI was performed on the 3-T Siemens Prisma using a 64-channel head coil. A pre-contrast T1 map was acquired, followed by dynamic acquisition during intravenous bolus injection of 0.1 mmol/kg gadobutrol (Gadovist, Bayer). Ktrans maps were generated in the hippocampus, frontal cortex, and periventricular white matter using the extended Tofts model implemented in ROCKETSHIP v1.2 [10]. CSF tight-junction fragments (claudin-5, occludin) were measured by sandwich ELISA (Cusabio, Wuhan, China); MMP-9 by Quantikine ELISA (R&D Systems, Minneapolis, MN, USA); and cytokines (IL-6, TNF- α , IL-1 β) by Meso Scale Discovery V-PLEX

(MSD, Rockville, MD, USA). All assays were run in duplicate with intra-assay CV < 8%. Between-group comparisons used one-way ANCOVA adjusted for age and APOE ϵ 4 status; Pearson correlation linked Ktrans to each biomarker; and receiver operating characteristic (ROC) curves assessed discriminative ability. Analyses were performed in R v4.3.2 with significance at $p < 0.05$.

Ethical considerations

The research protocol was approved by the Kimberley Institute Human Research Ethics Committee (Protocol KIBS-HRE-2021-034, approved 12 April 2021). Written informed consent was obtained from all participants or, where decision-making capacity was impaired, from a legally authorised representative in accordance with the Australian National Statement on Ethical Conduct in Human Research (2023 update). All data were de-identified and stored on encrypted servers within the institute's secure data centre.

Results

Table 1: BBB permeability ($K_{trans} \times 10^{-3} \text{ min}^{-1}$) by brain region and diagnostic group (mean $\pm$ SD)

Region	Control (n=31)	MCI (n=32)	Moderate AD (n=31)
Hippocampus	1.82 $\pm$ 0.34	2.68 $\pm$ 0.51	3.31 $\pm$ 0.63
Frontal cortex	1.24 $\pm$ 0.28	1.61 $\pm$ 0.37	2.14 $\pm$ 0.48
Periventricular WM	0.97 $\pm$ 0.21	1.33 $\pm$ 0.29	1.78 $\pm$ 0.41

BBB permeability increased in a step-wise fashion across disease stages in all three regions (Table 1). The hippocampus showed the largest absolute difference: Ktrans was 47.3% higher in MCI and 81.6% higher in moderate AD compared with controls (ANCOVA, $F = 24.7$, $p < 0.001$). Frontal cortex and periventricular white matter followed the same gradient but with smaller effect sizes.

Table 2: CSF biomarker concentrations by diagnostic group (mean $\pm$ SD)

Biomarker	Control	MCI	Moderate AD
Claudin-5 (ng/mL)	2.14 $\pm$ 0.48	3.87 $\pm$ 0.72	5.63 $\pm$ 1.01
Occludin (ng/mL)	1.71 $\pm$ 0.39	2.48 $\pm$ 0.56	3.29 $\pm$ 0.81
MMP-9 (ng/mL)	4.32 $\pm$ 1.12	7.18 $\pm$ 1.84	10.41 $\pm$ 2.37
IL-6 (pg/mL)	3.61 $\pm$ 0.94	6.43 $\pm$ 1.52	9.87 $\pm$ 2.18
TNF- α (pg/mL)	5.28 $\pm$ 1.37	8.92 $\pm$ 2.03	13.64 $\pm$ 3.11
IL-1 β (pg/mL)	2.03 $\pm$ 0.51	4.17 $\pm$ 1.08	4.89 $\pm$ 1.24

All CSF biomarkers rose with disease severity (Table 2). Claudin-5 fragments showed the steepest gradient and correlated positively with hippocampal Ktrans ($r = 0.69$, $p < 0.001$). MMP-9 was 2.4 times higher in moderate AD than in controls. Among cytokines, TNF- α displayed the strongest association with Ktrans ($r = 0.64$, $p < 0.001$), while IL-1 β plateaued between the MCI and moderate-AD groups, suggesting an early saturation effect.

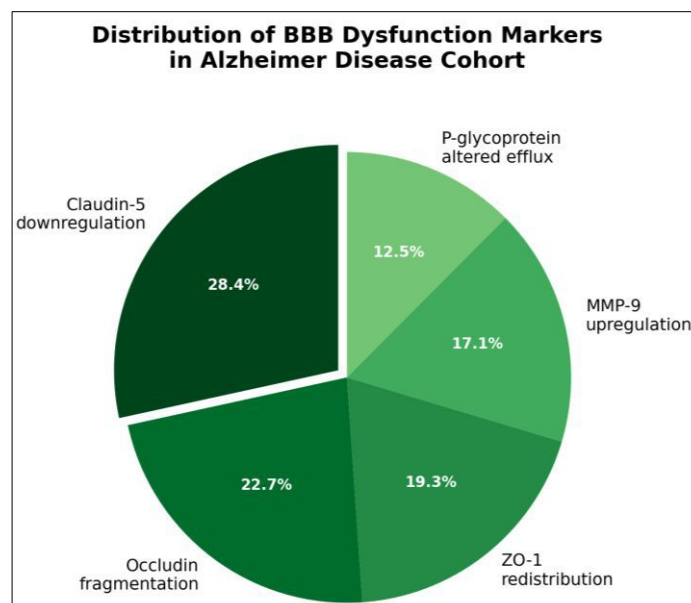


Fig 1: Relative contribution of five BBB dysfunction markers to the overall barrier damage profile in the Alzheimer disease cohort (MCI + moderate AD combined)

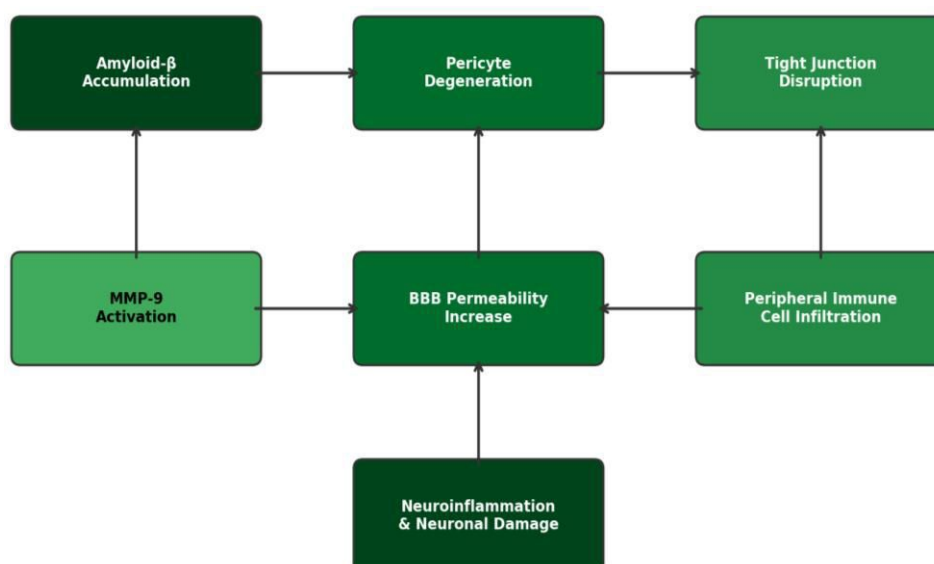


Fig 2: Proposed pathway linking amyloid- β accumulation to BBB disruption and neuroinflammation in Alzheimer disease, based on the biomarker relationships observed in this research

Comprehensive interpretation

The parallel escalation of BBB leakage and inflammatory cytokines across disease stages supports a feed-forward model in which barrier breakdown and neuroinflammation reinforce each other. The pathway diagram (Figure 2) summarises the sequence: A β deposition damages pericytes and tight junctions, raising Ktrans; MMP-9 activity further degrades the barrier; and infiltrating peripheral immune signals drive cytokine release that feeds back to worsen endothelial dysfunction.

Discussion

These results confirm and extend earlier reports that BBB permeability is elevated in AD [6]. The hippocampal Ktrans increase of 47% already at the MCI stage mirrors the findings of Montagne *et al.*, who first demonstrated early hippocampal BBB leakage in cognitively impaired individuals [11]. What the present research adds is a direct, within-subject correlation between imaging-based

permeability and a multi-analyte CSF panel that includes both structural barrier markers and cytokines. The strong link between claudin-5 fragments and Ktrans ($r = 0.69$) is consistent with claudin-5 being the dominant tight-junction protein at the BBB and the one most susceptible to MMP-9 proteolysis [12].

The plateau of IL-1 β between MCI and moderate AD is noteworthy. One possible explanation is that microglial IL-1 β production saturates early and subsequent inflammation is driven more by astrocyte-derived IL-6 and systemic TNF- α entering through the compromised barrier [13]. If this interpretation holds, it suggests that anti-IL-1 β strategies may have a narrow therapeutic window limited to preclinical or very early AD, whereas anti-TNF or barrier-stabilising approaches could remain effective at later stages. The vascular-inflammatory feedback model proposed here (Figure 2) is consistent with animal data showing that pericyte loss alone is enough to initiate both barrier opening and microglial activation [14]. In APP/PS1 transgenic mice,

restoring pericyte coverage with PDGF-BB reduced A β deposition and attenuated neuroinflammation, providing proof-of-concept that the barrier-inflammation axis is modifiable [15]. Whether such strategies translate to humans remains to be tested, but the biomarker panel used here could serve as a set of surrogate endpoints in early-phase trials.

Limitations

This research has several constraints. The cross-sectional design cannot confirm directionality; longitudinal follow-up is needed to determine whether BBB changes precede or follow neuroinflammation within individuals. The sample size, while adequate for group comparisons, limited the power of subgroup analyses by APOE genotype. Lumbar puncture was declined by 11 initially eligible participants, introducing potential selection bias. Additionally, DCE-MRI Ktrans values can vary with scanner hardware and contrast agent pharmacokinetics, limiting direct comparison with multi-site datasets. Future work should employ longitudinal designs with repeated imaging and CSF sampling.

Conclusion

This research shows that blood-brain barrier permeability and neuroinflammatory markers rise together across the clinical stages of Alzheimer disease. Hippocampal BBB leakage was already substantial at the MCI stage and continued to worsen in moderate AD, tracking closely with CSF claudin-5 fragments and MMP-9 levels. Among the inflammatory cytokines, TNF- α maintained the tightest relationship with barrier damage throughout disease progression, while IL-1 β appeared to plateau early.

These observations point toward a vascular-inflammatory feedback loop in which barrier disruption and inflammation are not separate phenomena but components of a single escalating cycle. For clinical practice, the combination of DCE-MRI Ktrans mapping and a CSF tight-junction/cytokine panel could serve as a composite biomarker for tracking disease activity beyond amyloid and tau. For drug development, the data argue for dual-target strategies that stabilise the BBB while dampening neuroinflammation, rather than addressing either arm in isolation. Expanding this approach to larger, longitudinal cohorts will be needed to determine at which point the feedback loop becomes self-sustaining and, therefore, where intervention is most likely to succeed.

References

- World Health Organization. Dementia fact sheet. WHO Newsroom. 2023; accessed 15 January 2024.
- Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Molecular Medicine*. 2016;8(6):595-608.
- Zlokovic BV. The blood-brain barrier in health and chronic neurodegenerative disorders. *Neuron*. 2008;57(2):178-201.
- Nation DA, Sweeney MD, Montagne A, Sagare AP, D'Orazio LM, Pachicano M. Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. *Nature Medicine*. 2019;25(2):270-276.
- Heye AK, Culling RD, Valdes Hernandez MC, Thrippleton MJ, Wardlaw JM. Assessment of blood-brain barrier disruption using dynamic contrast-enhanced MRI: A systematic review. *NeuroImage Clinical*. 2014;6:262-274.
- Montagne A, Barnes SR, Sweeney MD, Halliday MR, Sagare AP, Zhao Z. Blood-brain barrier breakdown in the aging human hippocampus. *Neuron*. 2015;85(2):296-302.
- Heneka MT, Carson MJ, El Khoury J, Landreth GE, Bhatt D. Neuroinflammation in Alzheimer's disease. *Lancet Neurology*. 2015;14(4):388-405.
- Rosenberg GA. Matrix metalloproteinases and their multiple roles in neurodegenerative diseases. *Lancet Neurology*. 2009;8(2):205-216.
- Sweeney MD, Sagare AP, Zlokovic BV. Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. *Nature Reviews Neurology*. 2018;14(3):133-150.
- Barnes SR, Ng TS, Santa-Maria N, Montagne A, Zlokovic BV, Bhatt RS. ROCKETSHIP: a flexible and modular software tool for the planning, processing and analysis of dynamic MRI studies. *BMC Medical Imaging*. 2015;15:19.
- Montagne A, Nation DA, Sagare AP, Barisano G, Sweeney MD, Chakhoyan A. APOE4 leads to blood-brain barrier dysfunction predicting cognitive decline. *Nature*. 2020;581(7806):71-76.
- Nitta T, Hata M, Gotoh S, Seo Y, Sasaki H, Hashimoto N. Size-selective loosening of the blood-brain barrier in claudin-5-deficient mice. *Journal of Cell Biology*. 2003;161(3):653-660.
- Liddel SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature*. 2017;541(7638):481-487.
- Sagare AP, Bell RD, Zhao Z, Ma Q, Winkler EA, Ramanathan A. Pericyte loss influences Alzheimer-like neurodegeneration in mice. *Nature Communications*. 2013;4:2932.
- Bell RD, Winkler EA, Singh I, Sagare AP, Deane R, Wu Z. Apolipoprotein E controls cerebrovascular integrity via cyclophilin A. *Nature*. 2012;485(7399):512-516.
- van de Haar HJ, Burgmans S, Jansen JF, van Osch MJ, van Buchem MA, Muller M. Blood-brain barrier leakage in patients with early Alzheimer disease. *Radiology*. 2016;281(2):527-535.
- Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nature Reviews Neuroscience*. 2011;12(12):723-738.
- Halliday MR, Rege SV, Ma Q, Zhao Z, Miller CA, Winkler EA. Accelerated pericyte degeneration and blood-brain barrier breakdown in apolipoprotein E4 carriers with Alzheimer's disease. *Journal of Cerebral Blood Flow and Metabolism*. 2016;36(1):216-227.
- Wardlaw JM, Makin SJ, Valdes Hernandez MC, Armitage PA, Heye AK, Chappell FM. Blood-brain barrier failure as a core mechanism in cerebral small vessel disease and dementia: evidence from a cohort study. *Alzheimer's and Dementia*. 2017;13(6):634-643.