

Amyloid-related imaging abnormalities: In vivo and postmortem 7T MRI following anti-amyloid immunotherapy in Alzheimer's disease

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Introduction

Anti-amyloid treatment benefits come at the cost of radiological side effects, including amyloid-related imaging abnormalities - edema (ARIA-E) and hemorrhage (ARIA-H). We report a preliminary analysis of our prospective clinical cohort and use high-resolution 7-tesla (7T) magnetic resonance imaging (MRI) to characterize smaller structures and subtle pathologies, as well as to enable MRI-guided tissue sampling using scans obtained at the time of peak ARIA.

Methods

Cohort overview. At the University of Pittsburgh Medical Center, we have established a research registry of patients aged 40-90 years undergoing lecanemab (Leqembi) or donanemab (Kisunla) infusion therapies since 2024. Patients undergo evaluation by a cognitive neurologist, baseline MRI, assessment of amyloid positivity by positron emission tomography (PET) or cerebrospinal fluid (CSF), ApoE genotyping, and psychometric testing prior to review at a newly established monthly multidisciplinary conference, where MRI findings are evaluated and final treatment eligibility is determined. Protocols for infusion schedules, MRI monitoring (baseline and prior to the 5th, 7th, and 14th infusions), and management of infusion reactions have been established.

Clinical MRI. All treated patients were imaged monthly on a 1.5T GE Signa scanner. Standard sequences included T1-weighted, FLAIR, SWI, DWI, and T2 fast spin-echo with fat saturation for assessment of brain morphometry, ARIA-E, ARIA-H, white matter microstructural changes, and other abnormalities.

Research MRI. When ARIA occurred, patients were imaged on a 7T Siemens Magnetom scanner using a Tic-Tac-Toe head coil [1][2]. In addition to standard T1-weighted, FLAIR, and SWI acquisitions for evaluating ARIA-E and ARIA-H, high-resolution multi-shell DWI was performed (80 slices, 1.5 mm isotropic; b = 3000 s/mm², 90 directions plus 9 b = 0 images; total 100 directions; TR = 6000 ms; TE = 78 ms; acceleration factor = 2; multiband factor = 2) to assess white matter microstructural changes. A CSF sequence (2 mm isotropic resolution; TR = 51 ms; TE = 10 ms) was acquired similarly to our prior work [3], in which CSF pulsation becomes visible after post-processing to inform brain fluid dynamics. Time-of-flight (TOF) angiography (2 slabs, 356 slices, 0.375 mm isotropic; TR = 16 ms; TE = 4.5 ms; acceleration factor = 3) was also acquired, enabling three-dimensional visualization of small arteries following image processing.

Results

As of June 8, 2026, 130 patients have been enrolled in the registry, with 72 having initiated treatment. Forty-two patients initiated lecanemab; of these, 38 remain on therapy and 4 have permanently discontinued. Thirty patients initiated donanemab; some discontinued due to adverse effects, while others completed treatment following amyloid clearance. Reported adverse events include infusion reactions and ARIA. Since initiation of the treatment program, 11 patients have developed ARIA: 3 (27%) with ARIA-E, 5 (46%) with ARIA-H, and 3 (27%) with both. Most affected patients (82%) were APOE34, with one (9%) APOE24 and one (9%) APOE44. Two of these patients consented to 7T MRI and were subsequently imaged at 7T.

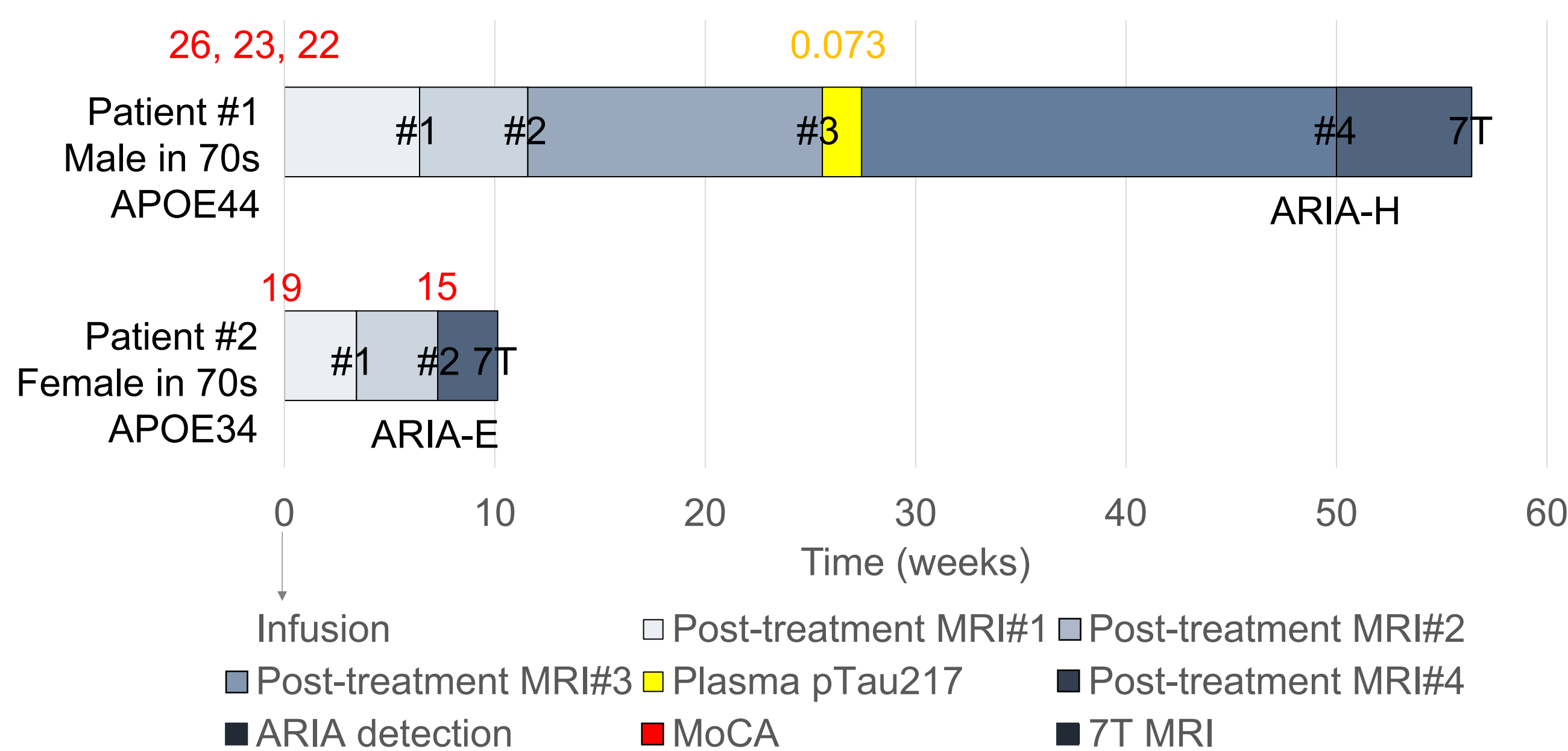


Figure 1. Timeline since infusion initiation. Patient #1, with a baseline MoCA score of 22, developed ARIA-H on post-treatment MRI #4 and had a plasma p-tau217 level of 0.073, which was below the commercial cutoff value. Patient #2, with a baseline MoCA score of 19, developed ARIA-E on post-treatment MRI #2; at the time of ARIA onset, the MoCA score was 15.

Results

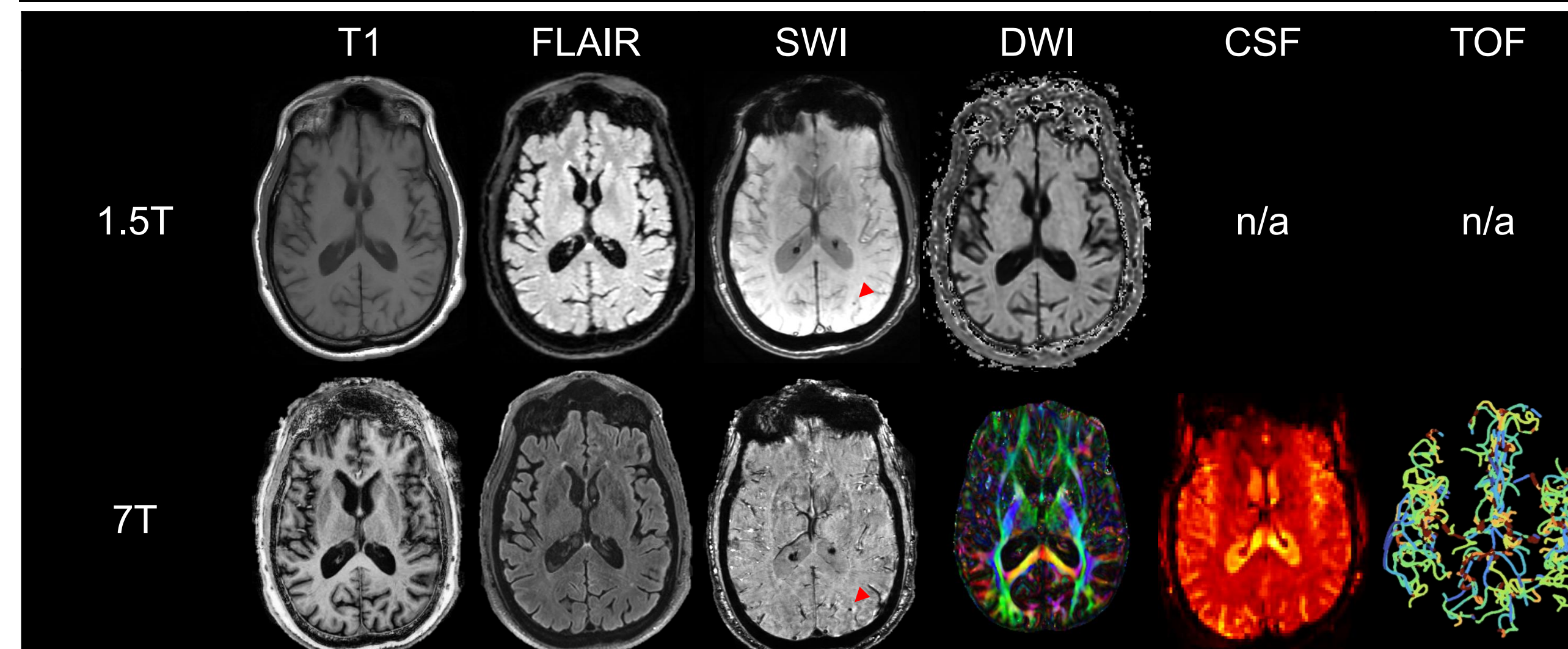


Figure 2. Patient #1 imaged at 1.5T and 7T. A microhemorrhage (arrowhead) was seen in the left hemisphere on SWI at both field strengths. No edema or sulcal effusion was detected on FLAIR, and high-resolution color fractional anisotropy (FA), CSF pulsation, and TOF images were also presented.

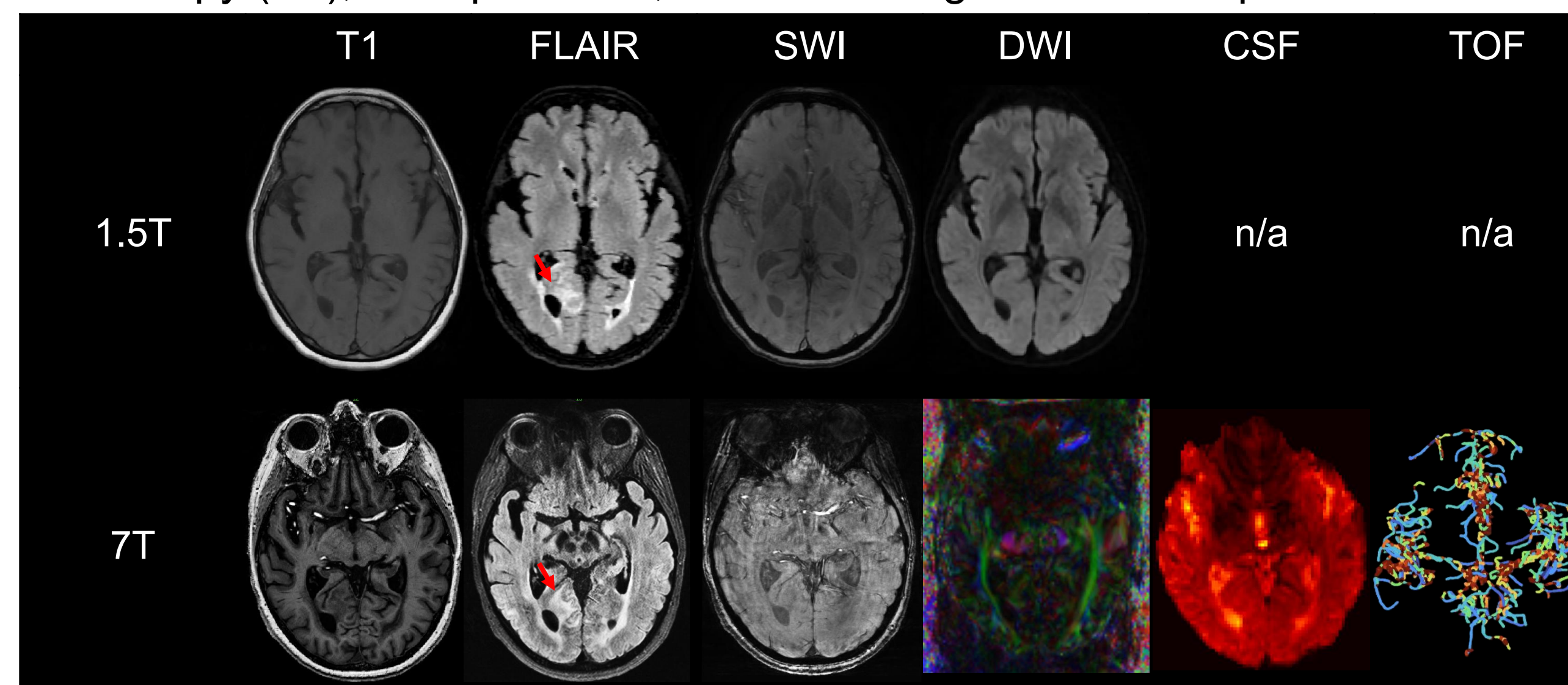


Figure 3. Patient #2 imaged at 1.5T and 7T. The edema (arrow) had not yet resolved at the time of the 7T scan. No microhemorrhage was detected on SWI. High-resolution FA and CSF images were degraded by excessive motion, and TOF images were also presented.

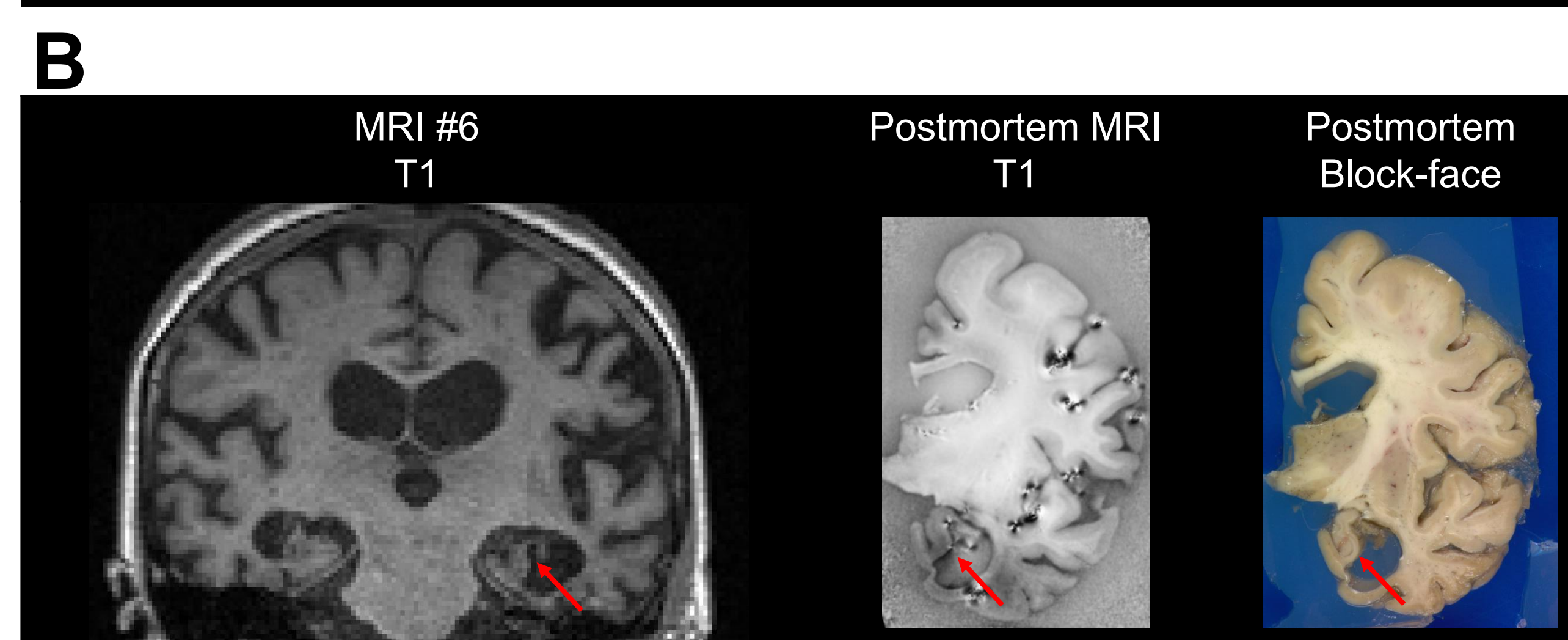
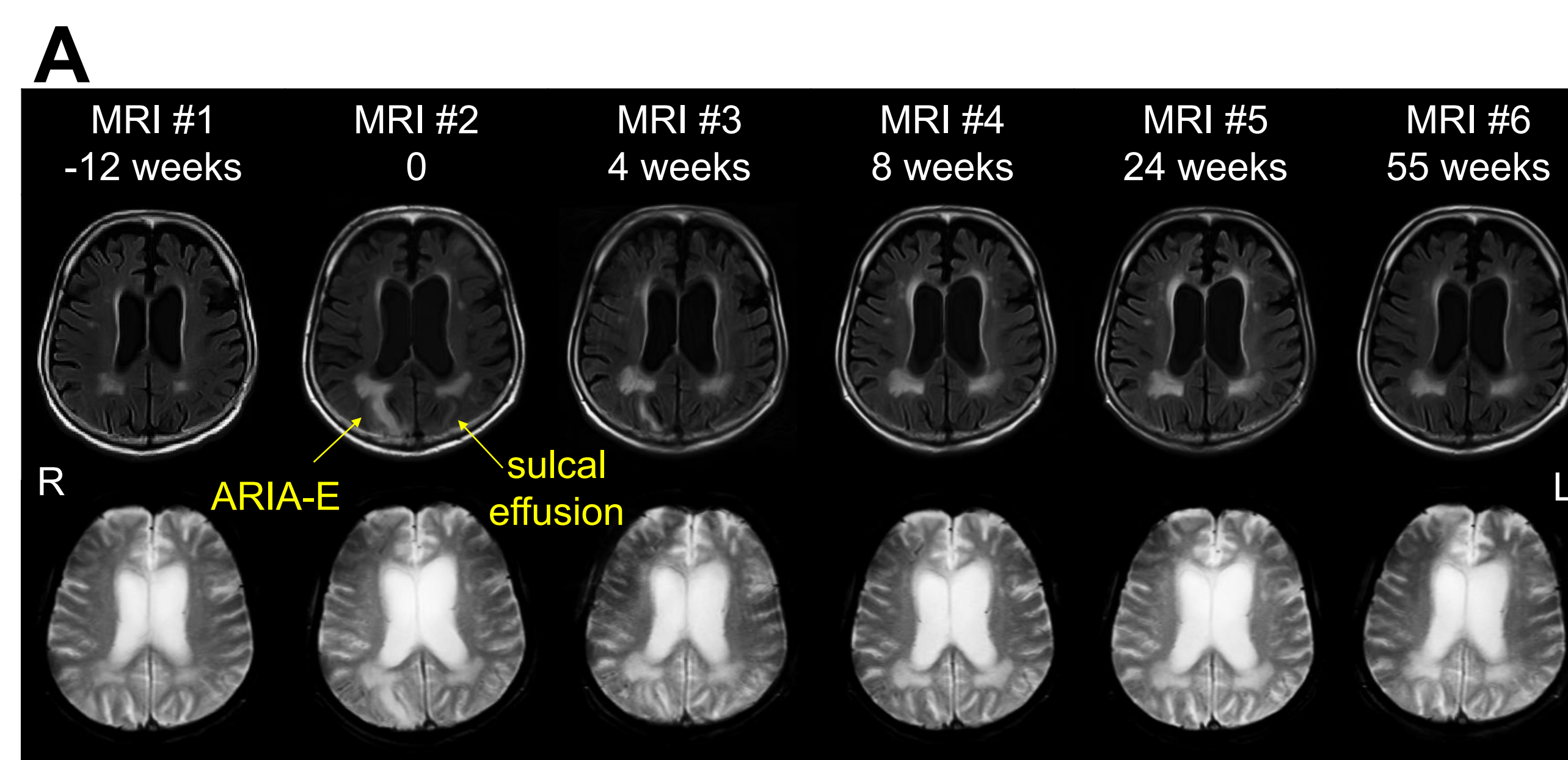


Figure 4. Brain #1, aducanumab, female in her 80s, ARIA-E. (A) She had previously participated in two consecutive aducanumab trials (low dose followed by high dose). During the second trial, she developed moderate ARIA-E. Her last clinical diagnosis was probable AD. Antemortem FLAIR demonstrated peak ARIA-E in the right hemisphere on MRI #2, which resolved over time, along with sulcal effusion on the left, suggesting possible failure of CSF suppression. Rapid progression of white matter hyperintensities remote from the ARIA-E was observed in both hemispheres, suggesting global inflammation or vasculopathy with features of small vessel disease. No hemorrhage was observed. (B) Antemortem scans showed no significant medial temporal lobe atrophy; however three years later postmortem MRI and block-face photographs demonstrated disproportionate hippocampal atrophy on the left (arrow). Postmortem neuropathology revealed end-stage hippocampal sclerosis and limbic-predominant age-related TDP-43 encephalopathy neuropathologic change stage 2.

Results

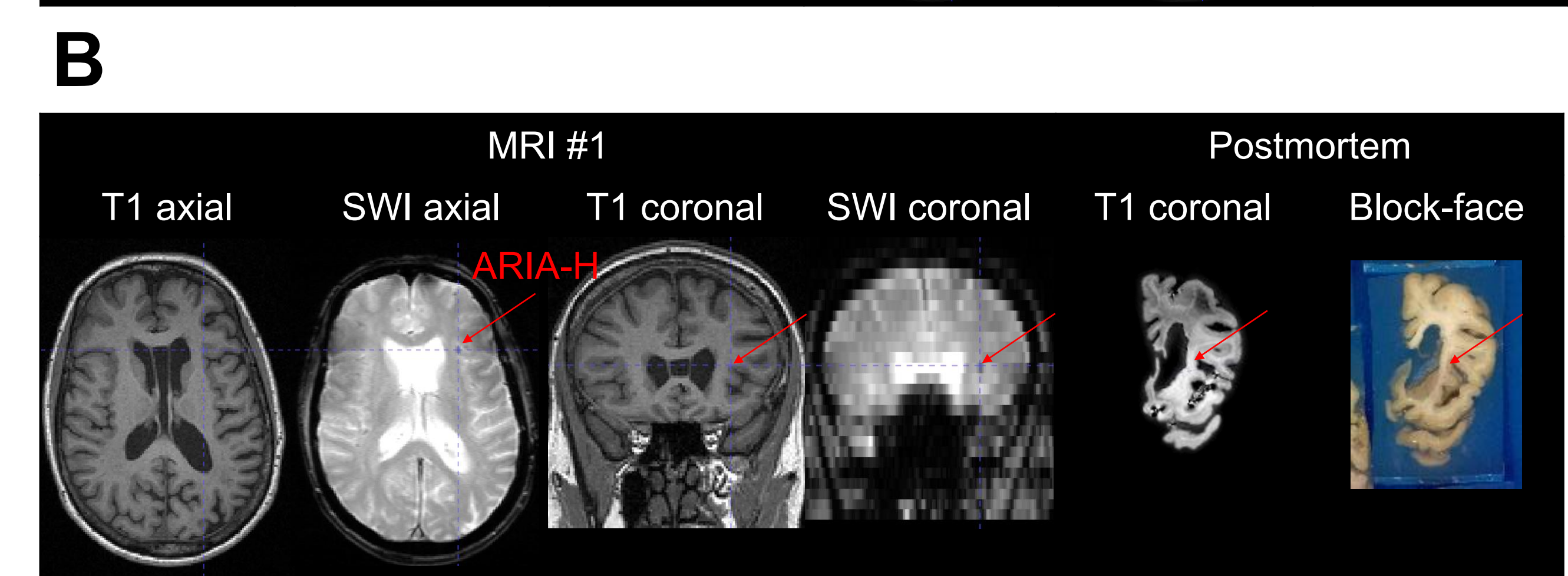
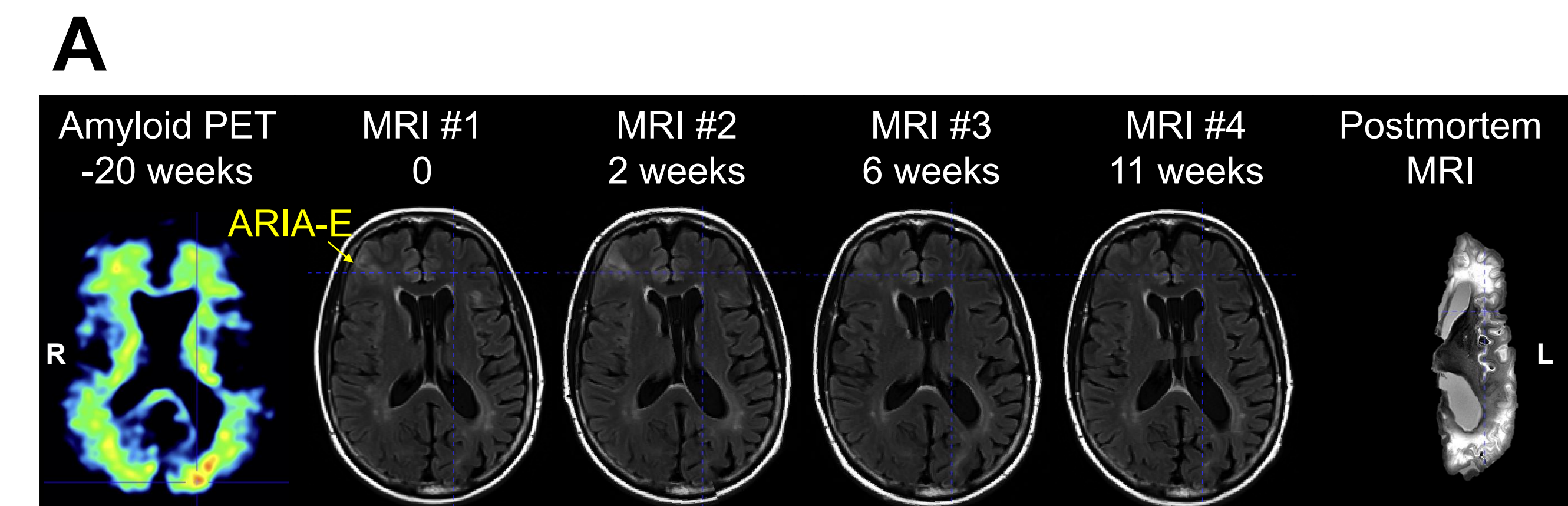


Figure 5. Brain #2, aducanumab, female in her 70s, ARIA-E & ARIA-H. (A) Axial slices of antemortem amyloid PET, antemortem T2-FLAIR from five clinical MRIs, and postmortem T2-SPACE were presented. At baseline PET with [18F]JAV-45 (florbetapir), the visual read was amyloid-positive, with signal concentrated in the left occipital lobe. Five months later, ARIA peaked, with edema in the right frontal and 15 microhemorrhages. The edema subsequently resolved, but the microhemorrhages persisted. Eight years later, postmortem MRI of the left hemisphere showed severe white matter hyperintensities surrounding the ventricles and involving both the frontal and occipital lobes. (B) Coronal view of antemortem MPRAGE, FLAIR, and SWI with postmortem MP2RAGE and SPACE images along with a block-face photograph. A watershed white matter hyperintensity in the left frontal lobe was observed, which had not been visible at the time of peak ARIA. One of the microhemorrhages was identified on antemortem SWI, co-registered, and sampled for immunohistochemistry.

Summary

This prospective registry study examines ARIA in patients treated with lecanemab or donanemab, integrating clinical 1.5T MRI with high-resolution 7T imaging. Among 72 treated patients, 11 (15%) developed ARIA, most of whom were APOE34 carriers.

7T MRI at peak ARIA improved detection of microhemorrhages, edema, and microstructural changes, though motion sometimes limited quality. Case analyses suggest ARIA may involve broader vascular and inflammatory processes, with persistent microhemorrhages and progressive white matter changes observed beyond acute episodes.

Ongoing Effort

- Continuous monitoring of treated patients
- In vivo 7T MRI
 - Longitudinal quantification of edema and microhemorrhages
 - Comparison of white matter microstructural changes inside and outside regions of edema and sulcal effusion
- Automated segmentation of ARIA-E and ARIA-H
- CSF comparisons between age-matched ARIA and non-ARIA subjects
- TOF comparisons between age-matched ARIA and non-ARIA subjects
- Postmortem 7T MRI
 - Postmortem diffusion SSFP analysis
 - MRI-guided immunohistochemistry of white matter hyperintensities
 - MRI-guided immunohistochemistry of cerebral microbleeds

Acknowledgement

Key references:

- [1] Santini et al. 2021 Sci Rep
- [2] Sajewski et al. 2025 Magn Reson Med
- [3] Martins et al. 2024 Front Neurosci
- [4] Liou et al. 2025 Alzheimers Dement
- [5] Liou et al. 2025 J Neuropathol Exp Neurol
- [6] Berardinelli et al. (under review)

Funding sources:

NIH U24NS141780, NIH P30 AG066468, and BrightFocus A2025009F

