ARIA ESSENTIALS

Radiology Perspectives

Elevating Care with Evidence-Based Imaging and Collaboration

This activity is supported by an educational grant from Lilly.

FACULTY

Petrice M. Cogswell, MD, PhD

Chair, Neuroradiology Research
Mayo Clinic
Rochester, MN, USA

Maria Vittoria Spampinato, MD

Assistant Professor, Radiology
Medical University of South Carolina
Charleston, SC, USA

Activity Overview

Target Audience

This activity is designed for neuroradiologists and radiologists as well as other members of the interdisciplinary team who are involved in the care of patients with Alzheimer's disease globally.

Educational Objectives

After completing this activity, learners will be better able to:

- **Identify** pathophysiologic features that put patients taking anti-amyloid monoclonal antibodies at increased risk for amyloid-related imaging abnormalities (ARIA)
- **Apply** standardized magnetic resonance imaging (MRI) protocols and grading scales to optimally monitor for, detect, and assess the severity of ARIA in patients receiving anti-amyloid monoclonal antibodies
- **Integrate** best practices for interdisciplinary communication to enhance coordination among radiologists, neurologists, and geriatricians in the management of ARIA

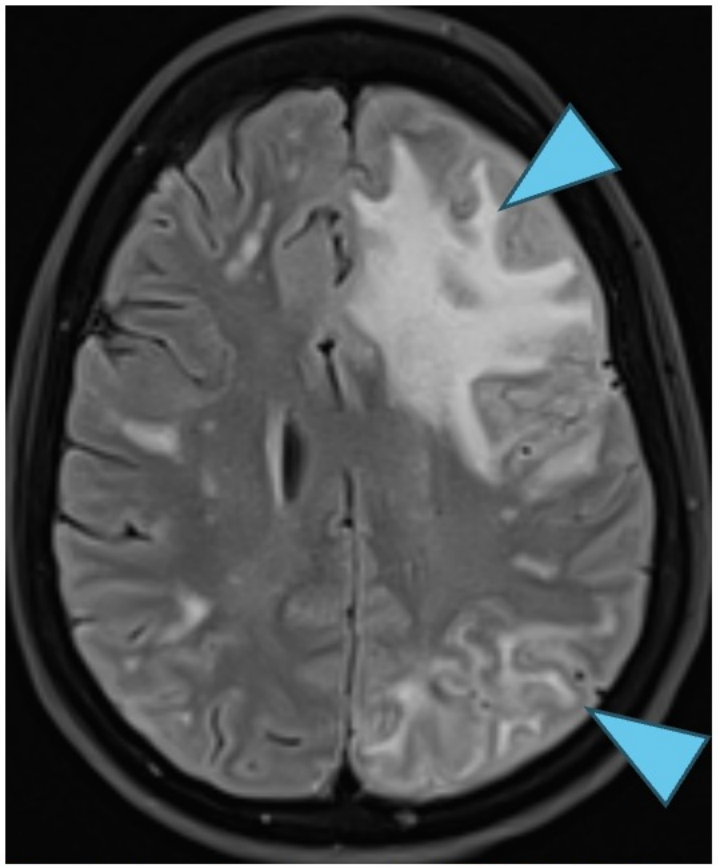
Agenda

- Pathophysiology and risk factors of ARIA
- Standardized MRI protocols and grading scales for ARIA detection
- Interdisciplinary communication for effective ARIA management

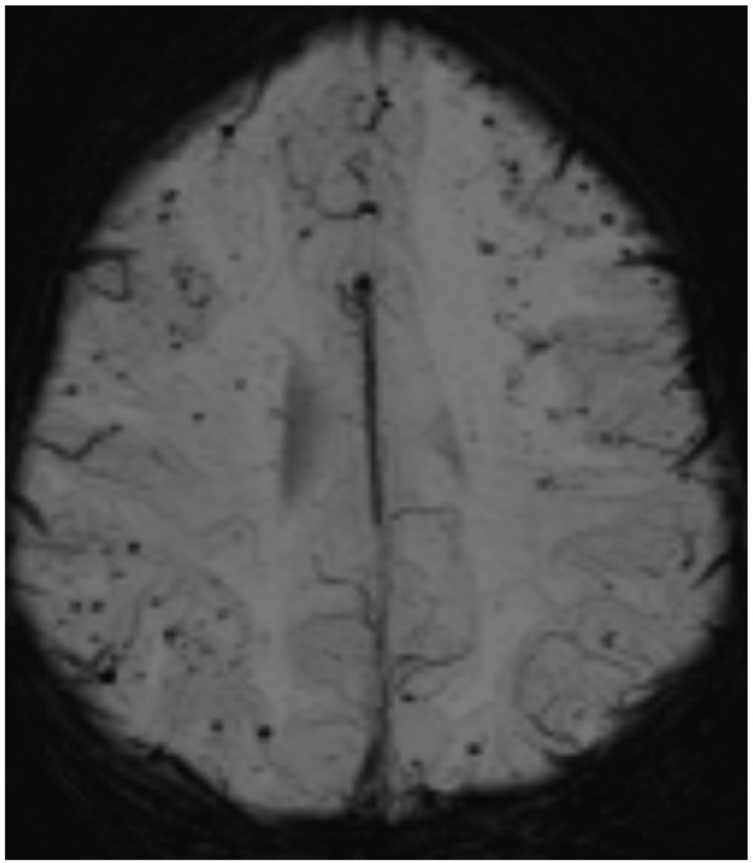
Is This ARIA?

Is This ARIA?

66-Year-old female with word-finding difficulty and headache



Cortical and subcortical T2 FLAIR hyperintense signal with local mass effect

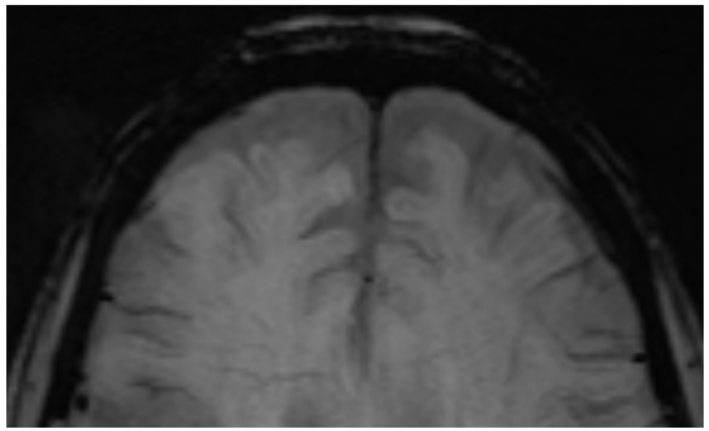


Innumerable cortical-subcortical microhemorrhages

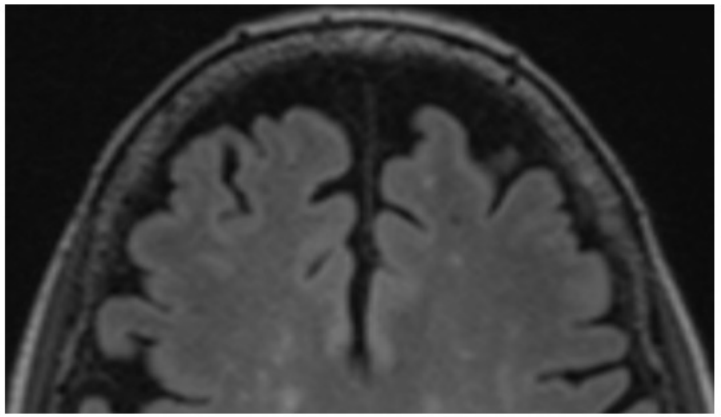
ARIA, amyloid-related imaging abnormalities; FLAIR, fluid-attenuated-inversion recovery.

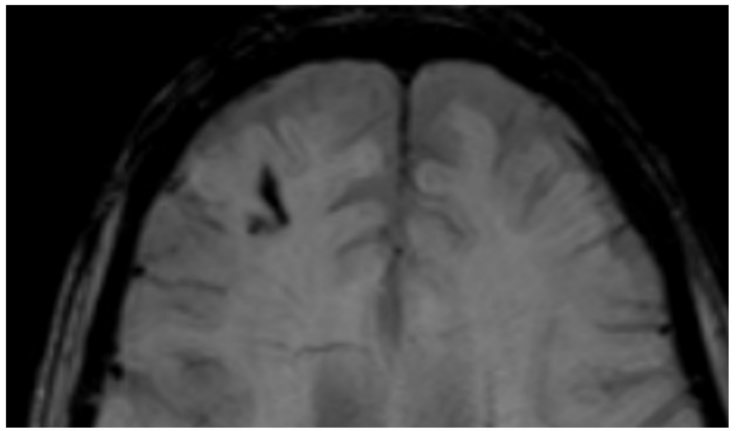
Is This ARIA?

78-Year-old female with memory loss on amyloid-targeting therapy

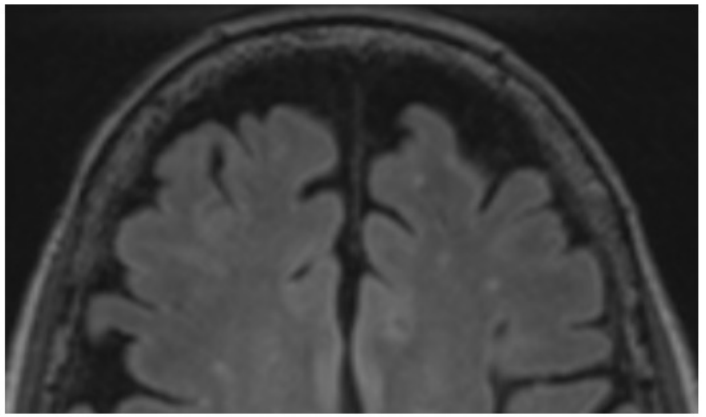


February 2024
Baseline MRI





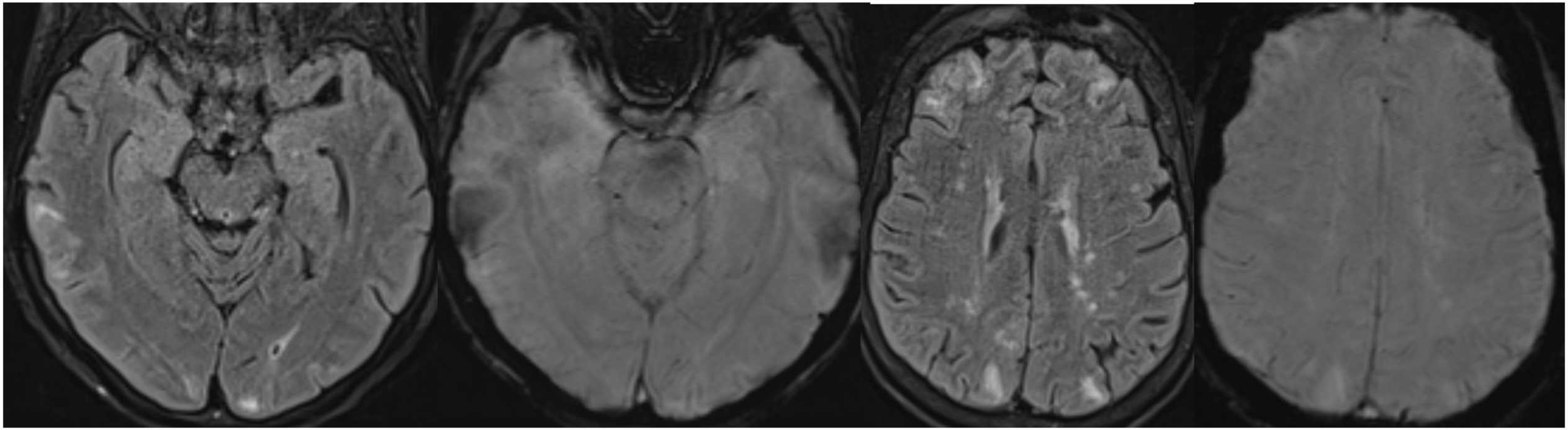
July 2024
Postdosing MRI



ARIA, amyloid-related imaging abnormalities; MRI, magnetic resonance imaging.

Is This ARIA?

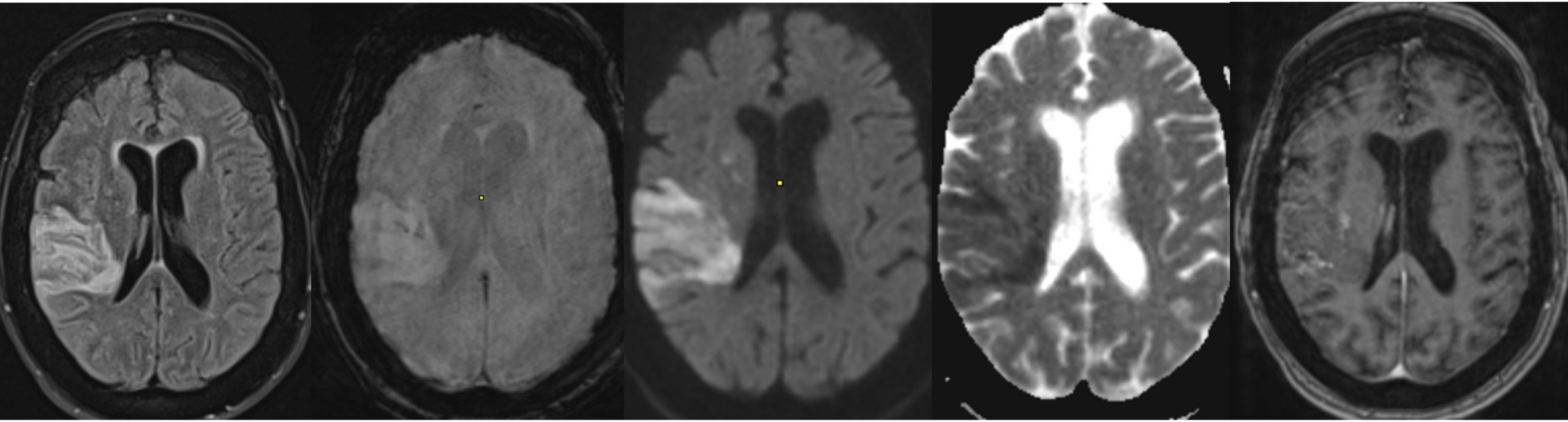
69-Year-old female with uncontrolled hypertension and new onset of seizures



ARIA, amyloid-related imaging abnormalities.

Is This ARIA?

68-Year-old female with history of dementia and atrial fibrillation, presenting with left-sided weakness



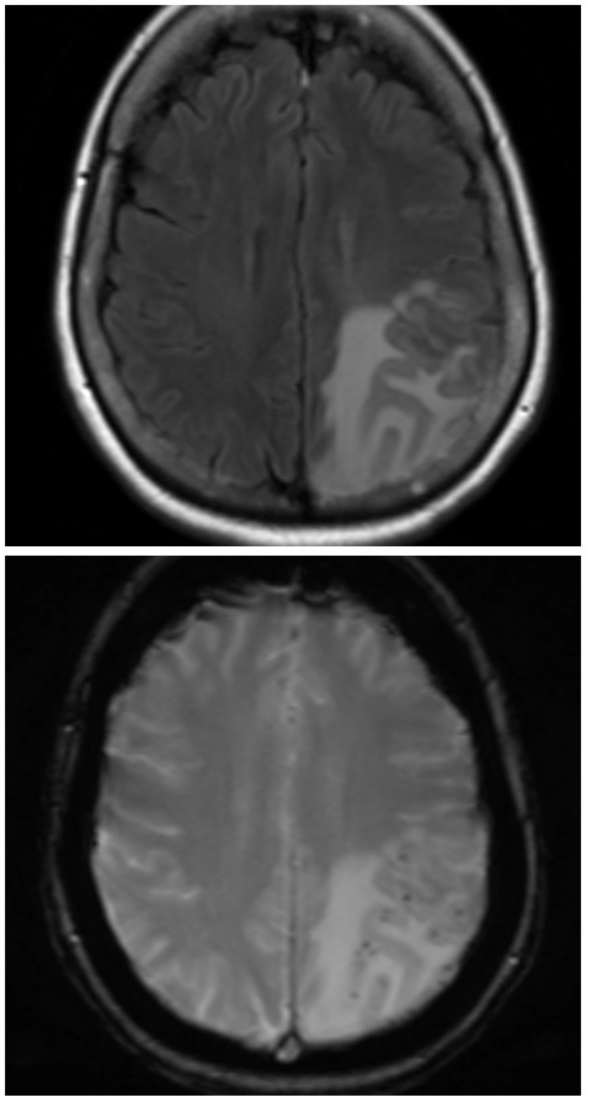
ARIA, amyloid-related imaging abnormalities.

Part 1:

Pathophysiology of and Risk Factors for ARIA

Amyloid-Related Imaging Abnormalities (ARIA)

- Edema (ARIA-E) and hemorrhage (ARIA-H) that occur in the setting of immunotherapies targeting beta-amyloid
- Common mechanism
  - Leak of exudate from vessel into extracellular or subarachnoid space
- Etiology
  - Vessel wall infiltration by amyloid, loss of vascular integrity when amyloid is removed from the vessels as well as the parenchyma



ARIA-E, amyloid-related imaging abnormalities-edema; ARIA-H, amyloid-related imaging abnormalities-hemorrhage.
Haller S et al. *Radiology*. 2024;310(2):e233381.

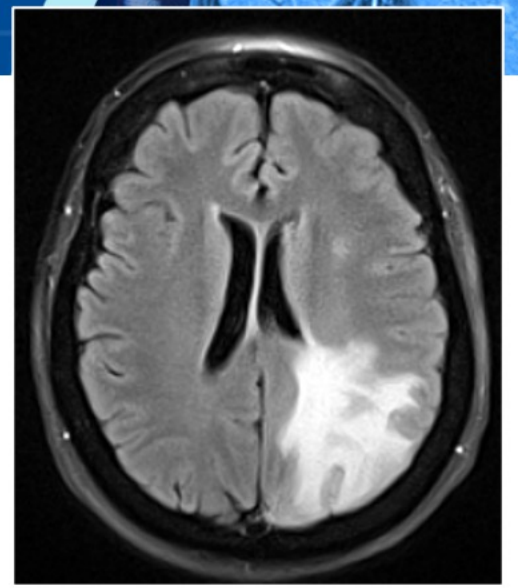
ARIA-E and ARIA-H

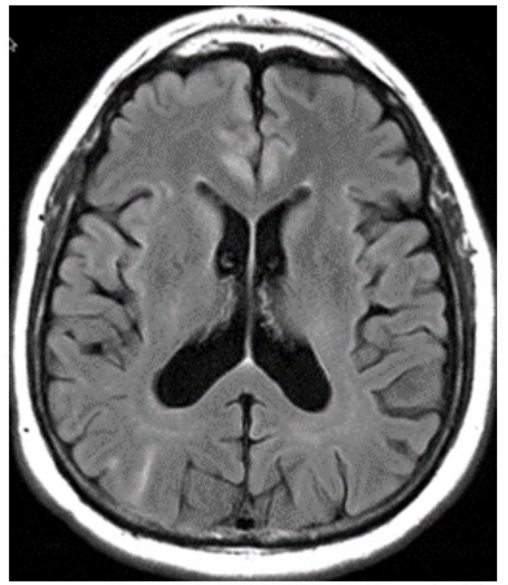
- ARIA-E occurs in 15% to 40% of patients with AD receiving amyloid-targeting therapies
- Most cases of ARIA-E are mild and reversible
  - Only a minority of cases (< 7%) are severe
- ARIA-H does not resolve with drug discontinuation and persists after identification on MRI
- ARIA typically occurs early during treatment
  - Resuming amyloid-targeting therapies at a lower dose is associated with ~15% development of ARIA-E relapse

AD, Alzheimer disease; ARIA-E, amyloid-related imaging abnormalities-edema; ARIA-H, amyloid-related imaging abnormalities-hemorrhage; MRI, magnetic resonance imaging.
Haller S et al. *Radiology*. 2024;310(2):e233381. Doran SJ et al. *Front Neurosci*. 2024;18:1326784.

ARIA-E on Imaging

- E = edema, effusion/exudate
- Imaging sequence: T2 FLAIR
- Imaging appearance
  - Parenchymal: vasogenic edema
    - T2 hyperintense signal in white matter ± gray matter
    - May have associated gyral swelling
  - Leptomeninges: sulcal effusion or exudate
- No restricted diffusion
- Occipital > parietal > frontal > cerebellum, brainstem
- Transient

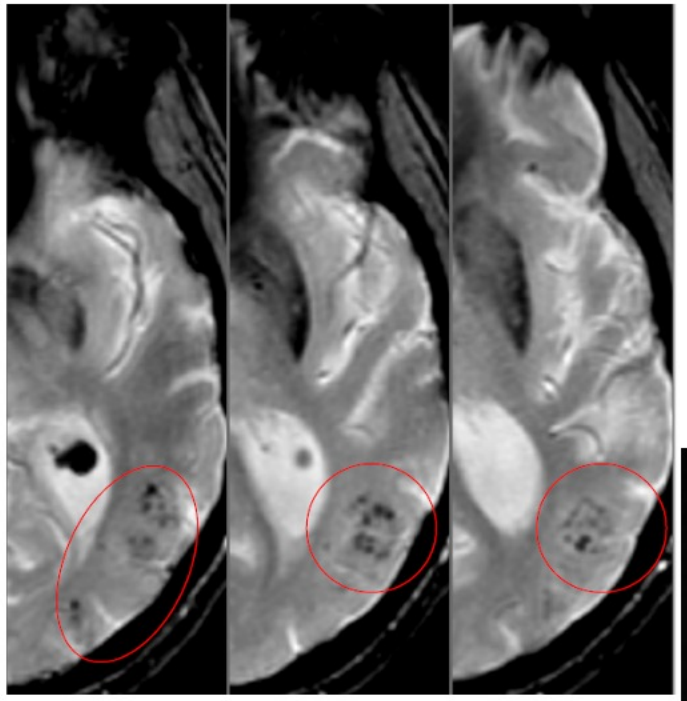


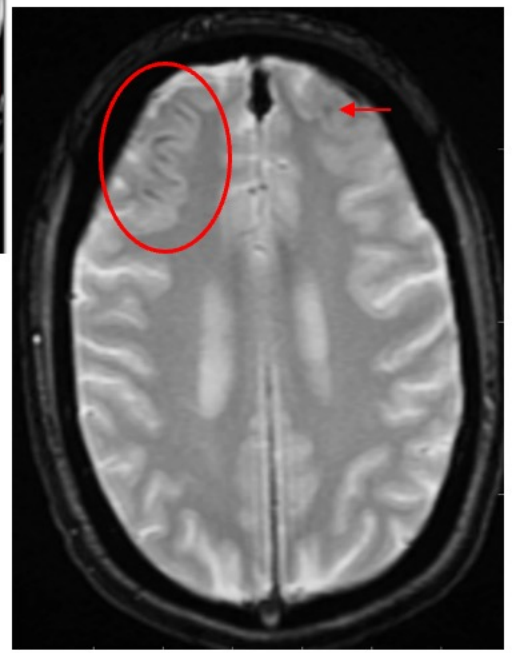


ARIA-E, amyloid-related imaging abnormalities-edema; FLAIR, fluid-attenuated-inversion recovery.
Cogswell PM et al. *AJNR Am J Neuroradiol*. 2022;43(9):E19-E35.

ARIA-H on Imaging

- Imaging sequence: GRE ± SWI
- Imaging appearance
  - Parenchyma: microhemorrhage
    - Focal, hypointensity that does not track with a vessel
    - In the brain parenchyma
  - Leptomeninges: superficial siderosis
    - Curvilinear hypointensity
    - Along the brain surface





ARIA-H, amyloid-related imaging abnormalities-hemorrhage; GRE, gradient echo; SWI, susceptibility-weighted imaging.
Cogswell PM et al. *AJNR Am J Neuroradiol*. 2022;43(9):E19-E35.

Genetic Risk Factors for ARIA

Mechanism	E4 allele carrier risk and increased age	Overproduction of toxic amyloid beta peptide	Regulates clearance of amyloid beta in the brain	Neuroinflammation
Genes	• Apolipoprotein E epsilon 4 allele (*APOE4*)	• Presenilin 1 and 2 (*PSEN1* and *PSEN2*) • Amyloid precursor protein (*APP*) • TP-binding cassette, sub-family A, member 7 (*ABCA7*)	• Clusterin (*CLU*)	• Complement receptor 1 (*CR1*) • Phosphatidylinositol-binding clathrin assembly protein (*PICALM*)

ARIA, amyloid-related imaging abnormalities.

National Institute on Aging. Alzheimer's Disease Genetics Fact Sheet. March 1, 2023. https://www.nia.nih.gov/health/alzheimers-causes-and-risk-factors/alzheimers-disease-genetics-fact-sheet.

ARIA Risk and Cerebrovascular Conditions

- Risk factors for ARIA-E and ARIA-H
  - Positive APOE4 carrier status
  - Prior multiple cerebral microhemorrhages
- Risk factors for ARIA-H
  - Age
  - Antithrombotic use
  - History of prior strokes

ARIA-E, amyloid-related imaging abnormalities-edema; ARIA-H, amyloid-related imaging abnormalities-hemorrhage.
Doran SJ et al. *Front Neurosci.* 2024;18:1326784.

Differentiating ARIA

- Other processes have imaging appearances similar to ARIA
  - CAA-RI: spontaneous sulcal effusions/edema and microhemorrhages/siderosis
  - PRES: edema and hemorrhages, including microbleeds, subarachnoid hemorrhage, and intraparenchymal hematoma
- Differences between ARIA and other processes
  - Use/non-use of monoclonal antibodies that remove amyloid plaque
  - Clinical presentation and components of imaging findings may differ

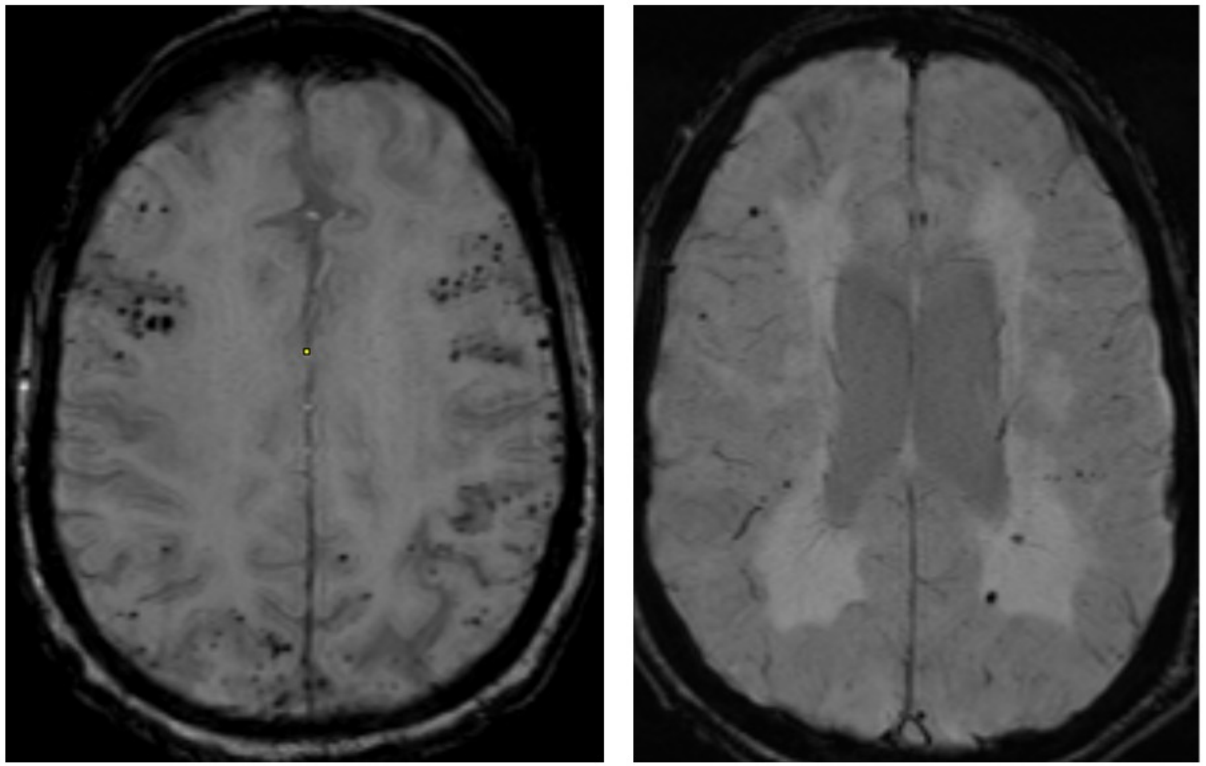
ARIA, amyloid-related imaging abnormalities; CAA-RI, cerebral amyloid angiopathy-related inflammation; PRES, posterior reversible encephalopathy syndrome.
Haller S et al. *Radiology*. 2024;310(2):e233381. Cogswell PM et al. *AJNR Am J Neuroradiol*. 2022;43(9):E19-E35.

Part 2:

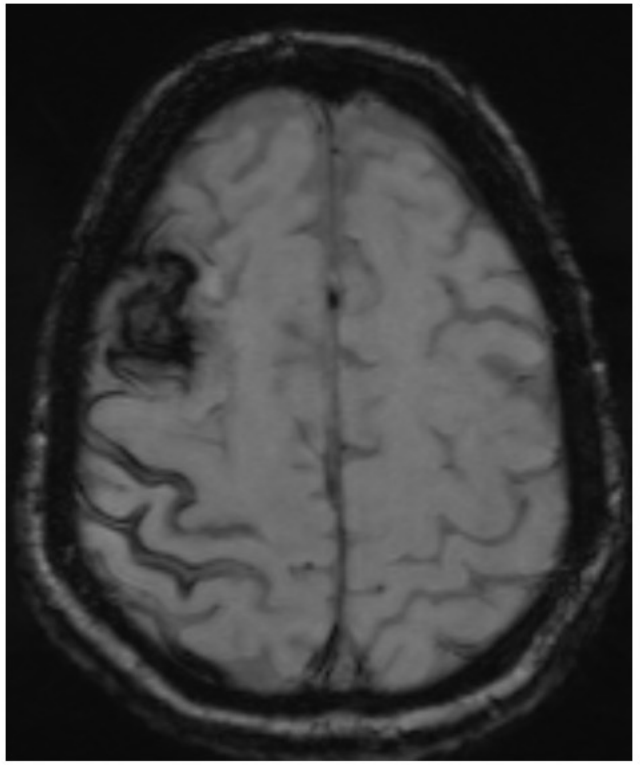
Standardized MRI Protocols and Grading Scales for ARIA Detection

Appropriate Use Recommendations

Exclusionary Findings - Intracranial Hemorrhage



>4 Microhemorrhages (< 10 mm)



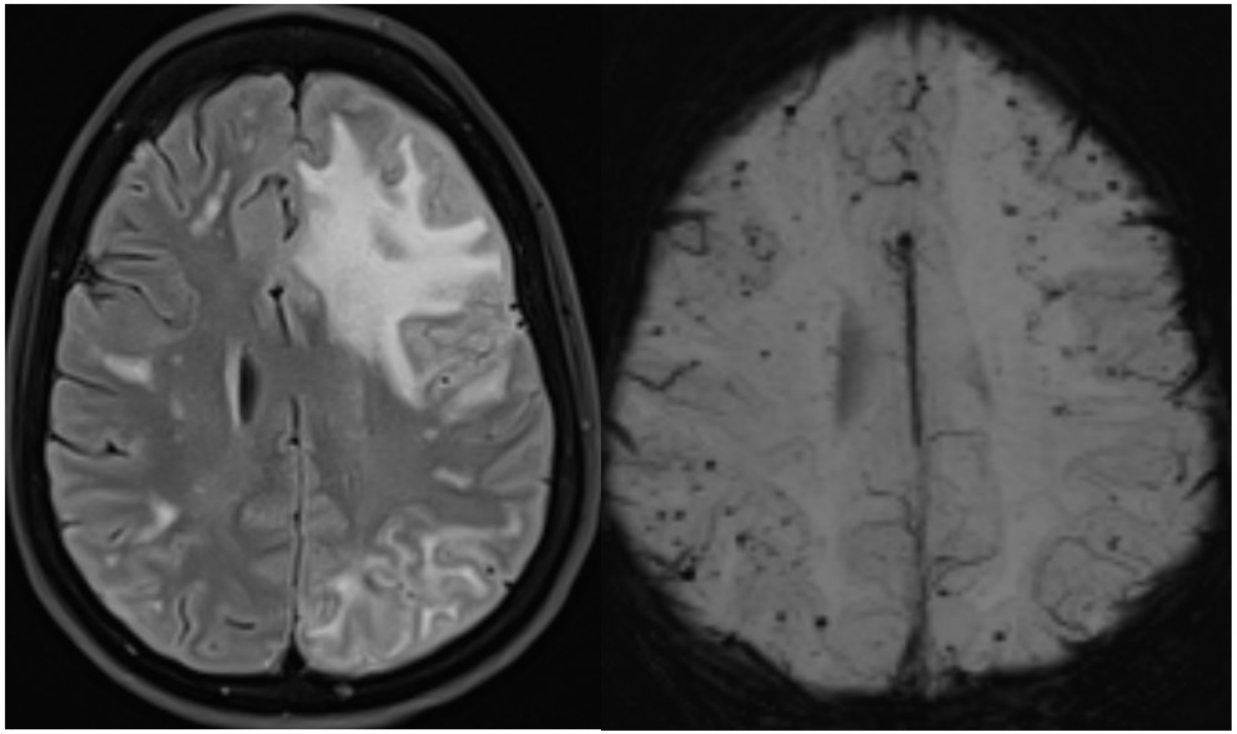
Superficial siderosis
Any macrohemorrhage (> 10 mm)

Cummings J et al. *J Prev Alzheimers Dis*. 2023;10(3):362-377.

Appropriate Use Recommendations

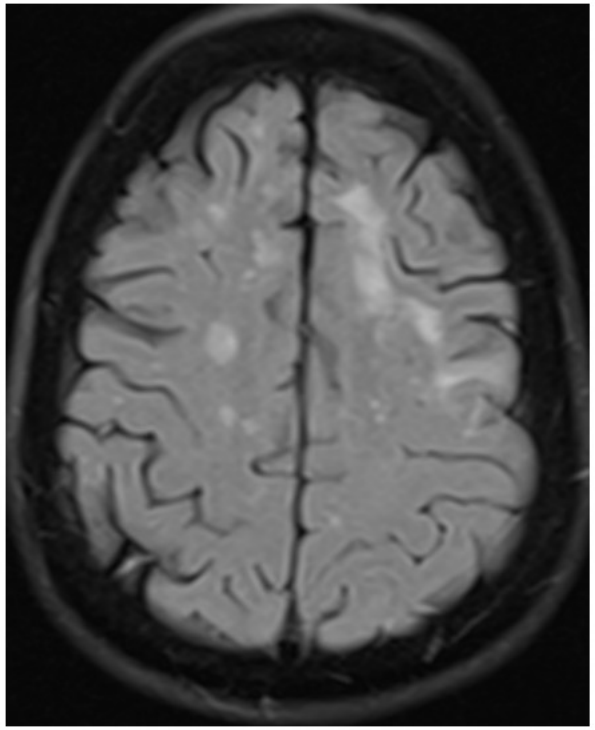
Exclusionary Findings - Cerebral Amyloid Angiopathy (CAA/CAA-RI)

Initial MRI



- Symptomatic, cognitive decline, seizures, and headaches
- Cortico-subcortical microbleeds

Follow-up



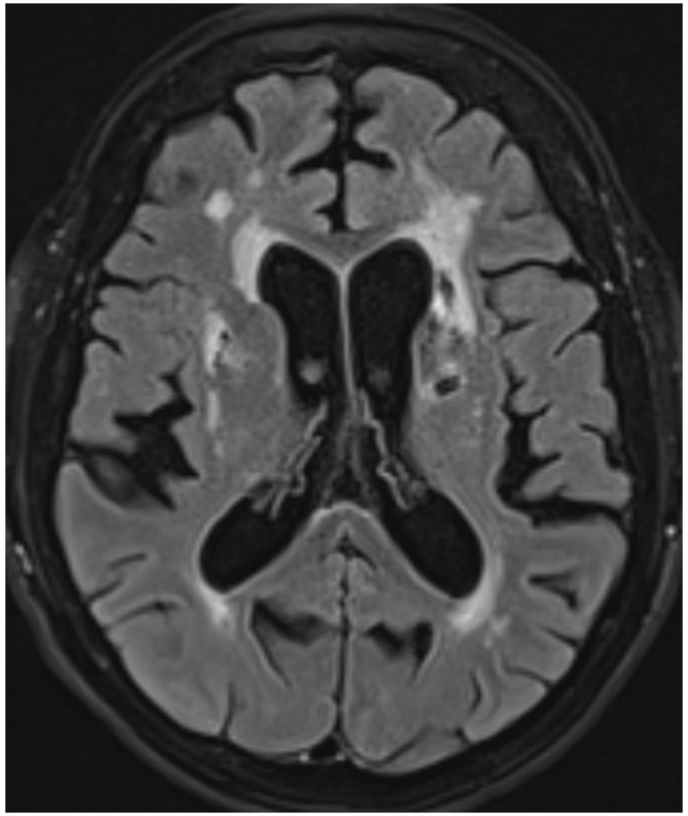
- Subcortical white matter hyperintensity w/ mass effect

CAA/CAA-RI, cerebral amyloid angiopathy-related inflammation.

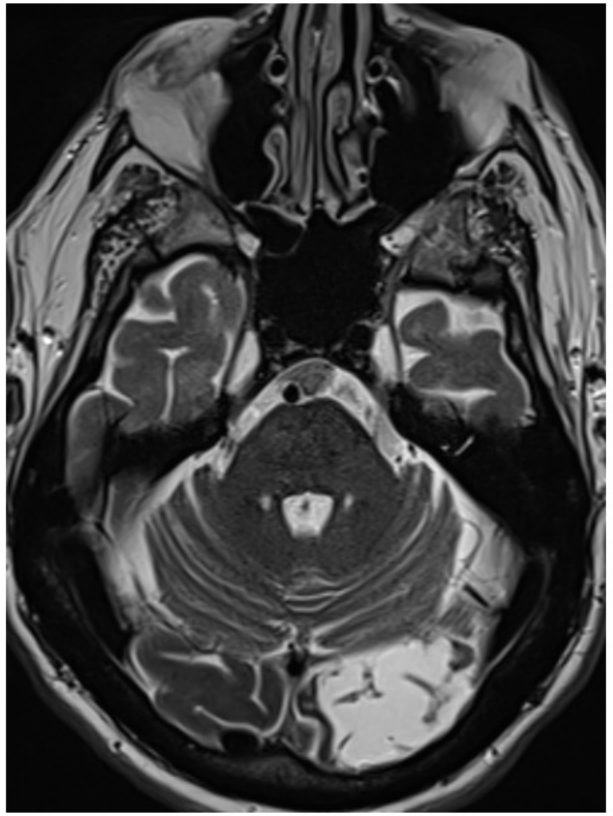
Cummings J et al. *J Prev Alzheimers Dis*. 2023;10(3):362-377. Agarwal A et al. *Radiographics*. 2023;43(9):e230009.

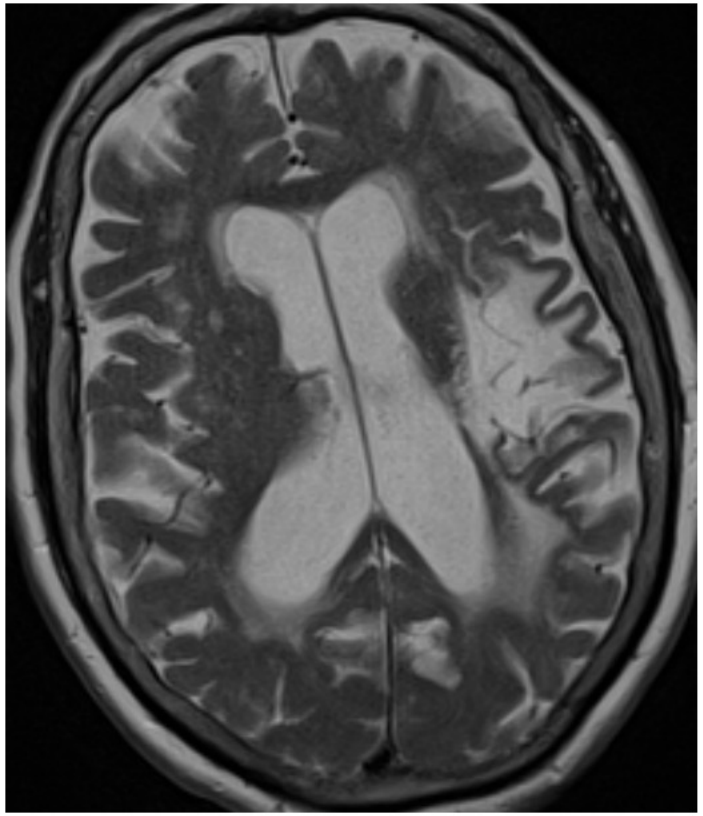
Appropriate Use Recommendations

Exclusionary Findings - Ischemic Stroke



>2 Lacunar infarcts



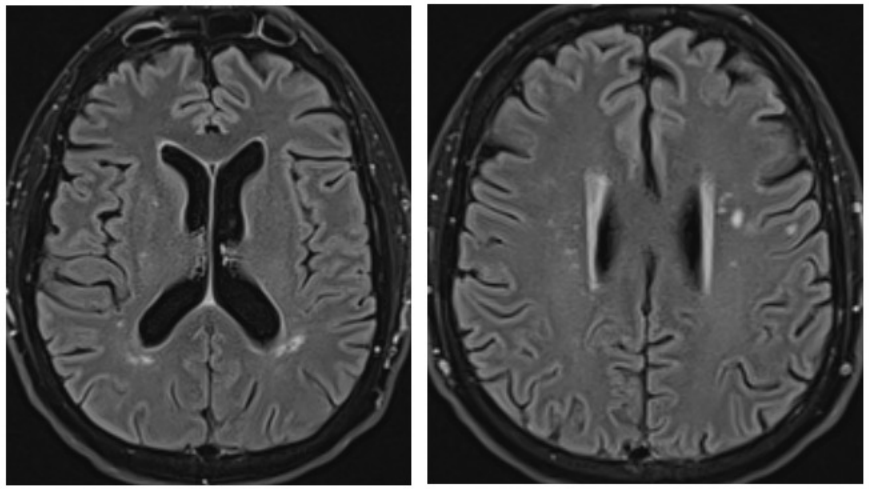


Territorial infarct

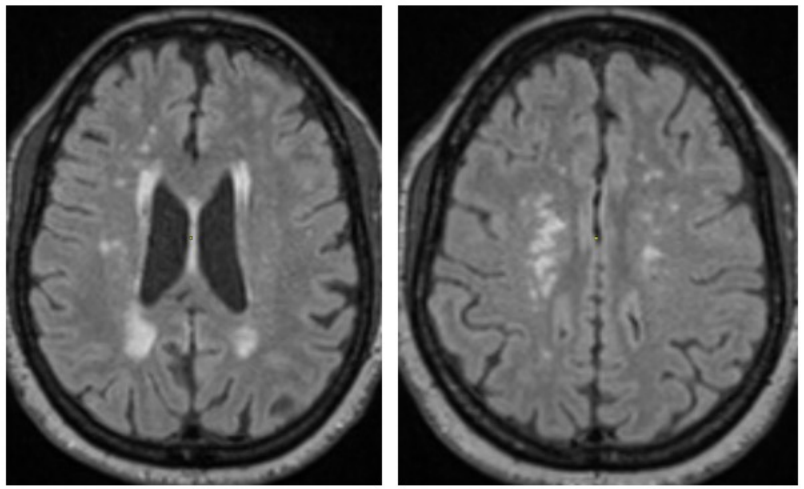
Cummings J et al. *J Prev Alzheimers Dis*. 2023;10(3):362-377.

Appropriate Use Recommendations

Exclusionary Findings – Advanced White Matter Hyperintensities

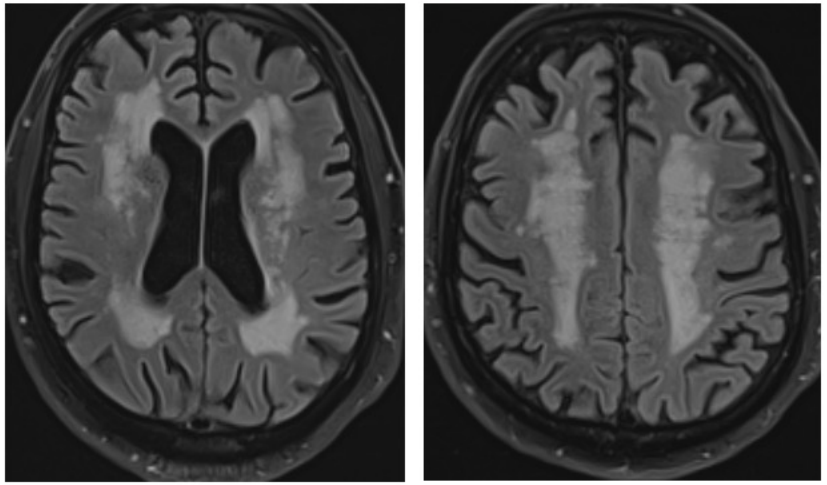


Fazekas grade 1



Fazekas grade 2

Eligible



Fazekas grade 3

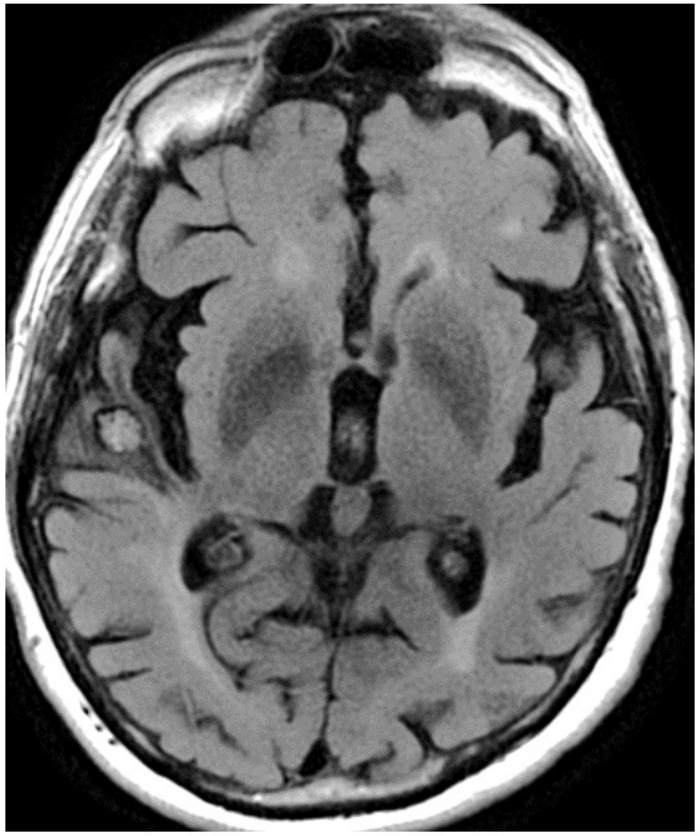
Not eligible

Cummings J et al. *J Prev Alzheimers Dis*. 2023;10(3):362-377.

Appropriate Use Recommendations

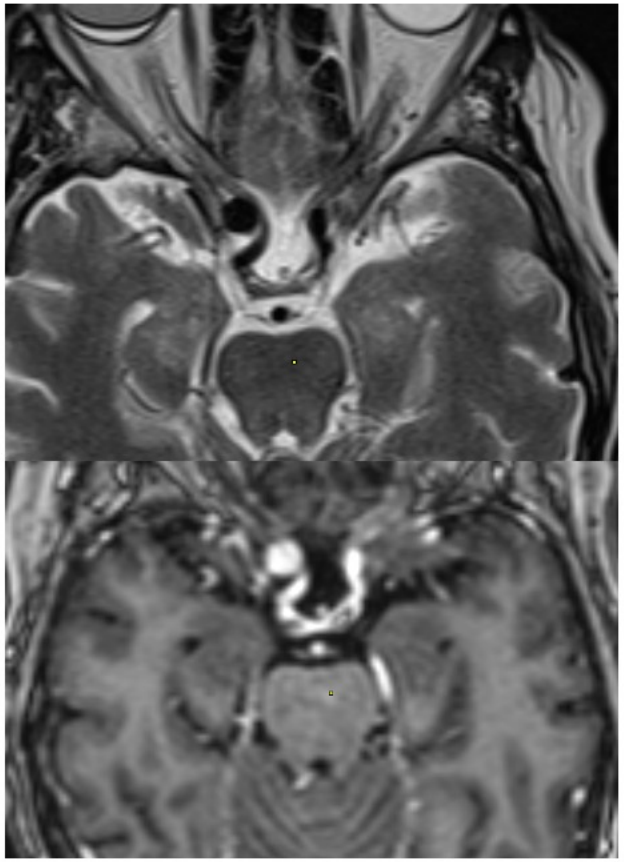
Exclusionary Findings

Male, 78 y with MCI



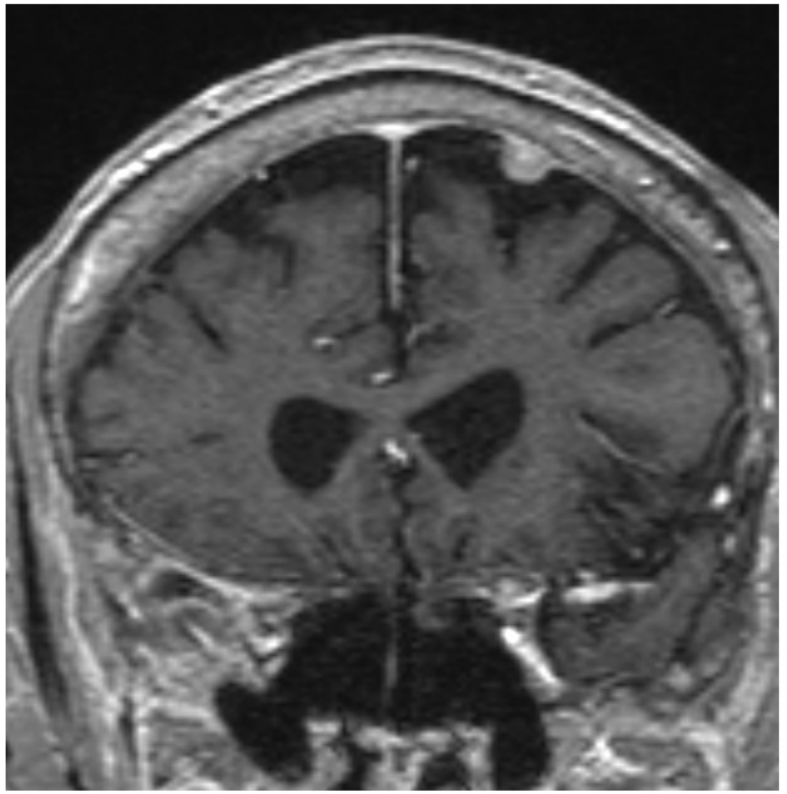
Cavernous malformation

Female, 76 y with memory loss



Aneurysm

Male 84 y with memory loss



Meningioma < 1 cm

van Dyck CH et al. *N Engl J Med*. 2023;388(1):9-21.

Appropriate Use Recommendations

- Consider disease, clinical, and biomarker characteristics when selecting candidates for treatment
- Importance of APOE4 genotyping for predicting risk of amyloid-related imaging abnormalities
- Need for pretreatment MRI to exclude patients with white matter disease or evidence of cerebral amyloid angiopathy
- Advisement against treatment for patients taking anticoagulants
- Contraindication of thrombolytics for patients on active amyloid-targeting therapy

APOE4, apolipoprotein E epsilon 4 allele.

17th annual Clinical Trials on Alzheimer's Disease (CTAD) conference. Donanemab: appropriate use recommendations. Pract Neurol. https://practicalneurology.com/news/donanemab-appropriate-use-recommendations-presented-at-ctad-2024.

Standard Reporting for ARIA and Emerging AD Therapeutics

TECHNIQUE: Blood-Sensitive Sequence: [<SWI>][<GRE/T2*>] Field Strength: [<3 T>][<1.5 T>]	
Category	**Details**
Findings	
Total microhemorrhages	Total number Describe locations in general, deep vs lobar
Superficial siderosis	None / < 1 focal area / < 2 focal areas / > 2 focal areas Describe locations
Extent of white matter hyperintensities	Mild, moderate, severe
Infarcts	Describe cortical and subcortical infarcts if present
Other findings	General description of other acute or chronic findings
Impression	
Total microhemorrhages	0-4 / 5-9 / ≥ 10
Superficial siderosis	Not detected vs present
Other findings	General description of other findings

AD, Alzheimer disease; ARIA, amyloid-related imaging abnormalities; GRE, gradient echo; SWI, susceptibility-weighted imaging.

Report templates available at: https://www.alznetproviders.org/Clinical-Care-Resources/Imaging-Resources

Assessment of ARIA + Therapy Monitoring

ARIA Type	Radiographic Severity		
	Mild	Moderate	Severe
ARIA-E	FLAIR hyperintensity confined to sulcus and/or cortex/subcortical white matter in 1 location < 5 cm	FLAIR hyperintensity 5-10 cm, or more than 1 site of involvement, each measuring < 10 cm	FLAIR hyperintensity measuring > 10 cm, often with significant subcortical white matter and/or sulcal involvement; ≥ 1 separate sites of involvement
ARIA-H microhemorrhage	≤ 4 new incident microhemorrhages	5-9 new incident microhemorrhages	≥ 10 new incident microhemorrhages
ARIA-H superficial siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	> 2 focal areas of superficial siderosis

Adapted from Aducanumab label. Adapted from Lecanemab. Prescribing information. Eisai Inc.; 2025.
ARIA-E, amyloid-related imaging abnormalities-edema; ARIA-H, amyloid-related imaging abnormalities-hemorrhage; FDA, U.S. Food and Drug Administration; FLAIR, fluid-attenuated-inversion recovery.

Patient Management Based on ARIA Severity and Symptoms

Clinical Symptom Severity	ARIA-E Severity			ARIA-H Severity		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Asymptomatic	C	S	D	C	S	D
Mild	S	S	D	S	S	D
Moderate	S	S	D	S	S	D
Severe	D	D	D	D	D	D

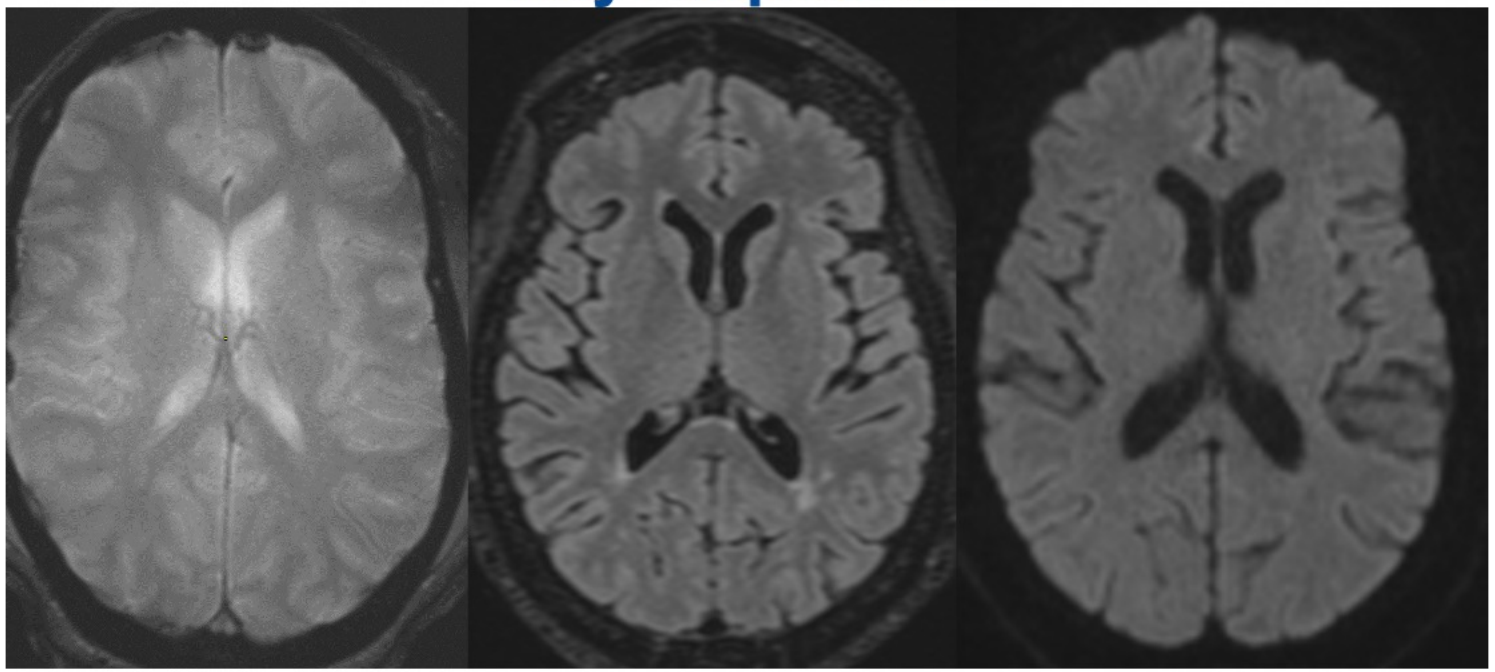
C	Continue dosing
S	Suspend dosing until resolution of ARIA-E and stabilization of ARIA-H, resumption of dosing based on patient-specific risk-benefit assessment
D	Discontinue dosing due to serious symptoms

Adapted from the aducanumab and lecanemab FDA labels.
AD, Alzheimer's disease; ARIA-E, amyloid-related imaging abnormalities-edema; ARIA-H, amyloid-related imaging abnormalities-hemorrhage; FDA, U.S. Food and Drug Administration.
Cogswell PM et al. *AJNR Am J Neuroradiol*. 2022;43(9):E19-E35.

Brain MRI for AD Therapy Enrollment

Workflow Integrating Standardized MRI Order, Protocol, and Standard Report

Key Sequences



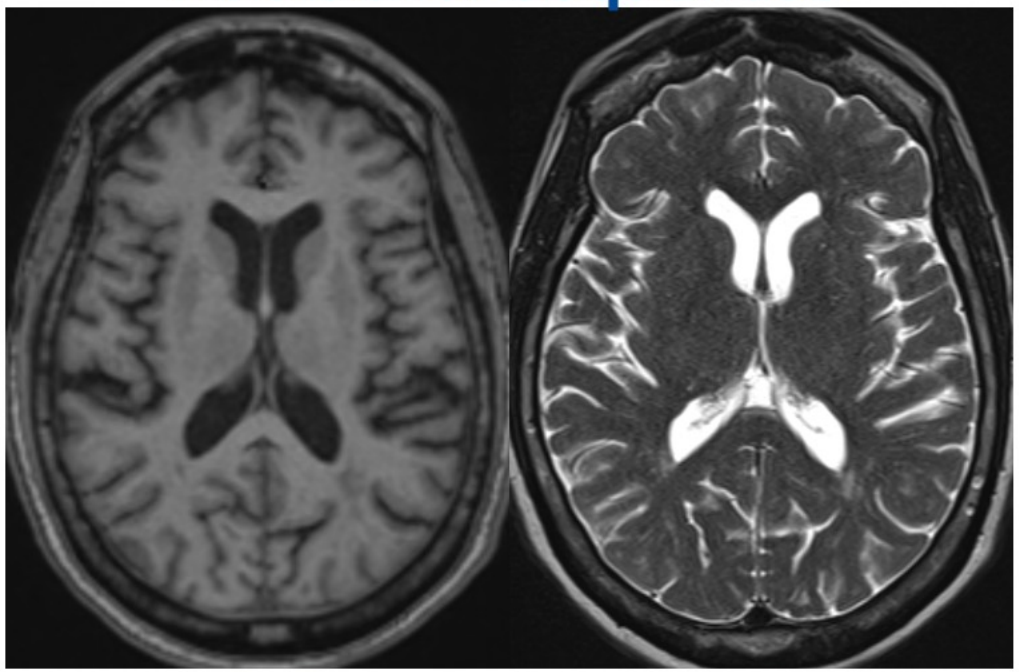
T2* GRE (SWI) | FLAIR | DWI

3T: TE = 15-20 ms ; 1.5T: TE 25-35 ms

Amyloid-Related Imaging Abnormalities with Emerging Alzheimer Disease Therapeutics: Detection and Reporting Recommendations for Clinical Practice

P.M. Cogswell, J.A. Barakos, F. Barkhof, T.S. Benzinger, C.R. Jack, Jr. T.Y. Poussaint, C.A. Raji, V.K. Ramanan, and C.T. Whitlow

Additional Sequences



3D T1 | T2

Alzheimer's Disease Anti-Amyloid Immunotherapies: Imaging Recommendations and Practice Considerations for ARIA Monitoring

Cogswell, Petrice M. Andrews, Trevor J. Barakos, Jerome A. Barkhof, Frederik. Bash, Suzie. Benayoun, Marc Daniel. Chiang, Gloria C. Franceschi, Ana M. Jack Jr, Clifford R. Pillai, Jay J. Poussaint, Tina Young. Raji, Cyrus A. Ramanan, Vijay K. Tanabe, Jody. Tanenbaum, Lawrence. Whitlow, Christopher T. Yu, Fang F. Zaharchuk, Greg. Zeinah, Michael. Benzinger, Tammie S. for the ASNR Alzheimer's, ARIA, and Dementia Study Group

3D, 3 dimensional; AD, Alzheimer disease; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated-inversion recovery; GRE, gradient echo; MRI, magnetic resonance imaging; SWI, susceptibility-weighted imaging.

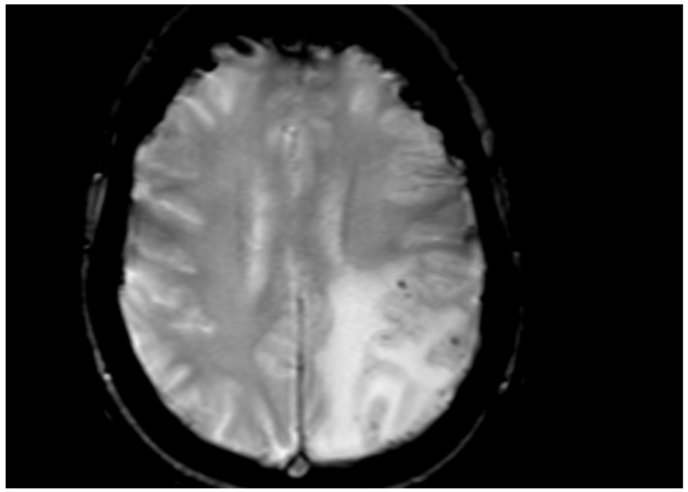
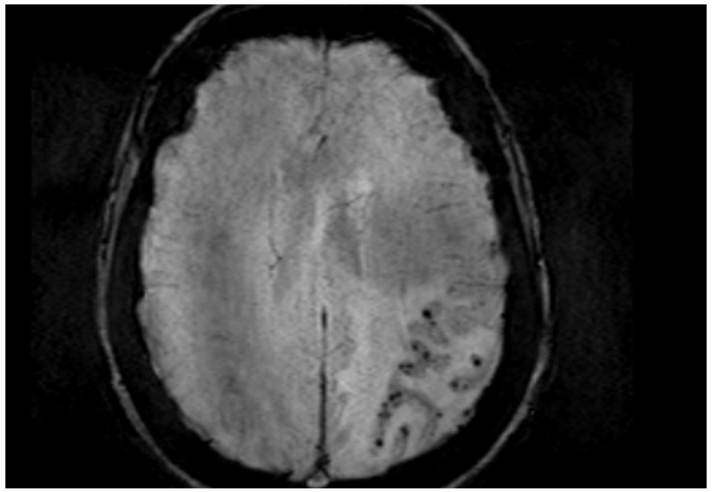
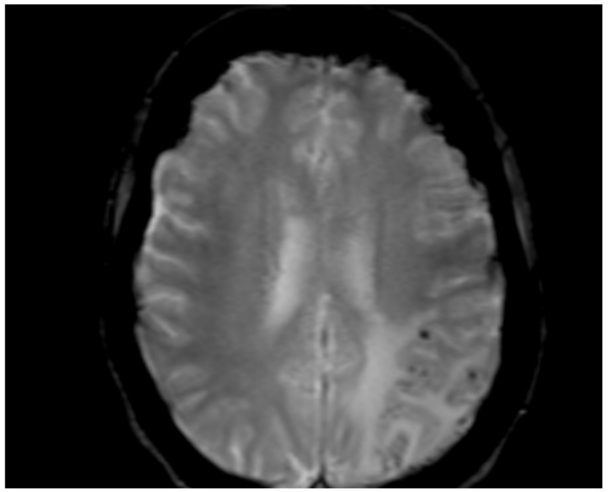
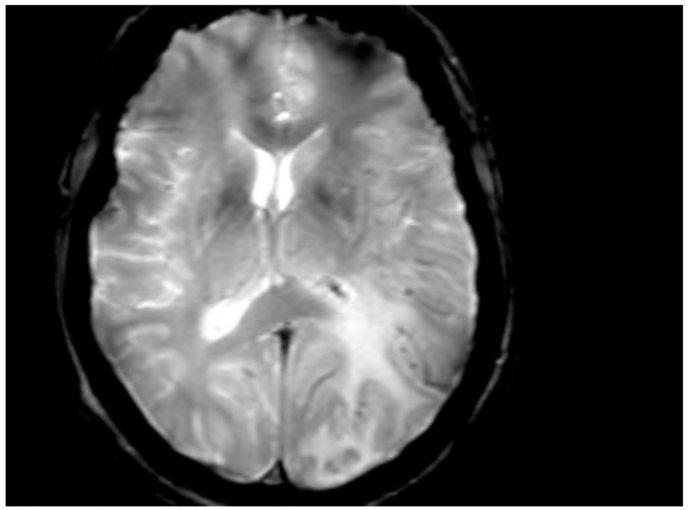
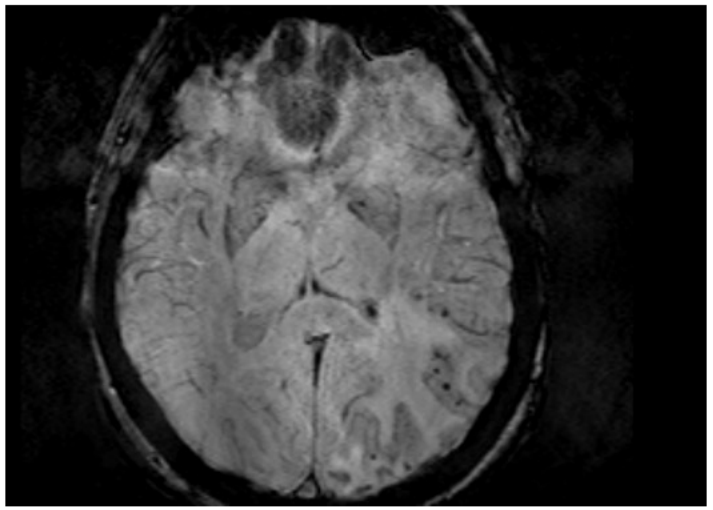
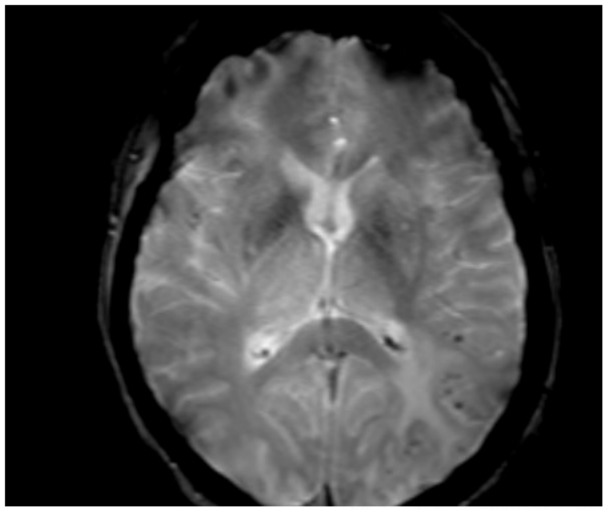
ARIA Imaging Protocols

	Minimum	Recommended	Notes
Field strength	1.5 T	3 T	Use of a consistent field of strength for serial imaging of a given patient is important. Imaging may be performed at 1.5 T if a patient is not a candidate for imaging at 3T or 3T scanners are not available at a site.
ARIA-E detection	2D FLAIR	2D or 3D FLAIR	Either 2D or 3D is acceptable, whichever can be performed with consistent quality and optimal CSF suppression.
ARIA-H detection	T2* GRE	T2* GRE (± SWI)	Recommendations for enrollment and dose suspension are based on T2* GRE detection of blood products. SWI may also be performed for confirmation and may be of value to gather data going forward.
	High quality GRE 3 T TE = 15-20 ms		
Infarct assessment	DWI	DWI	DWI required to differentiate ARIA from acute/subacute infarct and identification of incidental infarcts.

3D, 3 dimensional; ARIA-E, amyloid-related imaging abnormalities-edema; ARIA-H, amyloid-related imaging abnormalities-hemorrhage; CSF, cerebrospinal fluid; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated-inversion recovery; GRE, gradient echo; TE, echo time.

Cogswell PM et al. *AJNR Am J Neuroradiol*. 2022;43(9):E19-E35.

ARIA Imaging Protocols

GRE postdosing	SWI postdosing +1 mo	GRE postdosing +2 mo
		
		

ARIA, amyloid-related imaging abnormalities.

ARIA Imaging Protocols

AD Therapy Enrollment

- Exam: MRI brain dementia without IV contrast
- Indication: AD therapy enrollment

AD Therapy Monitoring

- Exam: MRI brain dementia without IV contrast
- Indication: AD therapy monitoring, week X

AD, Alzheimer disease; ARIA, amyloid-related imaging abnormalities; IV, intravenous; MRI, magnetic resonance imaging.
Cogswell PM et al. *AJNR Am J Neuroradiol*. 2022;43(9):E19-E35. Published 2025 Jan 8.

Baseline and Follow-Up MRI Scans

Donanemab

- MRI prior to therapy — T1 — W4
- MRI prior to 2nd infusion — T2 — W8
- MRI prior to 3rd infusion — T3 — W12
- MRI prior to 4th infusion — T4 — W16
- MRI prior to 7th infusion — T7 — W28

Lecanemab

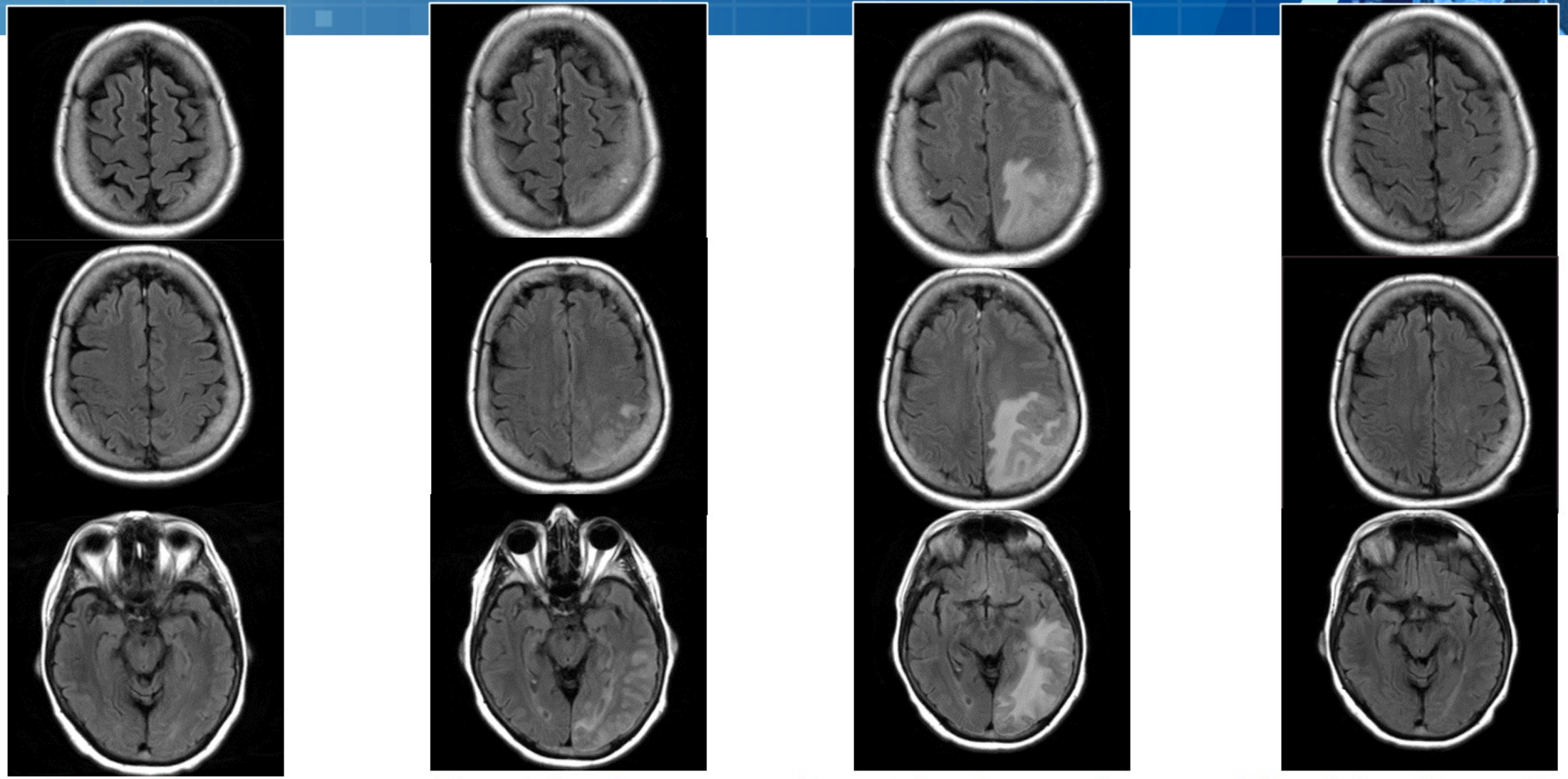
- T1 — W2 — MRI within 1 year prior to initiation
- T2 — W4
- T3 — W6
- T4 — W8
- T5 — W10 — MRI prior to 5th infusion
- T6 — W12
- T7 — W14 — MRI prior to 7th infusion
- T8 — W16
- T14 — W28 — MRI prior to 14th infusion
- T26 — W52 — MRI for selected patients

Perform MRI if any symptoms suggestive of ARIA occur

ARIA, amyloid-related imaging abnormalities; MRI, magnetic resonance imaging.

Lecanemab. Prescribing information. Eisai Inc.; 2025. Donanemab. Prescribing information. Eli Lilly and Company; 2024. Cummings J et al. *J Prev Alzheimers Dis*. 2023;10(3):362-377.

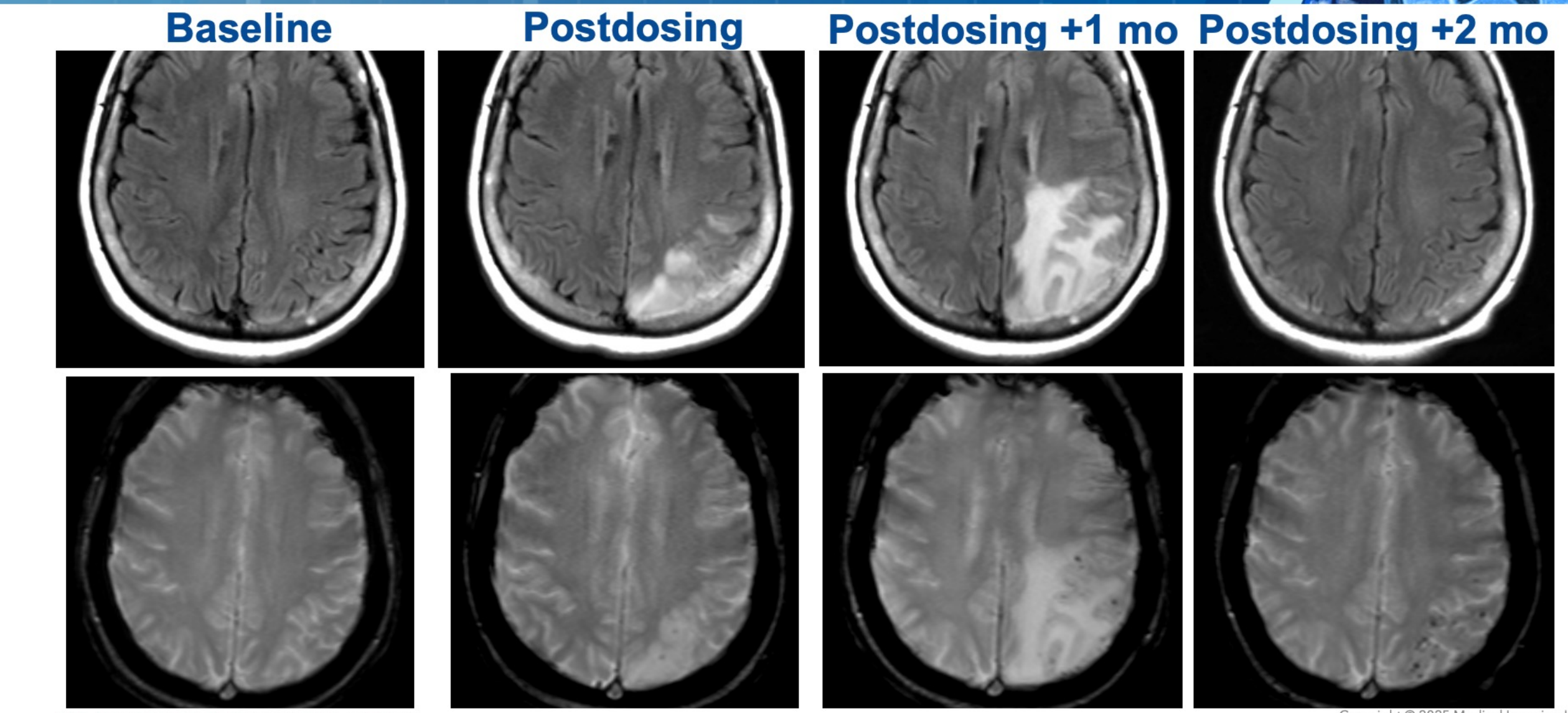
Severe ARIA-E
> 10 cm



Baseline | Postdosing | Postdosing +1 mo | Postdosing +2 mo

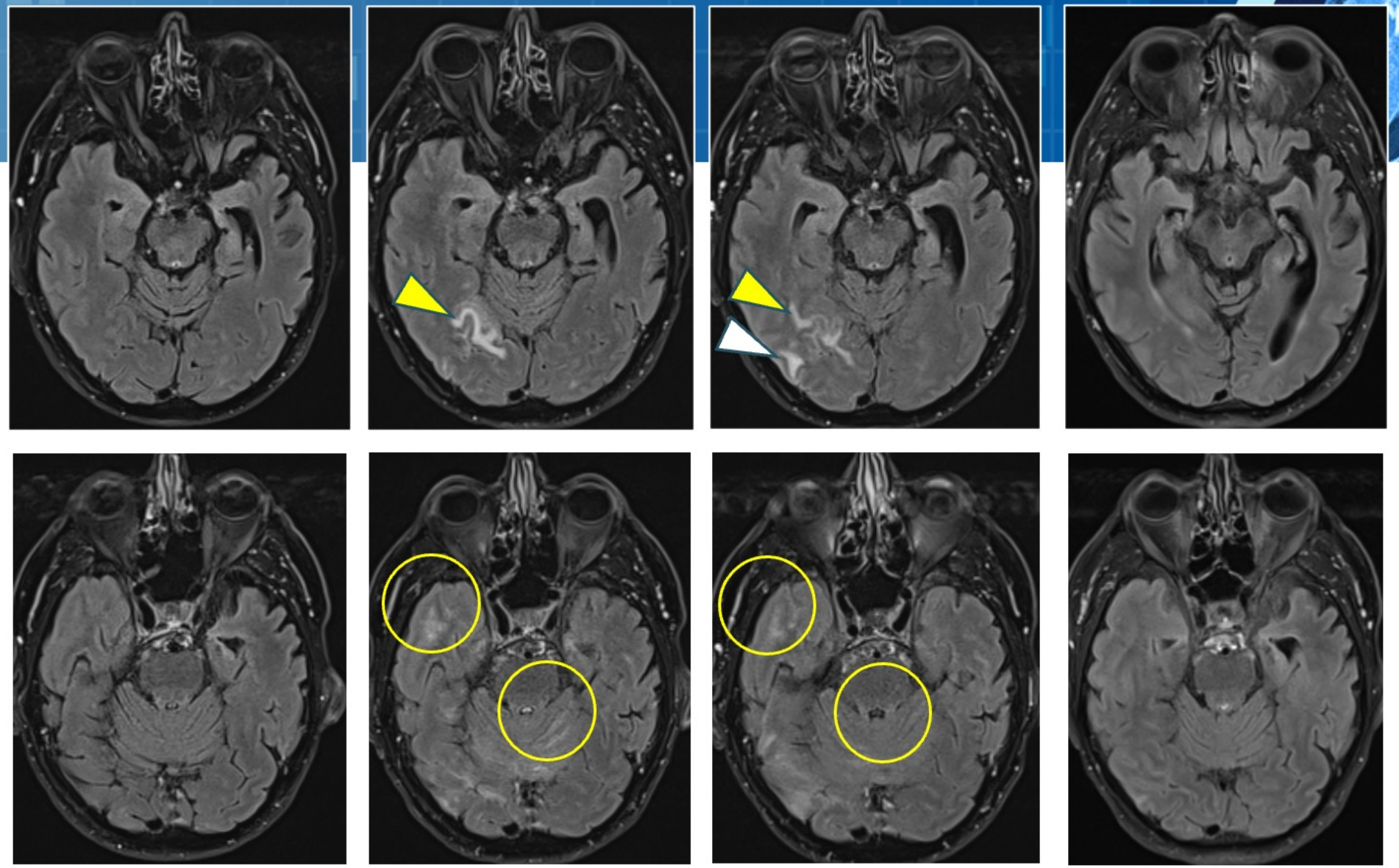
ARIA-E, amyloid-related imaging abnormalities-edema.

Severe ARIA-H
> 10 mH



ARIA-H, amyloid-related imaging abnormalities-hemorrhage.

ARIA-E



September 2023
Baseline MRI

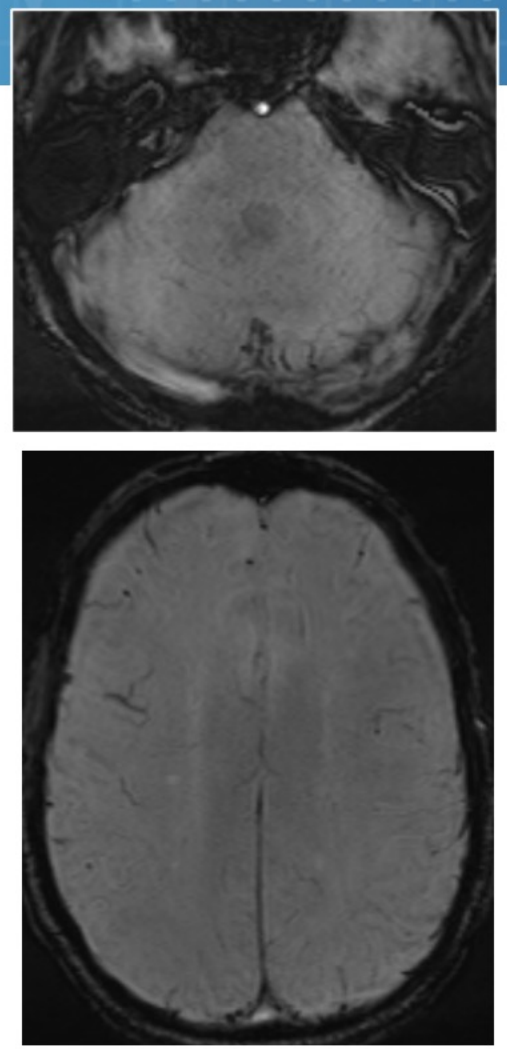
January 2024
Postdosing
Moderate ARIA-E
2 locations < 10 cm

February 2024
New subcortical signal abnormality (white arrowhead)

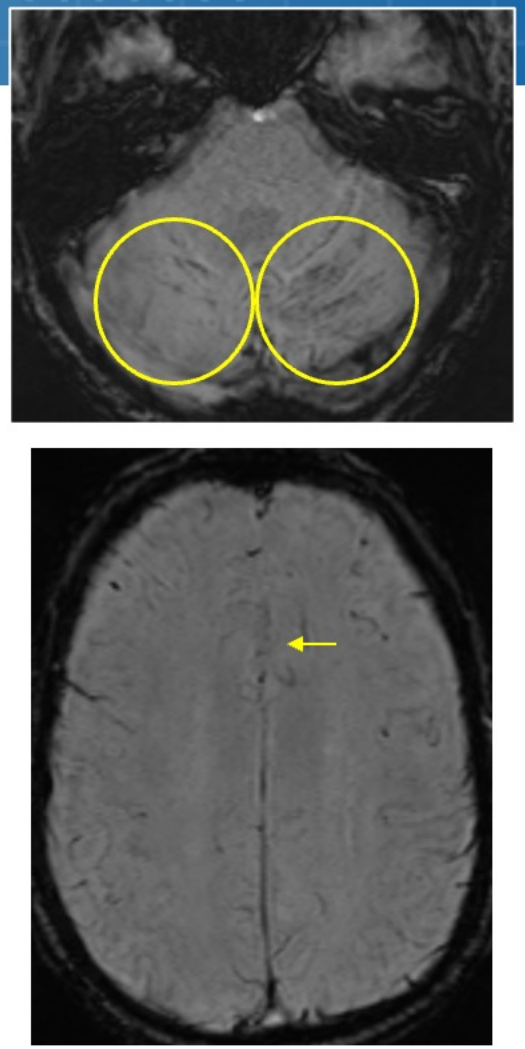
March 2024
Resolution of findings

ARIA-E, amyloid-related imaging abnormalities-edema.

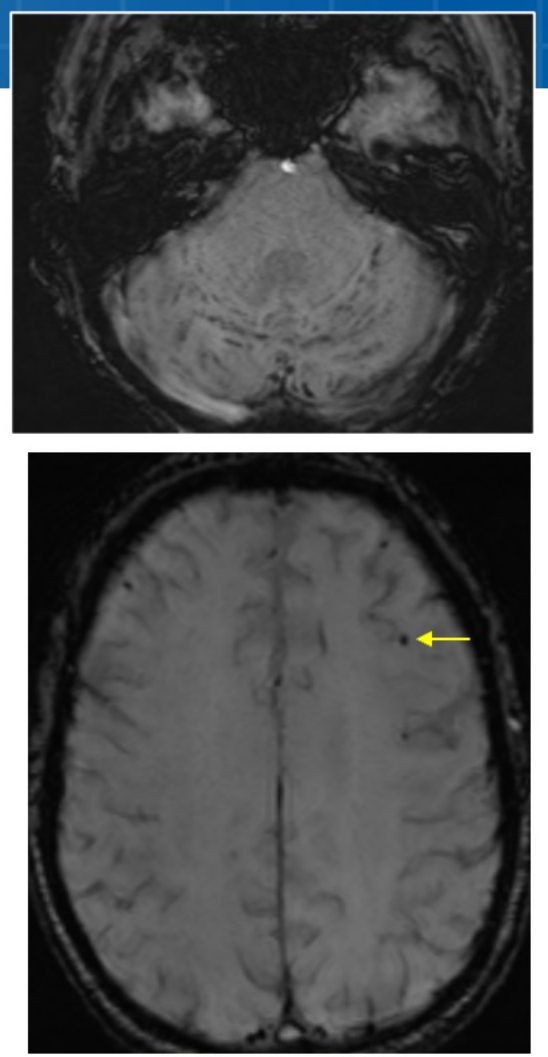
ARIA-H



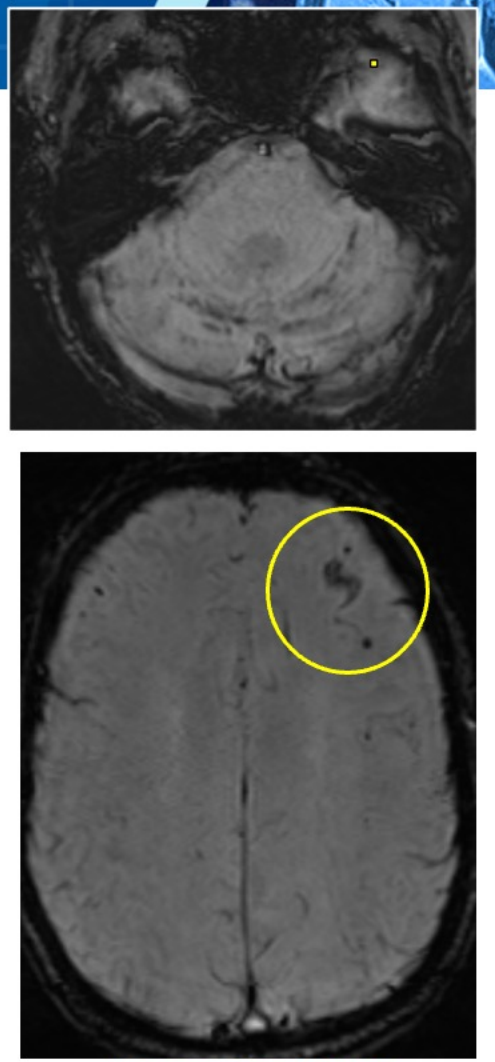
September 2023 Baseline MRI



January 2024 Postdosing Superficial siderosis and 1 microbleed



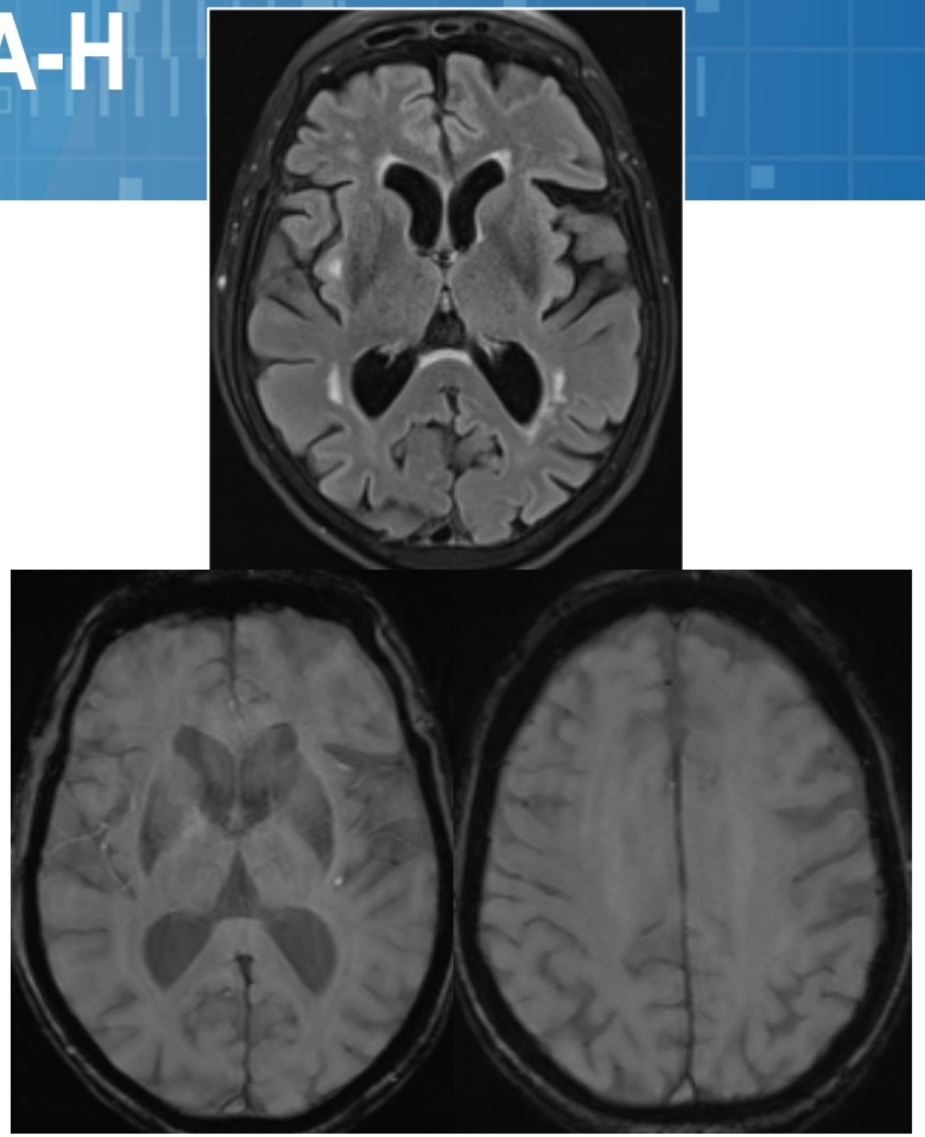
February 2024 Unchanged



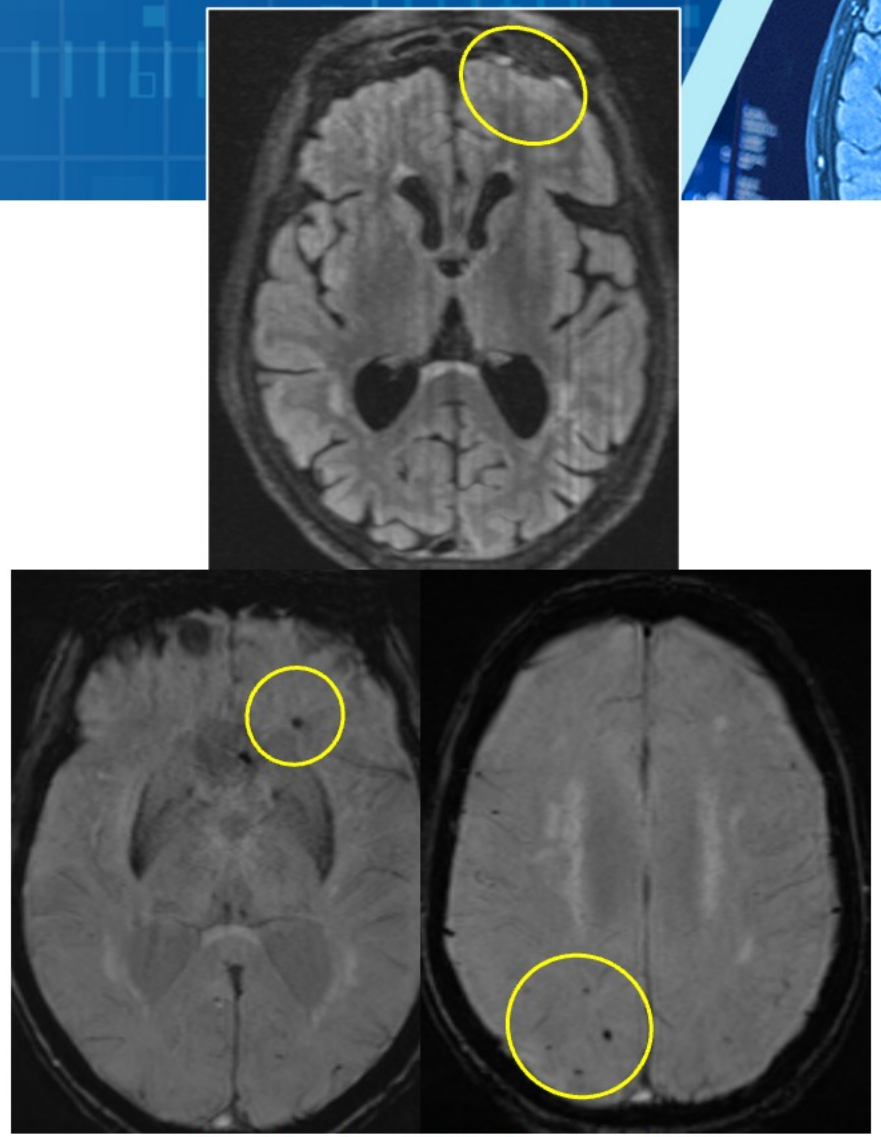
November 2024 New superficial siderosis

ARIA-H, amyloid-related imaging abnormalities-hemorrhage.

ARIA-H



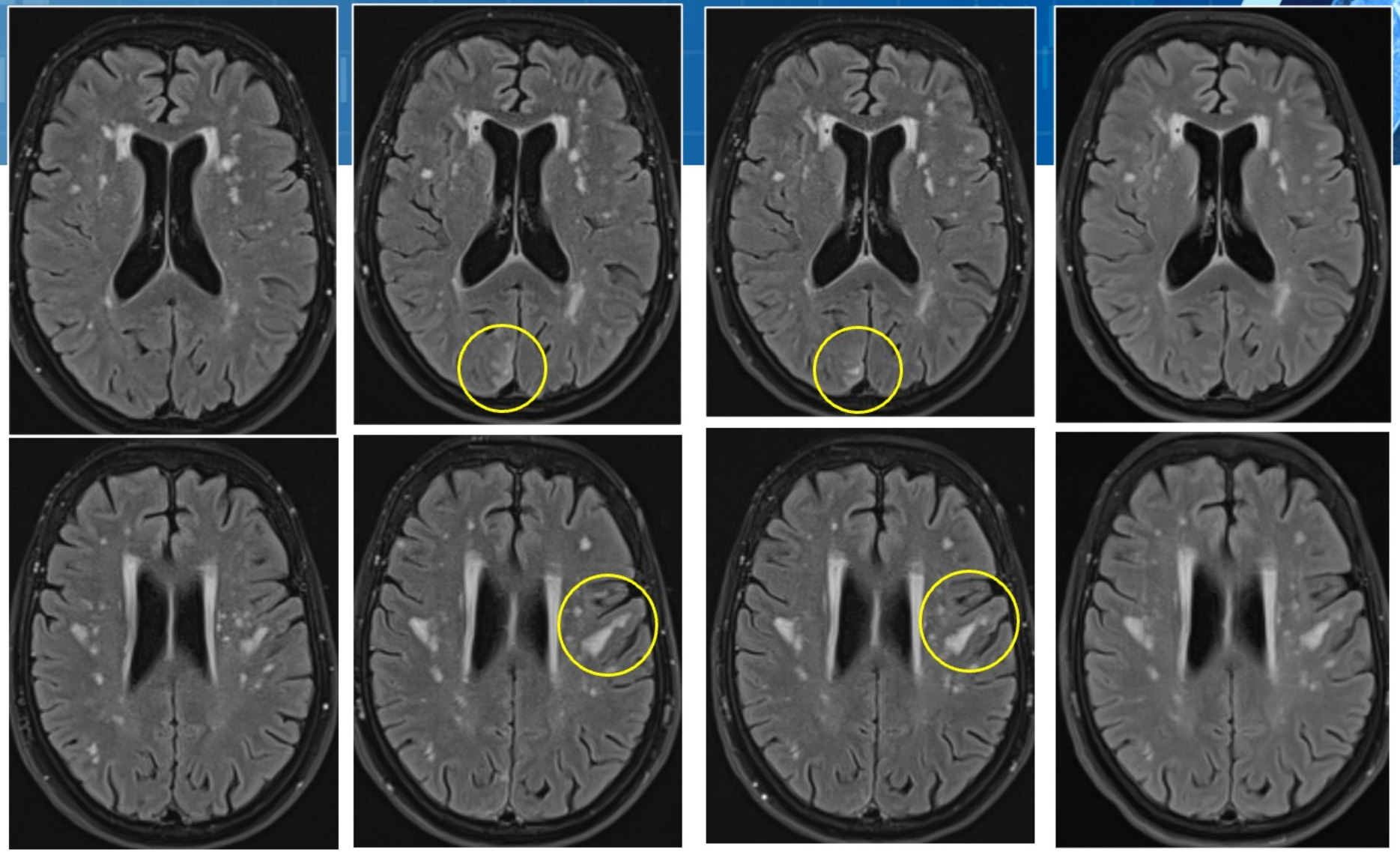
Baseline MRI, August 2024



Postdosing MRI, January 2025
Recent head trauma, small left frontal subdural hematoma,
5 new microbleeds, moderate ARIA-H?
Dosing suspended with plans for short-interval follow-up

ARIA-H, amyloid-related imaging abnormalities-hemorrhage; MRI, magnetic resonance imaging.

ARIA-E



September 2023 Baseline MRI

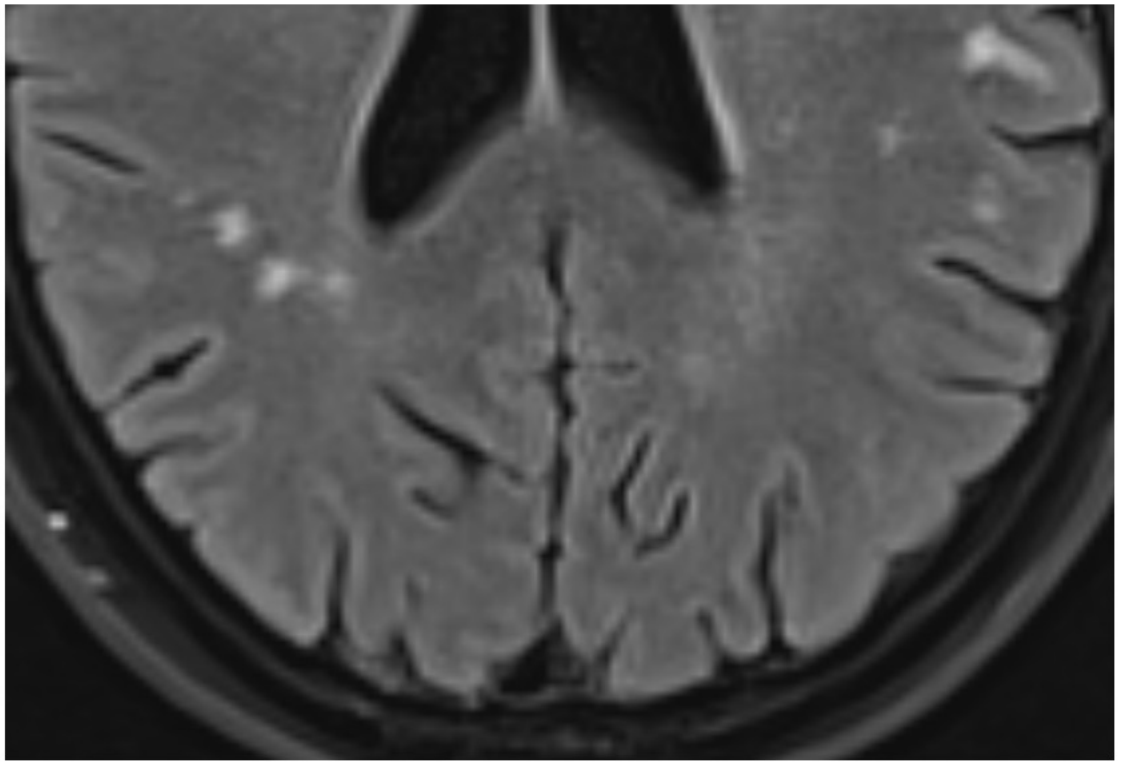
May 2024 Postdosing Moderate ARIA-E 2 locations < 10 cm

June 2024 Decreased conspicuity

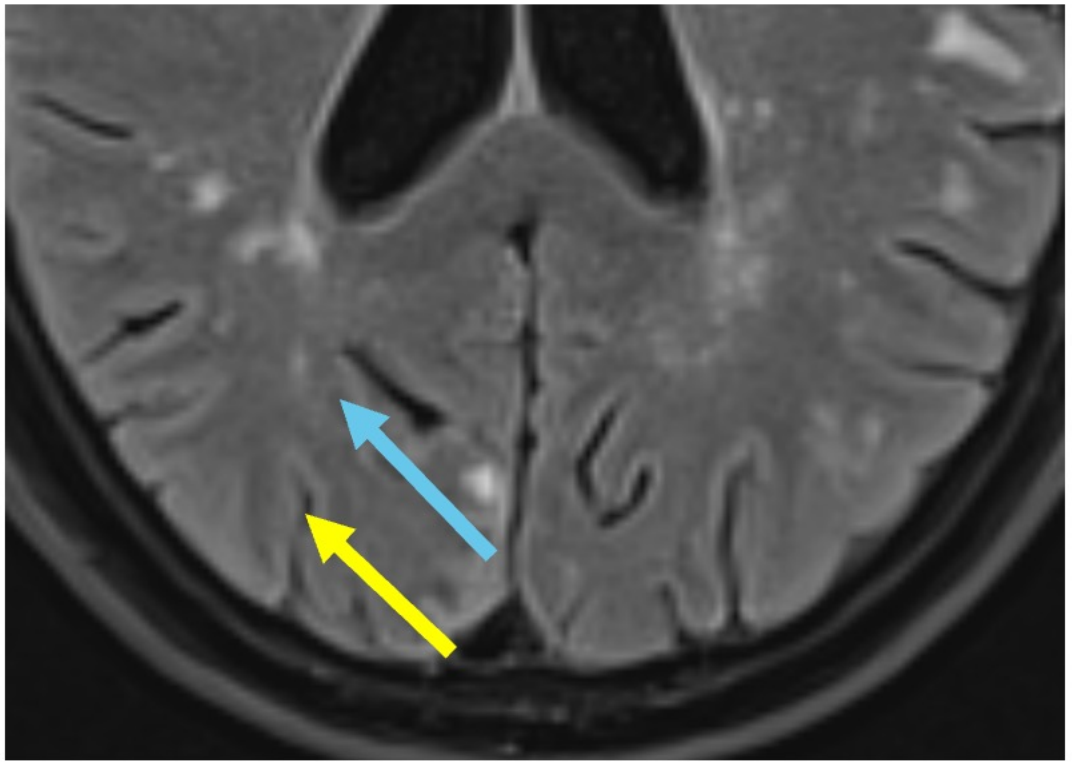
August 2024 Resolution of findings

ARIA-E, amyloid-related imaging abnormalities-edema.

Baseline

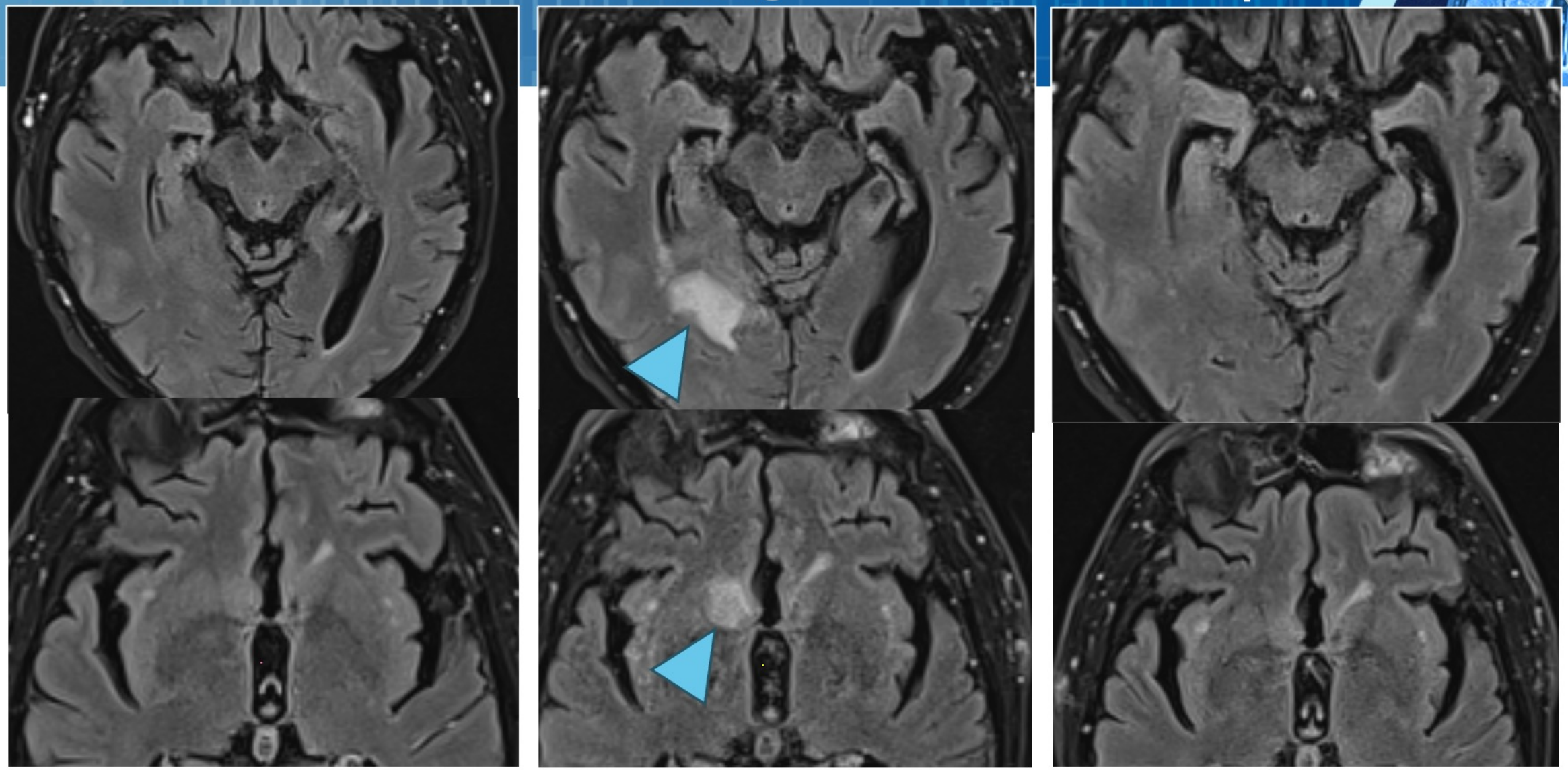


Postdosing



ARIA-E: Sulcal FLAIR hyperintensity (yellow arrow), subcortical hyperintensity (blue arrow)

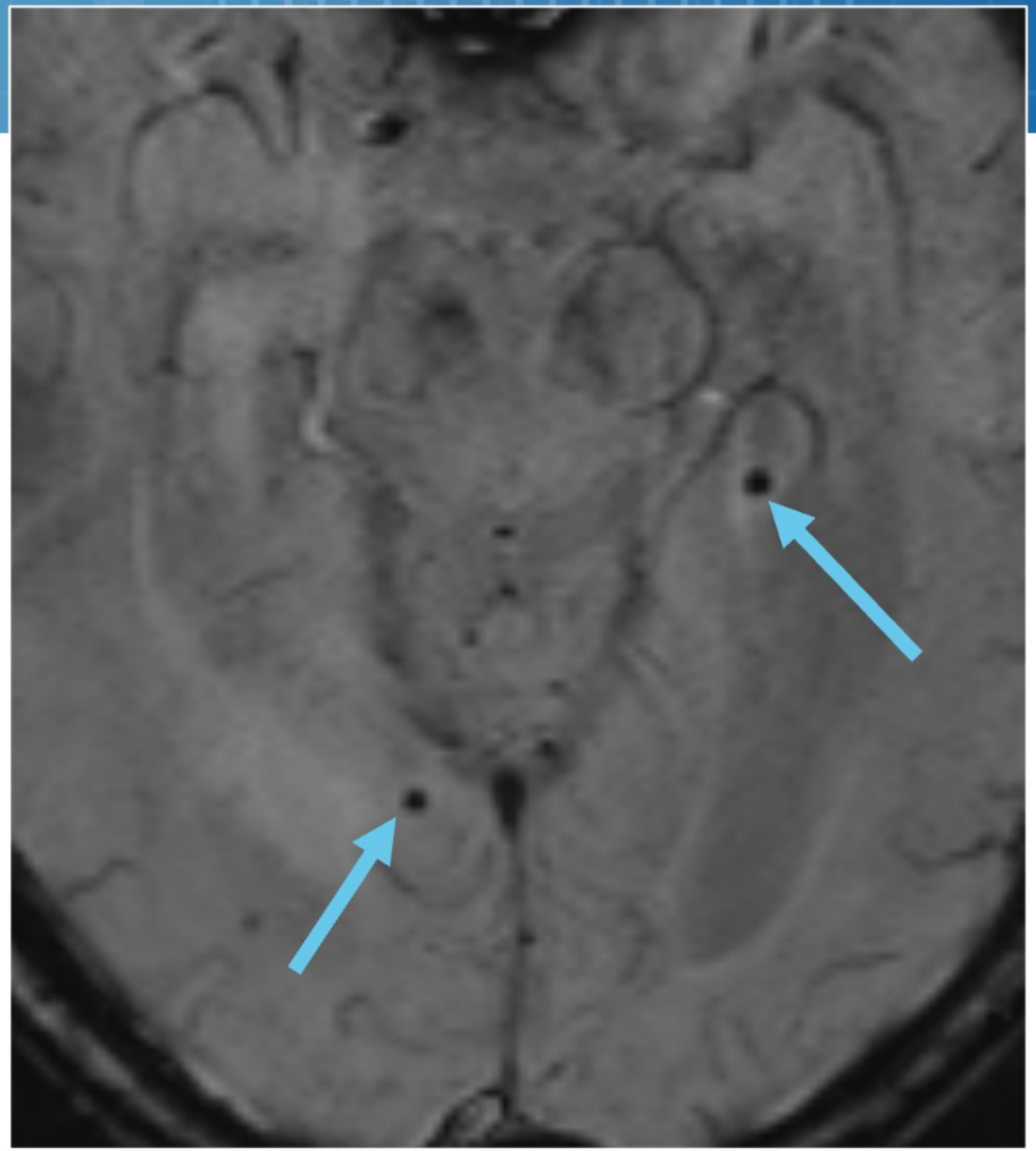
ARIA-E, amyloid-related imaging abnormalities-edema; FLAIR, fluid-attenuated-inversion recovery.



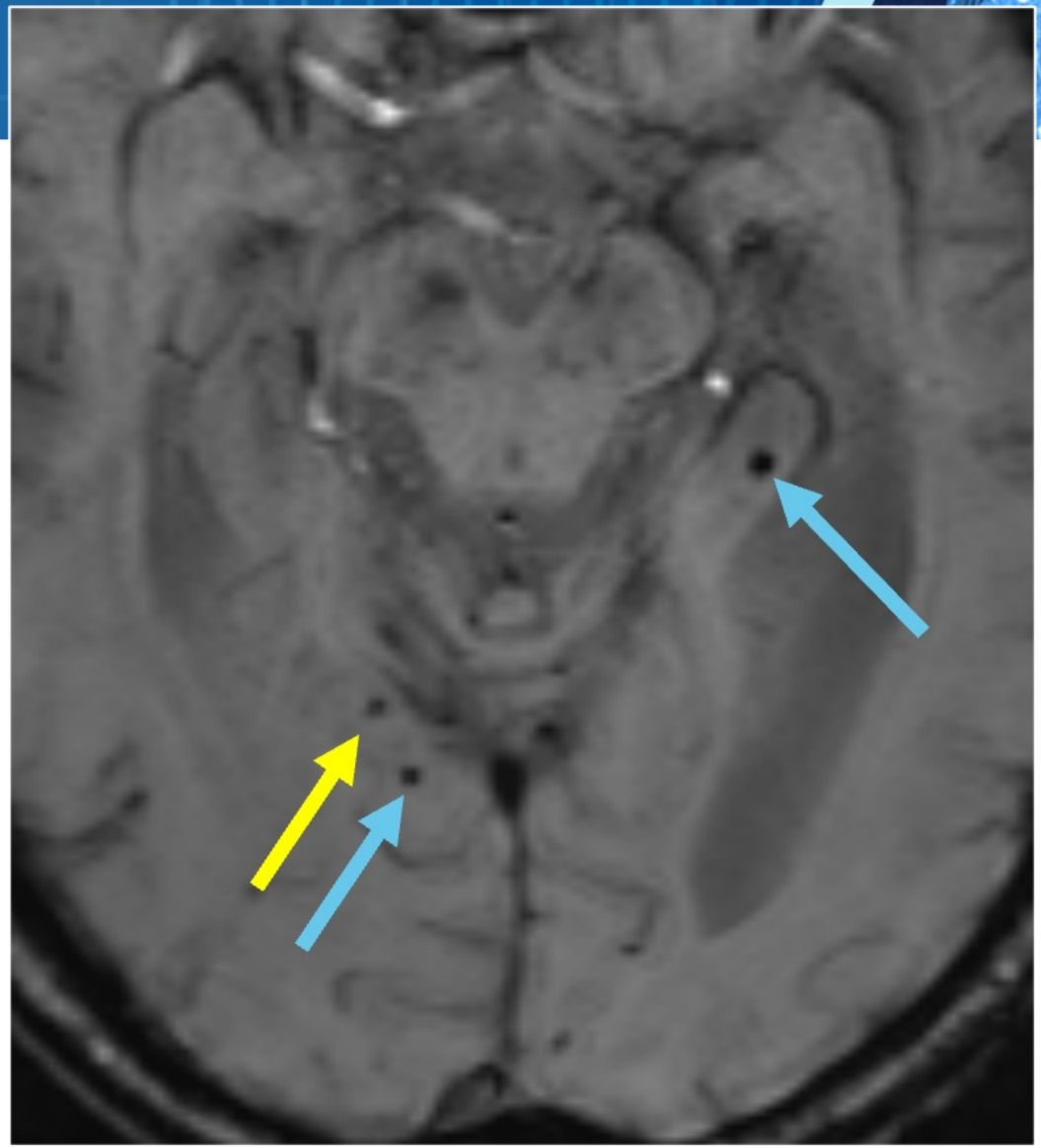
Moderate ARIA-E: At least 2 locations (< 10 cm)

ARIA-E, amyloid-related imaging abnormalities-edema.

Baseline



Postdosing

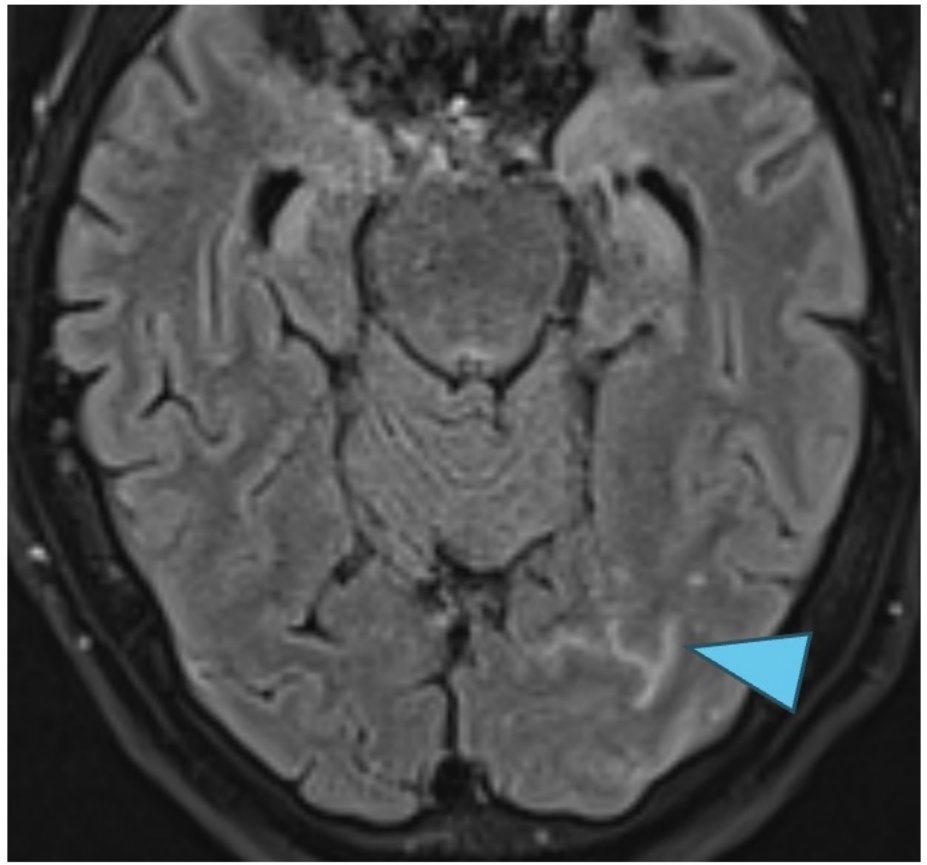


Mild ARIA-H: New microbleed (yellow arrow)

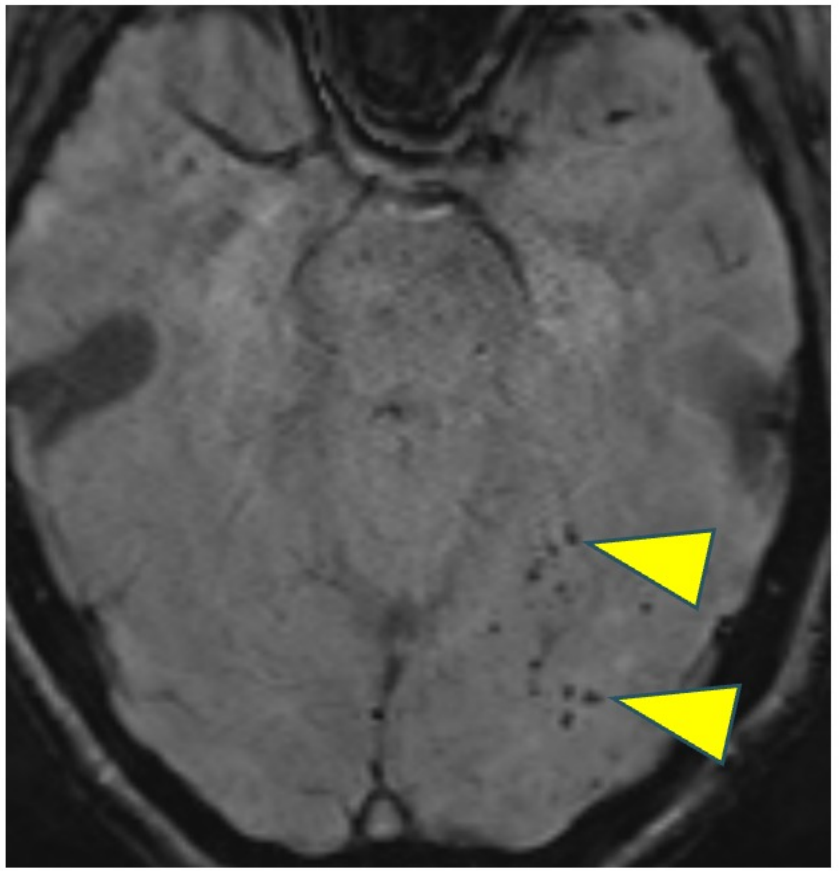
ARIA-H, amyloid-related imaging abnormalities-hemorrhage.

ARIA MIMICS:

65-Year-Old Female With Rapid Memory Decline. Is This ARIA?



Sulcal hyperintensity



> 10 Microhemorrhage

Patient is not on anti-amyloid drugs, working diagnosis of CAA

ARIA, amyloid-related imaging abnormalities; CAA, cerebral amyloid angiopathy.

Part 3:

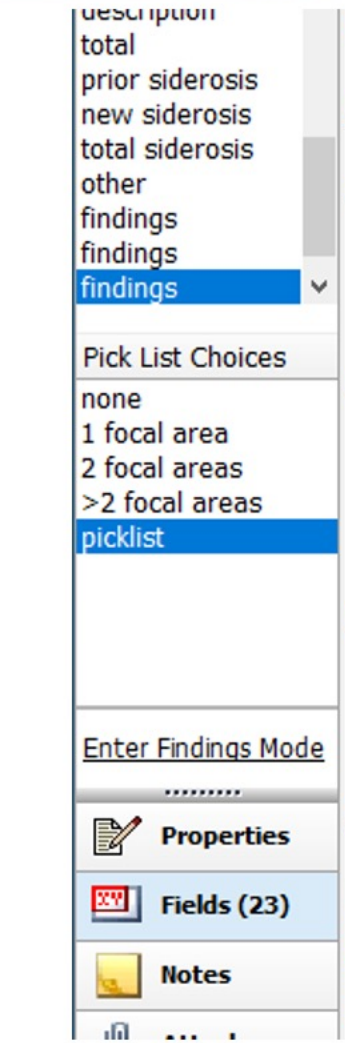
Interdisciplinary Communication for Effective ARIA Management

Interdisciplinary Discussions

- Establish clear communication channels
- Align imaging review with clinical context
- Foster timely decision-making on treatment adjustments
- Streamline interdisciplinary collaboration
- Standardize follow-up and documentation

Cogswell PM et al. *AJNR Am J Neuroradiol*. 2022;43(9):E19-E35. Published 2025 Jan 8.

Standardized Terminology and Structured Reporting Templates for ARIA



FINDINGS:

ASSESSMENT FOR ARIA:

ARIA-E
- Prior FLAIR hyperintensities concerning for ARIA-E: [describe location(s) and size][describe change]
- New/incident FLAIR hyperintensities concerning for ARIA-E: [describe location(s) and size]
- Total current regions of FLAIR hyperintensities concerning for ARIA-E: [picklist]

ARIA-H, Microhemorrhages
- Microhemorrhages at pre-treatment baseline: [number of microhemorrhages at pre-treatment baseline][describe locations]
- Prior treatment emergent microhemorrhages: [number of microhemorrhages present on prior monitoring exam][describe locations]
- New microhemorrhages: [number of new microhemorrhages since prior exam][describe locations]
- Total treatment emergent microhemorrhages = prior treatment emergent + new microhemorrhages: [picklist]

ARIA-H, superficial siderosis
- Prior treatment emergent siderosis: [number of prior focal areas of superficial siderosis]
- New siderosis: [number of new focal area of superficial siderosis]
- Total treatment emergent focal areas of superficial siderosis: [picklist]

ADDITIONAL FINDINGS: [...]

IMPRESSION:
1. Findings of [picklist] ARIA-E.
Findings of [picklist] ARIA-H related microhemorrhages.
Findings of [picklist] ARIA-H related siderosis.

Report templates available at: https://www.alznetproviders.org/Clinical-Care-Resources/Imaging-Resources

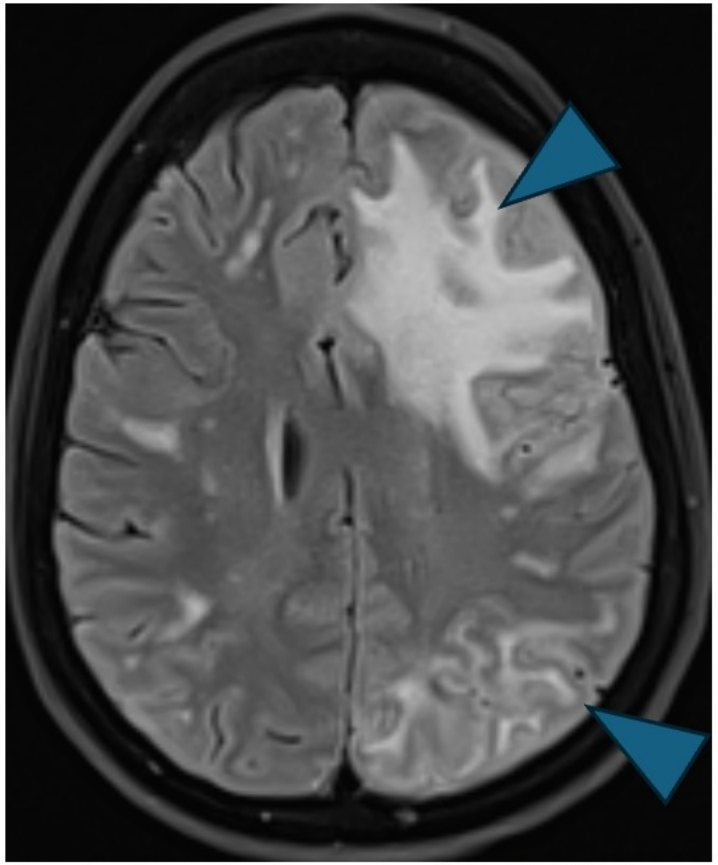
ARIA-E, amyloid-related imaging abnormalities-edema; ARIA-H, amyloid-related imaging abnormalities-hemorrhage; FLAIR, fluid-attenuated-inversion recovery.

Is This ARIA?

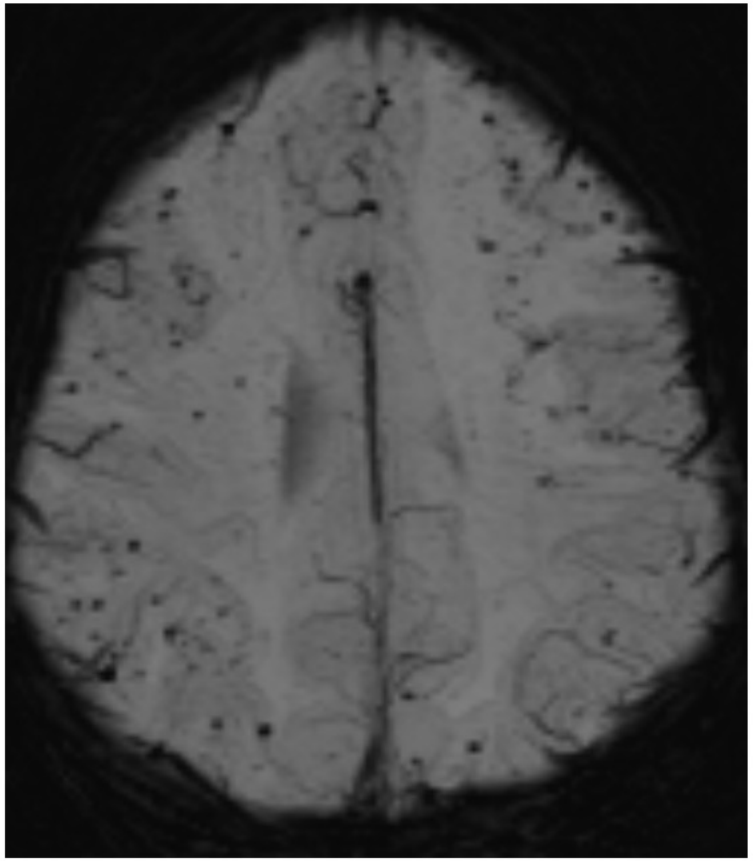
Did you get it correct?

Is This ARIA?

66-Year-old female with word-finding difficulty and headache



Cortical and subcortical T2 FLAIR hyperintense signal with local mass effect

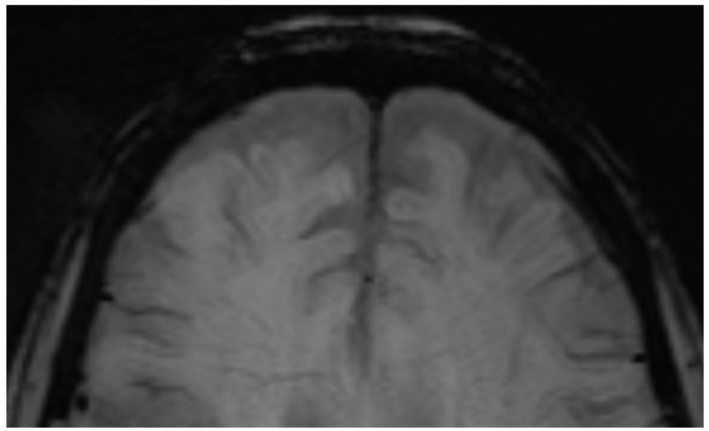


Innumerable cortical-subcortical microhemorrhages

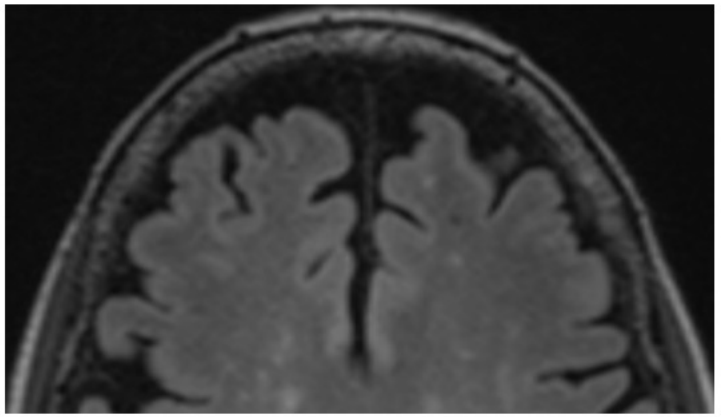
ARIA, amyloid-related imaging abnormalities; FLAIR, fluid-attenuated-inversion recovery.

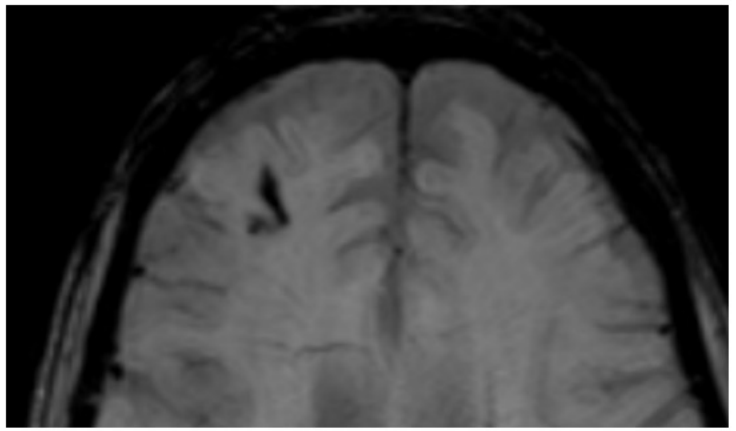
Is This ARIA?

78-Year-old female with memory loss on amyloid-targeting therapy

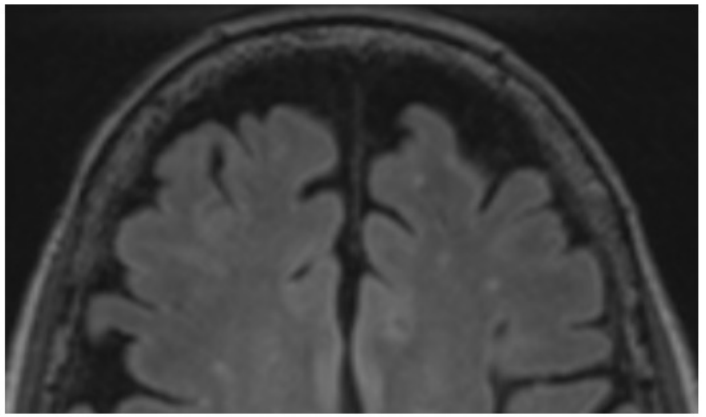


February 2024
Baseline MRI





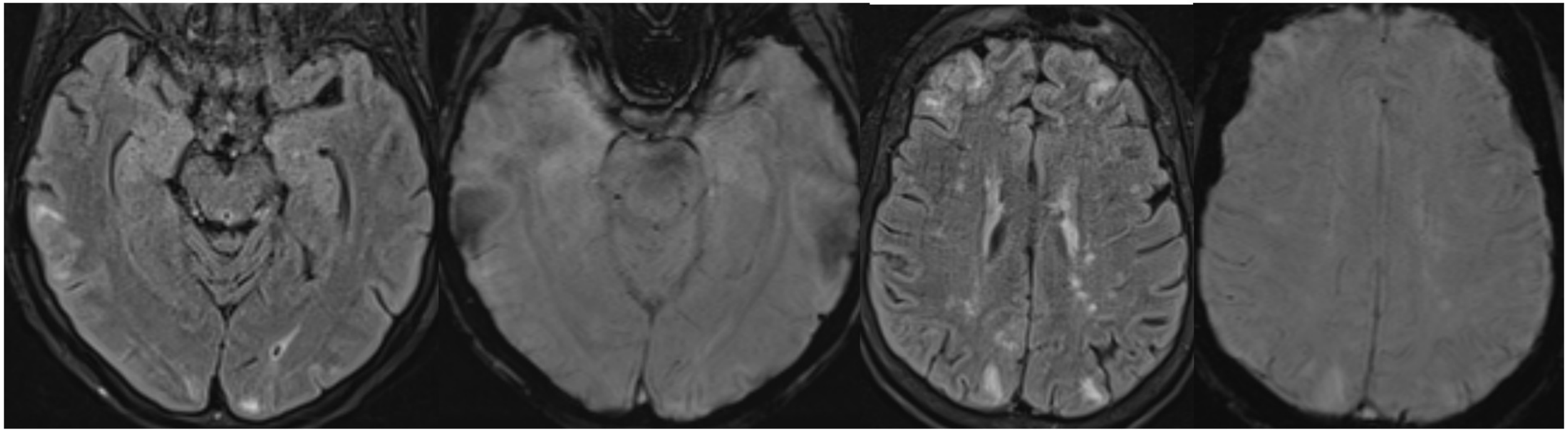
July 2024
Postdosing MRI



ARIA, amyloid-related imaging abnormalities; MRI, magnetic resonance imaging.

Is This ARIA?

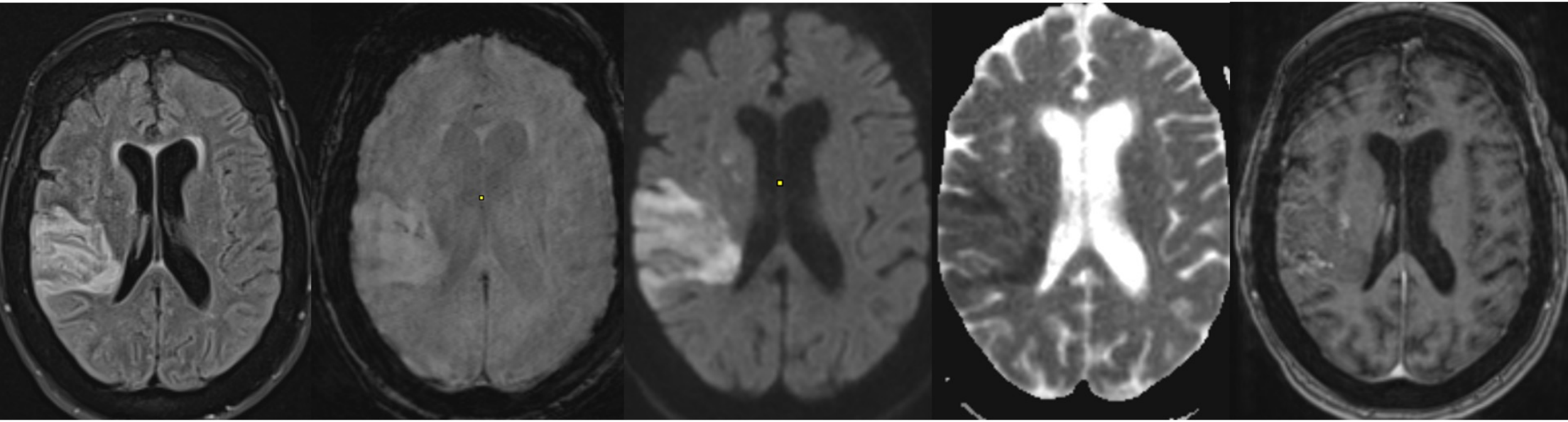
69-Year-old female with uncontrolled hypertension and new onset of seizures



ARIA, amyloid-related imaging abnormalities.

Is This ARIA?

68-Year-old female with history of dementia and atrial fibrillation, presenting with left-sided weakness



ARIA, amyloid-related imaging abnormalities.

THANK YOU!

www.mlieducation.org

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This activity is supported by an educational grant from Eli Lily and Company.