Understanding Amyloid-Related Imaging Abnormalities (ARIA)

Comprehensive

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Contents

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

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Introducing Amyloid-Related Imaging Abnormalities (ARIA)

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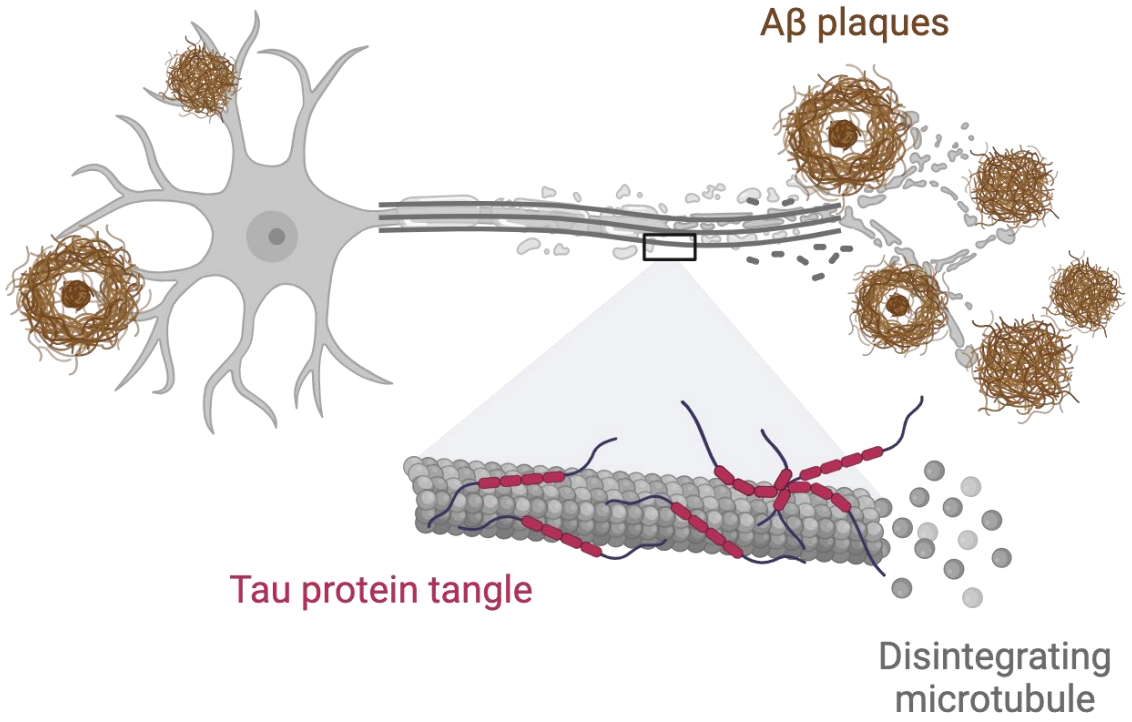
The 2 Pathological Hallmarks of AD Are Amyloid Plaques and Tau Neurofibrillary Tangles



- **Amyloid-β (Aβ) plaques accumulate at the earliest stage of disease and, along with tau neurofibrillary tangles, are a hallmark of AD[1,2]**
- In addition to plaques and tangles, inflammation, synaptic degeneration, and irreversible neuronal loss occur[1,2]
- Neurodegeneration and the levels of tau neurofibrillary tangles correlate with clinical symptoms[3,4]

Aβ, amyloid beta; AD, Alzheimer's disease.

1. Serrano-Pozo A, et al. Cold Spring Harb Perspect Med. 2011;1(1):a006189; 2. Jack CR, et al. Alzheimers Dement. 2024;20(8):5143–5169; 3. Horie K, et al. Brain 2021;144(2):515–527; 4. Bejanin A, et al. Brain. 2017 Dec 1;140(12):3286–3300.

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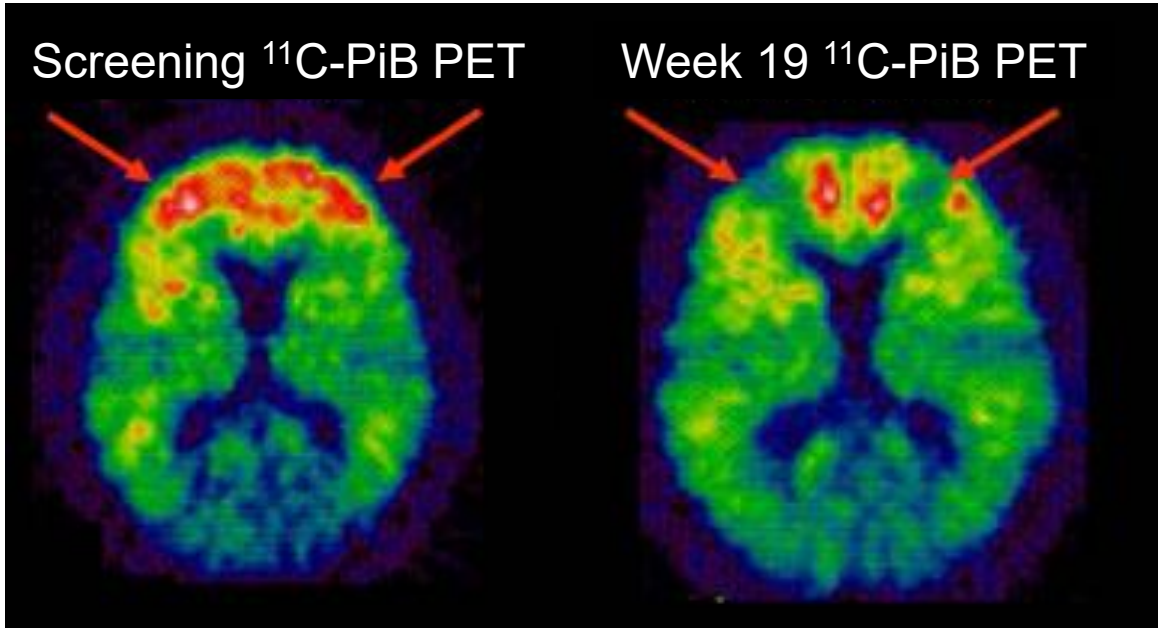
Currently Available Monoclonal Antibody Therapies for AD Target and Remove Amyloid

Following the administration of a monoclonal antibody that removes amyloid

Monoclonal Antibodies That Remove Amyloid

- Strategies to target and remove Aβ interfere with the underlying pathophysiologic mechanisms of the AD process, and have been shown to slow cognitive and functional decline in the early symptomatic stages of AD[1,2]



Baseline PiB retention consistent with high fibrillar burden[3]

Week 19 PiB uptake is reduced representing clearance of fibrillar amyloid from plaque and cerebral vessels[3]

Image used with permission from Sperling et al (2012)[3] (CC-BY 4.0: http://creativecommons.org/licenses/by/4.0/).

Aβ, amyloid beta; AD, Alzheimer's disease; PET, positron emission tomography; PiB, Pittsburgh compound B.

1. van Dyck CH, et al. N Engl J Med. 2023;388(1):9–21; 2. Sims JR, et al. JAMA. 2023;330(6):512–527; 3. Sperling R, et al. Lancet Neurol. 2012;11(3):241–249.

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ARIA Were First Reported in 2009 in Amyloid Modifying Therapeutic Trials

Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: Recommendations from the Alzheimer's Association Research Roundtable Workgroup

Reisa A. Sperling[a,b,*], Clifford R. Jack, Jr.,[c], Sandra E. Black[d], Matthew P. Frosch[e], Steven M. Greenberg[f], Bradley T. Hyman[g], Philip Scheltens[h], Maria C. Carrillo[i], William Thies[i], Martin M. Bednar[j], Ronald S. Black[k], H. Robert Brashear[l], Michael Grundman[m], Eric R. Siemers[n], Howard H. Feldman[o,p], Rachel J. Schindler[q]

- MRI signal changes, thought to represent **vasogenic edema and cerebral microhemorrhages**, were first reported in 2009 in clinical trials of monoclonal antibodies that remove amyloid[2,3]
- The Alzheimer's Association Research Roundtable convened a Workgroup in July 2010[1]
- The Workgroup suggested referring to this spectrum as "**amyloid-related imaging abnormalities (ARIA)"**[1]
- Despite the likelihood of shared underlying mechanisms, the Workgroup further refined the terminology:
  - **ARIA-edema/effusion (ARIA-E)**
  - **ARIA-hemosiderin/hemorrhage (ARIA-H)**

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; MRI, magnetic resonance imaging.

Image: Sperling RA, et al. Alzheimers Dement. 2011;7(4):367–385[1]

1. Sperling RA, et al. Alzheimers Dement. 2011;7(4):367–385; 2. Filippi M, et al. JAMA Neurol. 2022;79(3):291–304; 3. Black RS, et al. Alzheimer Dis Assoc Disord. 2010;24(2):198–203.

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What Are Amyloid-Related Imaging Abnormalities (ARIA)?

- **ARIA** are a consequence of the presence of amyloid in blood vessel walls (CAA)[1,2]
- They are thought to be related to the **increased permeability of blood vessels** to fluid or blood products[1,2]
- ARIA can occur **spontaneously or as a result of the mobilization of amyloid by monoclonal antibodies that remove amyloid**[1,2a]

- There is an increased risk of ARIA with the use of monoclonal antibodies that remove amyloid[1]
- MRI monitoring is an essential part of the therapeutic regimen[4]

[a] The FDA and the Alzheimer's Association Research Roundtable Workgroup defining publication recognizes that ARIA can occur spontaneously as part of the natural history of AD or CAA in the absence of monoclonal antibodies that remove amyloid.[1,5] Cogswell et al.[4] define ARIA as occurring only in the setting of monoclonal antibodies that remove amyloid.

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

1. Sperling RA, et al. Alzheimers Dement. 2011;7(4):367–385; 2. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35; 3. Filippi M, et al. JAMA Neurol. 2022;79(3):291–304; 4. Cogswell PM, et al. AJNR Am J Neuroradiol. 2025;46(1):24–32; 5. US Food and Drug Administration. Eisai Inc. Briefing Document. Published Jun 9, 2023. https://www.fda.gov/media/169264/download (Accessed August 2025)

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Introducing Cerebral Amyloid Angiopathy (CAA)

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What is Cerebral Amyloid Angiopathy (CAA)?

What is CAA?

- An age-related cerebrovascular disorder characterized by the **accumulation of Aβ within the leptomeninges and within small- and medium-sized cerebral blood vessels** with or without symptoms[1]

Estimated prevalence

- CAA occurs **sporadically** in cognitively normal elderly individuals (prevalence: ~30%)
- CAA is present in nearly all cases of AD at the neuropathological level[2]

Presentation

- Aβ deposition makes vessels fragile, which can cause:
  - **Microhemorrhages or superficial siderosis**
  - **Lobar intracerebral hemorrhage**
- May also cause **non-hemorrhagic lesions,** such as CAA-related white matter changes[1,4]

Aβ, amyloid beta; AD, Alzheimer's disease; CAA, cerebral amyloid angiopathy; MRI, magnetic resonance imaging

1. Kuhn J, Sharman T. Cerebral amyloid angiopathy. 2022 Jun 6. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan; 2. Thomas DX, et al, Sci Rep. 2020;10(1):14579; 3. Kozberg MG, et al. Int J Stroke. 2021;16:356–369; 4. Greenberg SM, et al. Nat Rev Neurol. 2020;16:30–42

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CAA Can Result in Hemorrhagic and Non-Hemorrhagic Lesions

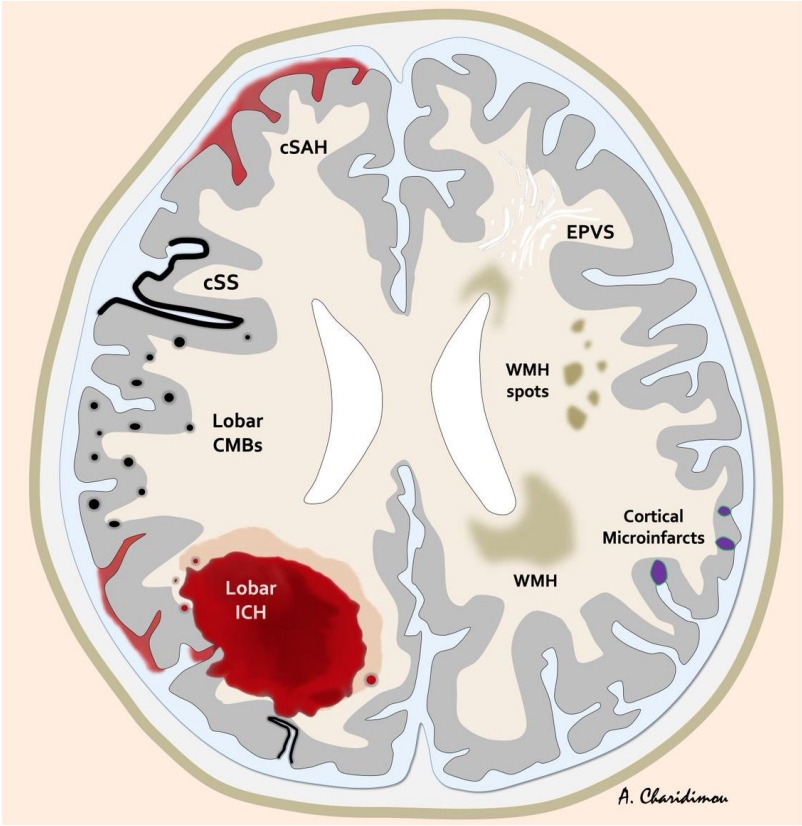
Aβ deposition makes vessels fragile, which can cause hemorrhagic and non-hemorrhagic lesions that can be detected using MRI

Hemorrhagic Lesions

- Microhemorrhages (cerebral microbleeds)
- Superficial siderosis
- Lobar intracerebral hemorrhage
- Convexal subarachnoid hemorrhage

Non-Hemorrhagic Lesions

- White matter hyperintensities
- Enlarged perivascular spaces
- Cortical microinfarcts



Case courtesy of Rohit Sharma, Radiopaedia.org, rID: 97818 (illustration created by Andreas Charidimou).

Aβ, amyloid beta; CAA, cerebral amyloid angiopathy; CMB, cerebral microbleed; cSAH, convexity subarachnoid hemorrhage; cSS, cortical superficial siderosis; EPVS, enlarged perivascular spaces; ICH, intracerebral hemorrhage; MRI, magnetic resonance imaging; WMH, white matter hyperintensities.

Charidimou A, et al. Lancet Neurol. 2022;21(8):714–725.

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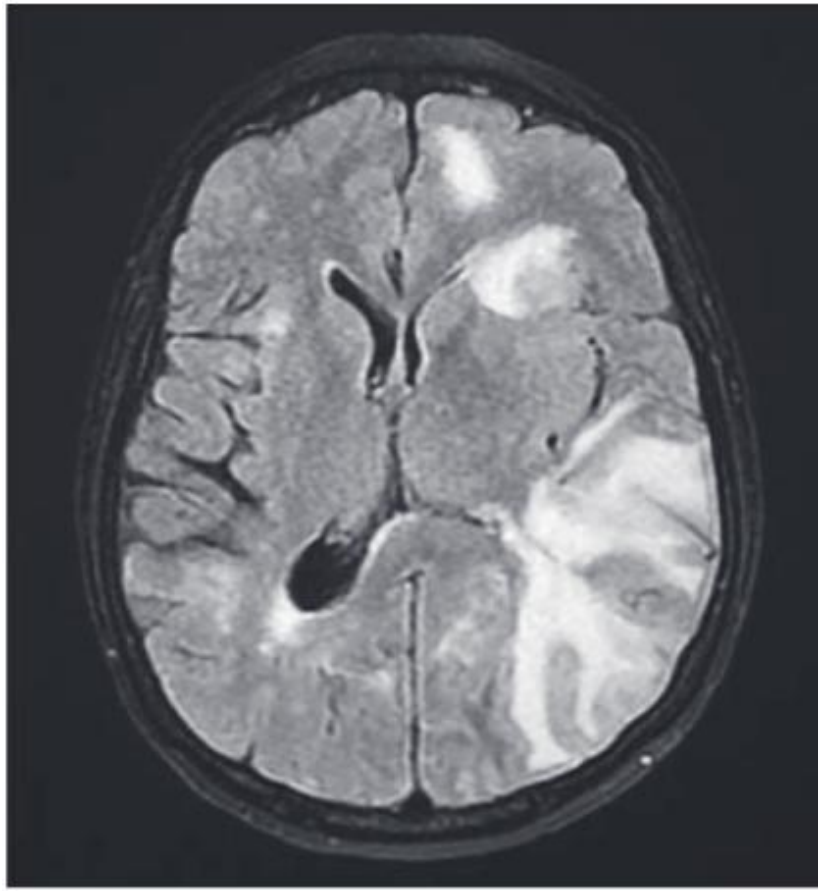
Inflammatory CAA Is a Rare Complication of CAA

- **Inflammatory CAA** is thought to be driven by a **spontaneous autoimmune response** to the deposited Aβ in the vasculature[1–3]
- It is a potentially **reversible condition** responsive to immunosuppressive therapies[1,4]
- There are 2 subtypes of inflammatory CAA, with shared clinical and radiographical presentation, but with characteristic neuropathology:
  - **Cerebral amyloid angiopathy-related inflammation (CAA-ri)**
  - **Amyloid beta-related angiitis (ABRA)**



CAA-ri observed as white matter hyperintensities on FLAIR MRI[5]

Aβ, amyloid beta; ABRA, amyloid beta-related angiitis; CAA, cerebral amyloid angiopathy; CAA-ri, cerebral amyloid angiopathy-related inflammation; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

1. Chwalisz BK. J Neurol Sci. 2021;424:117425; 2. Wu JJ, et al. Chin Med J (Engl). 2021;134(6):646–654; 3. Sperling RA, et al. Alzheimers Dement. 2011;7(4):367–385; 4. Antolini L, et al. Neurology 2021;97(18):e1809–e1822; 5. Roytman M, et al. AJR Am J Roentgenol. 2023;220(4):562–574.

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Subtypes of ARIA

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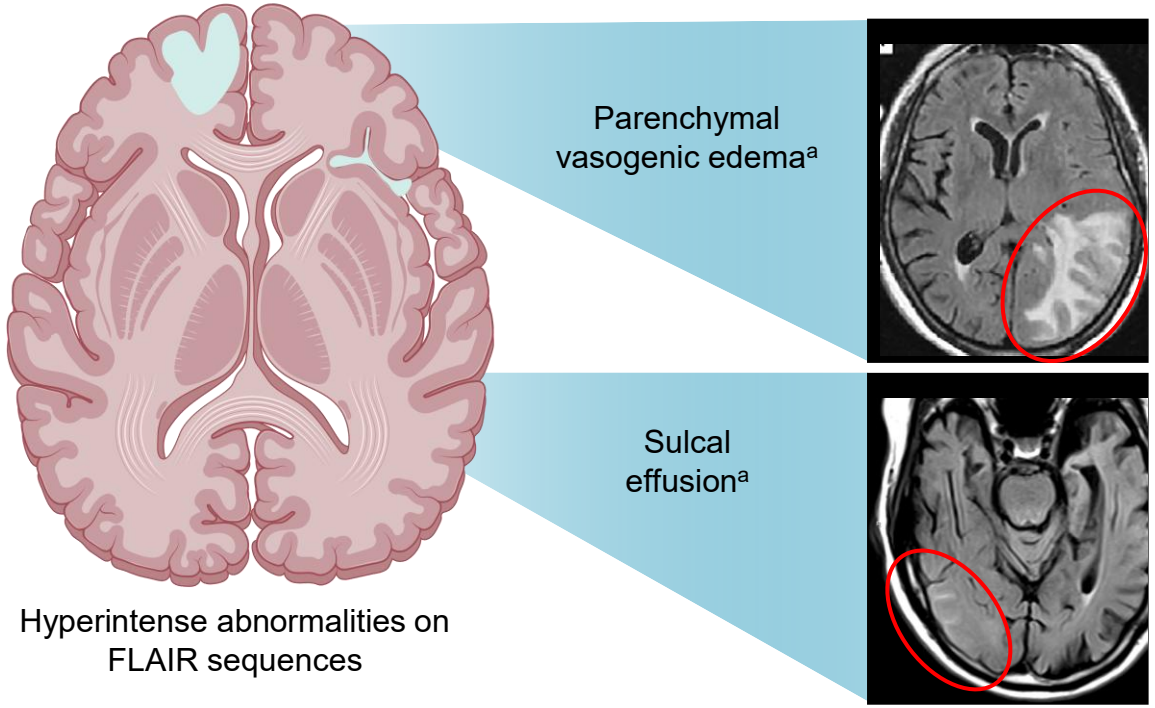
There Are 2 Subtypes of ARIA: ARIA-E and ARIA-H

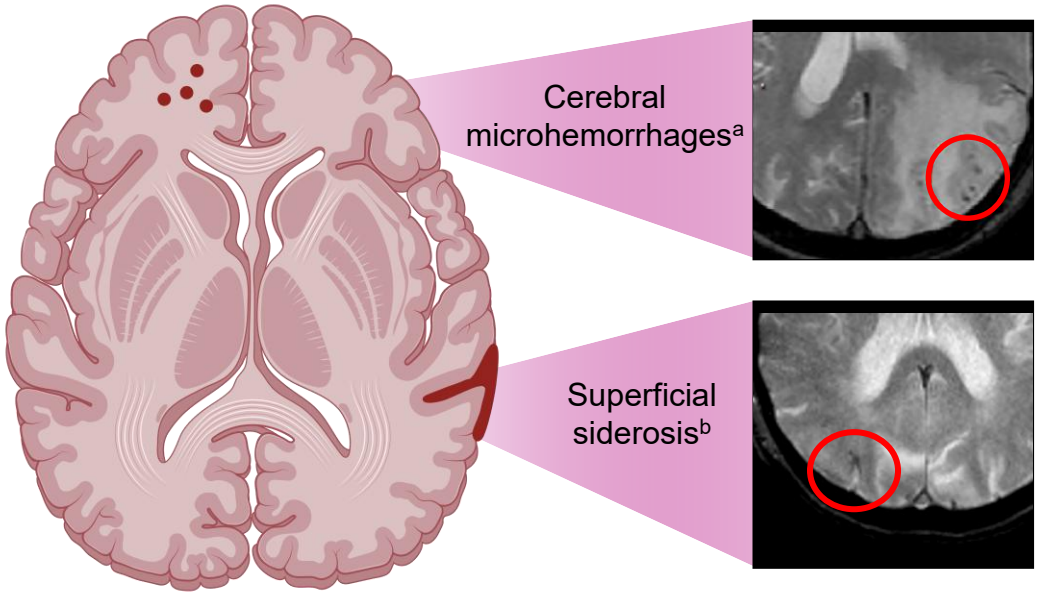
ARIA is an umbrella term used to describe 2 types of amyloid-related imaging abnormalities:[1]

ARIA-Edema/Effusion (ARIA-E)[1]
Interstitial vasogenic edema or sulcal effusion that manifests as parenchymal or sulcal hyperintensities

ARIA-Hemosiderin/Hemorrhage (ARIA-H)[1]
Microhemorrhages observed as hypointense hemosiderin deposition in the parenchyma or leptomeningeal/subpial space (superficial siderosis)



Hyperintense abnormalities on FLAIR sequences



Hypointense abnormalities on T2* GRE sequences

Rare lobar intracerebral hemorrhage, also termed macrohemorrhages, can also occur[2]

Figures created in Biorender.com. MRI images reproduced with permission from [a] Barakos et al (2022)[1] (CC BY 4.0 http://creativecommons.org/licenses/by/4.0/); [b] MRI image data on file.

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; FLAIR, fluid-attenuated inversion recovery; GRE, gradient-recalled echo; MRI, magnetic resonance imaging.

1. Barakos J, et al. J Prev Alzheimers Dis. 2022;9(2):211–220; 2. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35.

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ARIA-E and ARIA-H Have Distinct Characteristics

	ARIA-E[1,2]	ARIA-H[1,2]
Primary diagnostic imaging sequence	FLAIR	T2* GRE
Nature of leakage products	Proteinaceous fluids	Blood-degradation products
Location of increased vascular permeability	**Leptomeninges:** sulcal effusions (ie, exudates) **Parenchyma:** vasogenic edema	**Leptomeninges:** superficial hemosiderin deposits (superficial siderosis) **Parenchyma:** microhemorrhages (typically defined as <10 mm) Intracerebral hemorrhage (macrohemorrhage; ≥10 mm)
Evaluation of severity	MRI severity scales[3] and assessment of symptoms	The number of microhemorrhages and hemosiderin deposits on MRI and assessment of symptoms

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; FLAIR, fluid-attenuated inversion recovery; GRE, gradient-recalled echo; MRI, magnetic resonance imaging.

1. Sperling RA, et al. Alzheimers Dement. 2011;7(4):367–385; 2. Barakos J, et al. AJNR Am J Neuroradiol. 2013;34(10):1958–1965; 3. Barkhof F, et al. AJNR Am J Neuroradiol. 2013;34(8):1550–1555.

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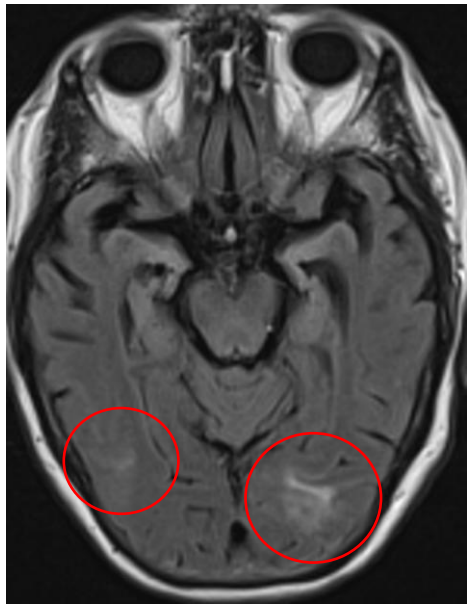
There Are 2 ARIA-E Subtypes

Identified on T2-FLAIR sequences

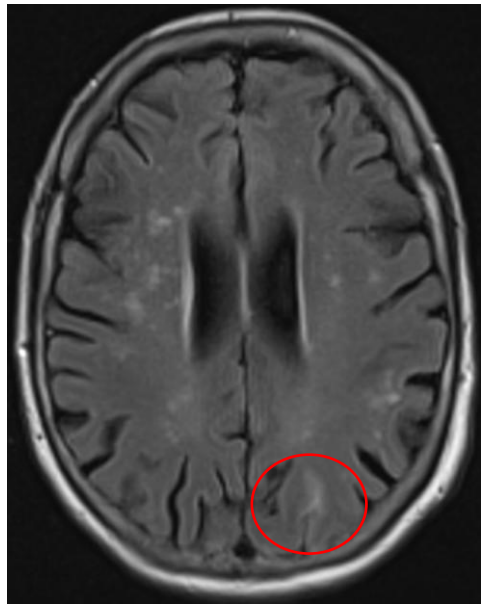
Parenchymal Signal Abnormalities (ARIA-E Edema)

- Imaging features of **ARIA-E edema** are thought to reflect **leakage of intravascular fluid and proteins into the parenchymal interstitial compartment**[1]
- Parenchymal signal abnormalities can be quite subtle in a single region, multifocal, or nearly pan-hemispheric[2]



Sulcal FLAIR Hyperintensities (ARIA-E Effusion)

- The imaging features of **ARIA-E effusion** are thought to reflect **leakage or effusion of proteinaceous fluid from meningeal vessels**[2]
- Sulcal FLAIR hyperintensity in the leptomeningeal or sulcal space may be seen in isolation or near gray matter disturbances[2]



ARIA-E is undetectable on conventional T2 sequences

MRI images: data on file.

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; MRI, magnetic resonance imaging; T2-FLAIR, T2-weighted fluid-attenuated inversion recovery.

1. Barakos J, et al. AJNR Am J Neuroradiol. 2013;34(10):1958–1965; 2. Sperling RA, et al. Alzheimers Dement. 2011;7(4):367–385.

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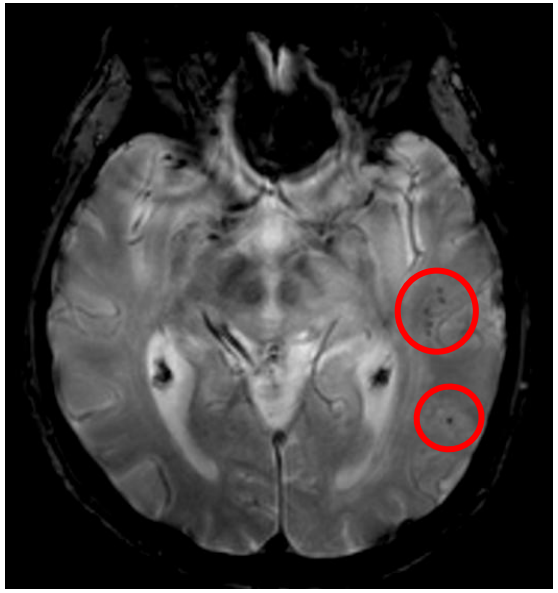
There Are 2 ARIA-H Subtypes

Identified on T2* GRE or SWI sequences

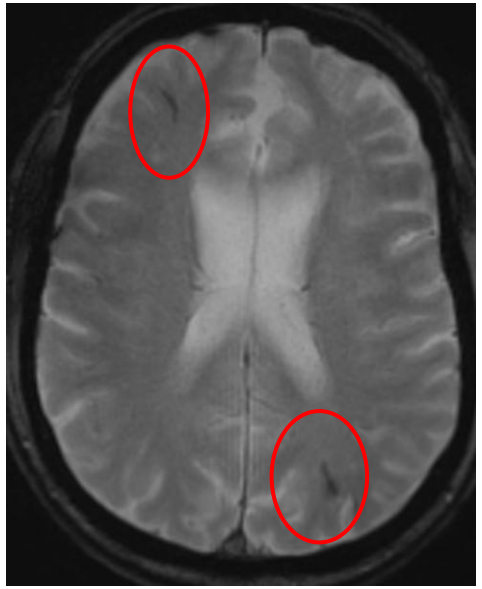
Microhemorrhages

- Hemosiderin deposits ≤10 mm in diameter on the T2* sequence, usually round in shape[1]



Superficial Siderosis

- Diffuse deposition of hemosiderin along the meninges, represented as curvilinear low intensities on T2* sequence that lie adjacent to the surface of the brain[1]
- Sometimes referred to as leptomeningeal hemosiderosis[2]



Intracerebral hemorrhages (hemosiderin deposits >10 mm in diameter on the T2* sequence) are rare but can also occur[3]

MRI images: data on file.

ARIA, amyloid-related imaging abnormalities; ARIA-H, ARIA-hemosiderin/hemorrhage; GRE, gradient-recalled echo; MRI, magnetic resonance imaging; SWI, susceptibility-weighted imaging.

1. Sperling RA, et al. Alzheimers Dement. 2011;7(4):367–385; 2. Barakos J, et al. J Prev Alzheimers Dis. 2022;9(2):211–220; 3. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35.

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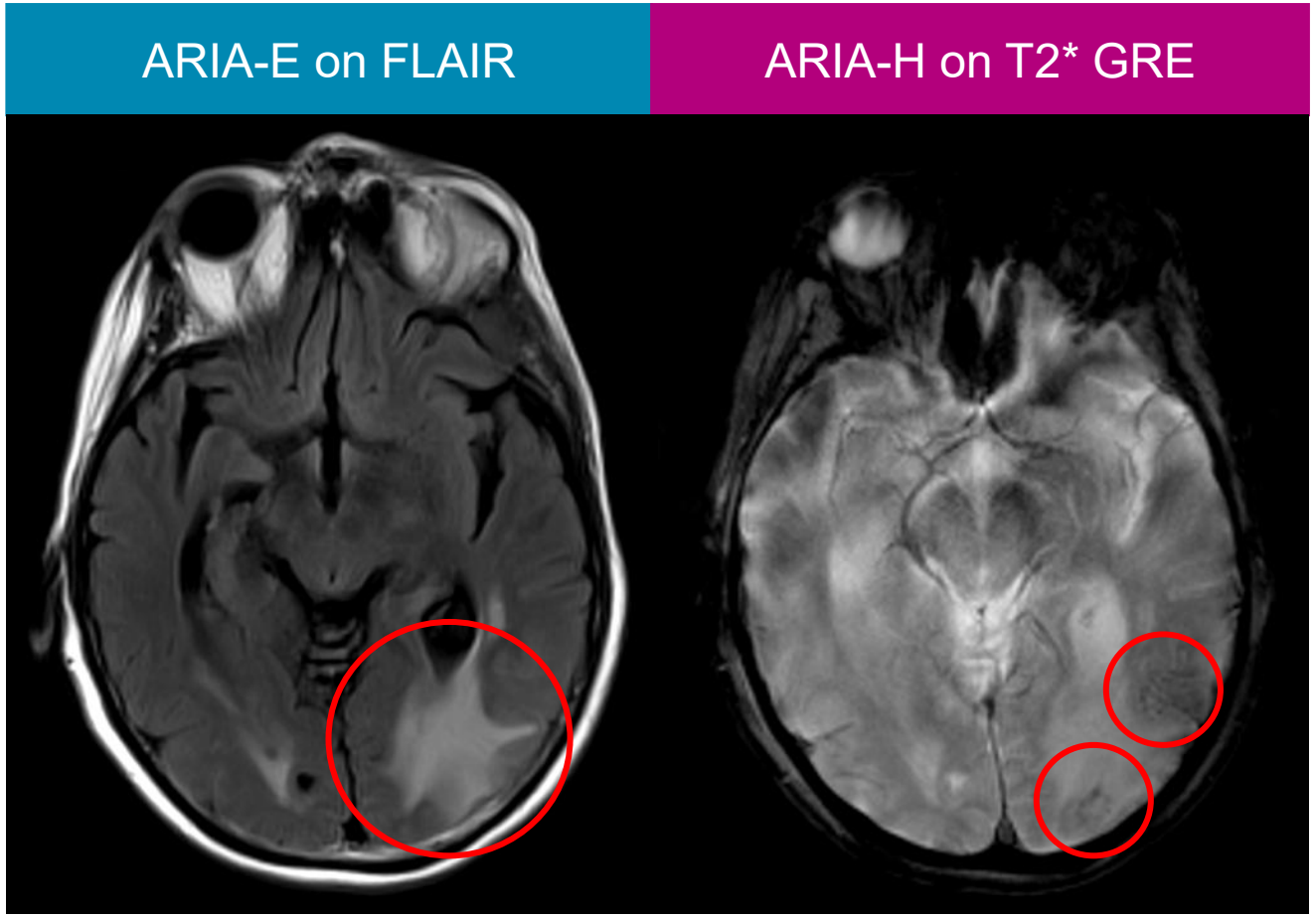
ARIA-E and ARIA-H Can Occur Simultaneously

A leakage of heme products in the parenchyma, as a result of ARIA-E, can result in microhemorrhages (ARIA-H)



MRI images data on file.

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; FLAIR, fluid-attenuated inversion recovery; GRE, gradient-recalled echo; MRI, magnetic resonance imaging.

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

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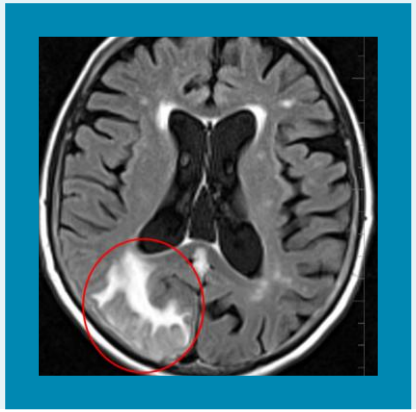
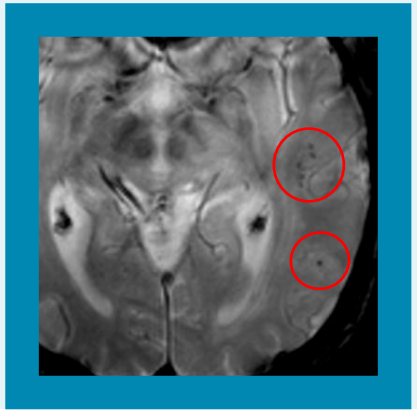
MRI Findings are Similar Whether ARIA Occurs Spontaneously, or in the Presence of Monoclonal Antibodies That Remove Amyloid

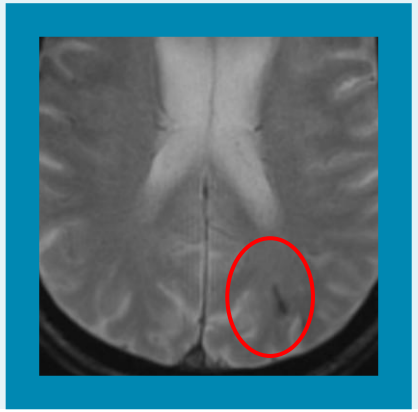
ARIA occurring in the presence of monoclonal antibodies that remove amyloid



ARIA-E edema

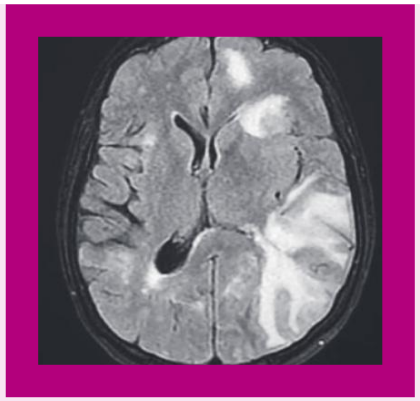


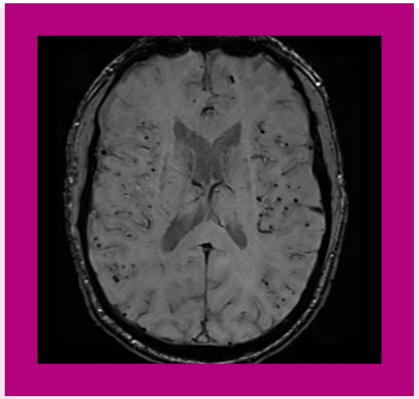
ARIA-H (microhemorrhages)

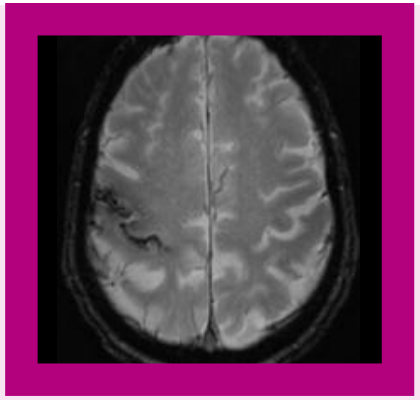


ARIA-H (superficial siderosis)

Spontaneously-occurring ARIA







Images 1–3: Eisai internal MRI images; Image 4, used with permission from Roytman M, et al (2023)[1]; Image 5, case courtesy of Frank Gaillard, Radiopaedia.org, rID: 46082[2]; Image 6, used with permission from Andersen NH, et al. BMC Neurol. 2023;23:252.[3] (CC-BY 4.0: http://creativecommons.org/licenses/by/4.0/)
ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage.
1. Roytman M, et al. AJR Am J Roentgenol. 2023;220(4):562–574; 2. Frank Gaillard, Radiopaedia.org, rID: 46082. 2016. Available from: https://radiopaedia.org/cases/cerebral-amyloid-angiopathy-12?lang=gb (Accessed August 2025); 3. Andersen NH, et al. BMC Neurol. 2023;23:252

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Pathophysiology of ARIA

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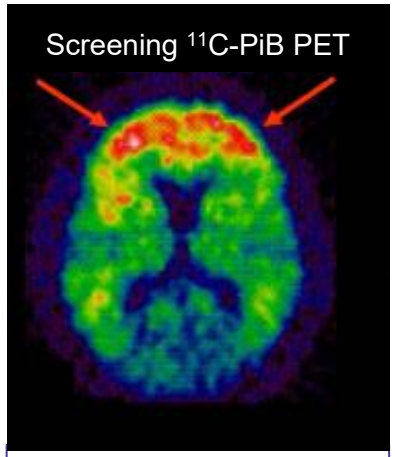
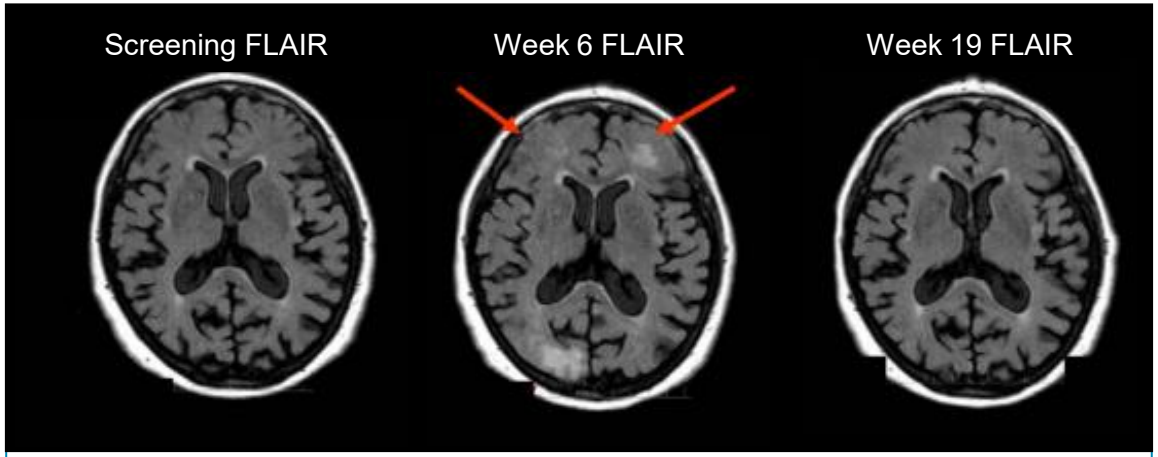
There is an association between Amyloid Removal With Monoclonal Antibodies and ARIA

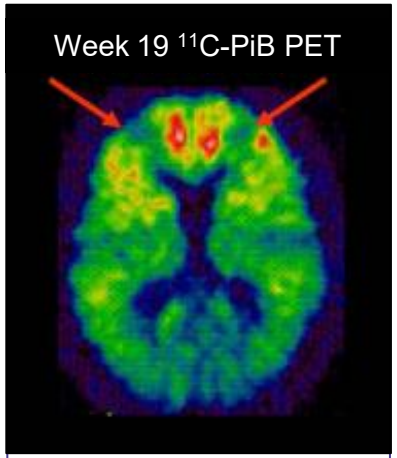


Baseline ^{11}C-PiB retention consistent with high fibrillar burden



At Week 6 after treatment initiation, FLAIR MRI reveals bifrontal parenchymal hyperintensity (ARIA-E), which resolves by **Week 19**

At Week 19, T2* GRE sequence reveals the development of bifrontal microhemorrhages (ARIA-H)



Week 19 ^{11}C-PiB uptake is reduced representing clearance of fibrillar amyloid from plaque and cerebral vessels. ARIA-E and ARIA-H developed in some of these regions

Reduced PiB retention on amyloid PET (which measures amyloid deposition) is temporally and regionally associated with ARIA-E and ARIA-H

Images used with permission from Sperling et al (2012) (CC-BY 4.0: http://creativecommons.org/licenses/by/4.0/).

Aβ, amyloid beta; AD, Alzheimer's disease; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; CAA, cerebral amyloid angiopathy; FLAIR, fluid-attenuated inversion recovery; GRE, gradient-recalled echo; MRI, magnetic resonance imaging; PET, positron emission tomography; PiB, Pittsburgh compound B.

Sperling R, et al. Lancet Neurol. 2012;11(3):241–249.

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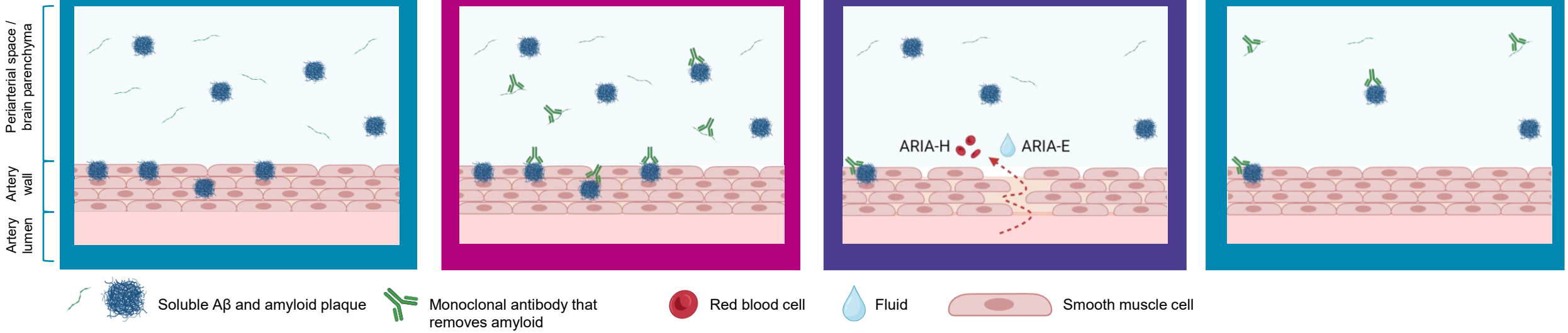
The Pathophysiology of ARIA Is Thought to Be Driven by a Transient Increase in Vascular Permeability Upon Amyloid Removal

Aggregation of **toxic Aβ species in the brain parenchyma** (culminating in **amyloid plaques**) and **blood vessels (CAA)** contributes to AD pathogenesis[1]

After the introduction of monoclonal antibodies that remove amyloid, vascular amyloid deposits begin to clear leading to **increased vascular permeability**[2]

This **loss of vascular integrity is a consequence of the presence of amyloid in cerebral blood vessel walls (CAA)**. The leakage of fluid could give rise to an increased signal detected on FLAIR images (ARIA-E), while leakage of red cells would result in ARIA-H[2,3]

Limited evidence suggests that with repeated immunization and **continued Aβ clearance, the integrity of vessels and efficiency of clearance can improve and diminish the risk of ARIA**[3]



Although ARIA is thought to be mediated by amyloid removal, it does not indicate that an individual is amyloid negative

Figure created with BioRender.com.

Aβ, amyloid beta; AD, Alzheimer's disease; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; CAA, cerebral amyloid angiopathy; FLAIR, fluid-attenuated inversion recovery.

1. Cogswell, PM et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35; 2. Sperling RA, et al. Alzheimers Dement. 2011;7(4):367–385; 3. Sperling R, et al. Lancet Neurol. 2012;11(3):241–249.

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Preclinical and Clinical Evidence Support the Proposed Pathophysiology of ARIA

Preclinical

Vascular alterations after treatment with a murine form of monoclonal antibodies that remove amyloid[1]

Clinical

Increased risk of ARIA-E and ARIA-H in carriers of *APOE ε4* and in those with baseline MRI evidence of CAA (eg, microhemorrhages)[2]

The risk of ARIA-E is increased with higher therapeutic doses and there is a potential relation between ARIA-E and amyloid clearance[2,3]

Reduced PiB retention on amyloid PET (which measures amyloid deposition) is both temporally and regionally associated with ARIA-E and ARIA-H[2]

ARIA-E typically occurs early in treatment, and the incidence declines with longer exposure[4,5,6]

APOE ε4, apolipoprotein E ε4; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; CAA, cerebral amyloid angiopathy; MRI, magnetic resonance imaging; PET, positron emission tomography; PiB, Pittsburgh compound B.

1. Zago W, et al. Alzheimers Dement. 2013;9(5 Suppl.):S105–S115; 2. Sperling R, et al. Lancet Neurol. 2012;11(3):241–249; 3. Wang H, et al. Alzheimers Dement. 2025;21(4):e70062; 4. Ketter N, et al. J Alzheimers Dis. 2017;57(2):557–573; 5. Salloway S, et al. N Engl J Med. 2014;370(4):322–333; 6. Honig LS, et al. Alzheimers Res Ther. 2024.10;16(1):105.

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Risk Factors for ARIA

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ARIA Has 3 Key Known Risk Factors

Treatment With Monoclonal Antibodies That Remove Amyloid[1,2]

The use of monoclonal antibodies that remove amyloid increases the risk of ARIA[2]

APOE ε4 Carrier Status[1–3]

APOE ε4 is also a risk factor for CAA. It results in earlier and greater Aβ deposition in plaques and vessels[4–6]

Pre-Existing Microhemorrhage[2,3]

Pre-existing microhemorrhages (measured at prior to treatment initiation) are a marker of CAA and a risk factor for ARIA[6]

Aβ, amyloid beta; APOE ε4, apolipoprotein E ε4; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; CAA, cerebral amyloid angiopathy.

1. Sperling RA, et al. Alzheimers Dement. 2011;7(4):367–385; 2. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35; 3. Filippi M, et al. JAMA Neurol. 2022;79(3):291–304; 4. Charidimou A, et al. Brain 2017;140(7):1829–1850;
5. Kuhn J, Sharman T. Cerebral Amyloid Angiopathy. [Updated 2023 Jun 5]. In: StatPearls [Internet]. 2025 Jan. https://www.ncbi.nlm.nih.gov/books/NBK556105/ (Accessed April 2025);
6. Arrighi HM, et al. J Neurol Neurosurg Psychiatry 2016;87(1):106–112.

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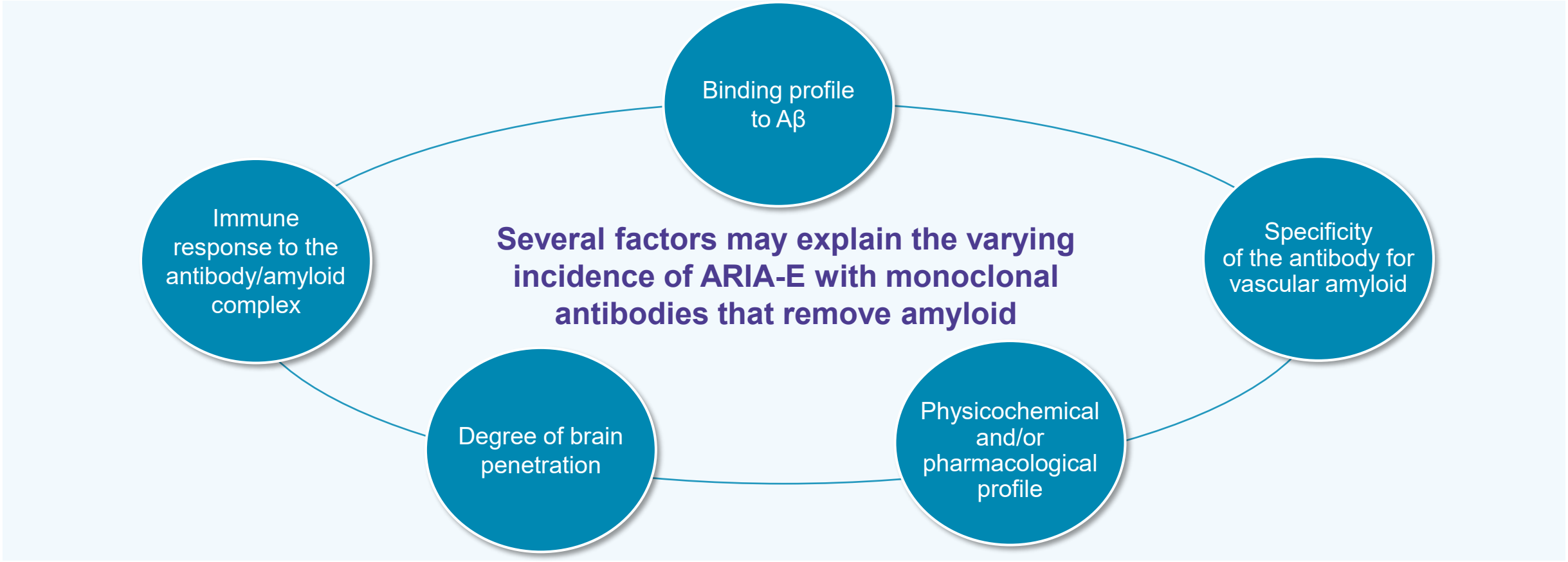
ARIA-E Frequency Appears to Vary by the Monoclonal Antibody That Removes Amyloid



Incidence of ARIA-E varies across different studies of monoclonal antibodies that remove amyloid. ARIA-E occurrence appears to be dose-dependent and associated with the APOE ε4 allele.

Aβ, amyloid beta; APOE ε4, apolipoprotein E ε4; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion.

Majid O, et al. CPT Pharmacometrics Syst Pharmacol. 2024;13(12):2111–2123; Cummings JL. Neurotherapeutics. 2025;22(3):e00570.

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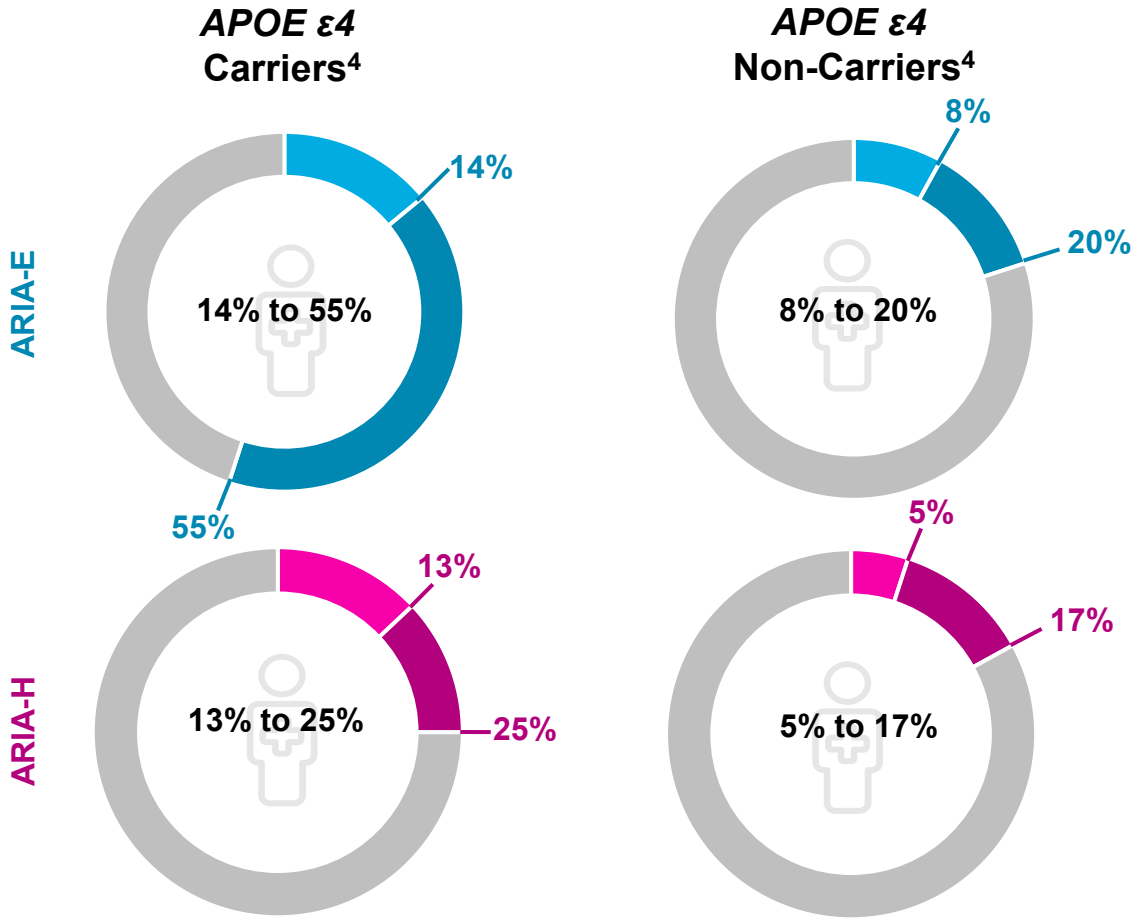
In Trials of Monoclonal Antibodies That Remove Amyloid in Patients With AD, the Presence of 1 or More *APOE ε4* Alleles Is a Risk Factor for ARIA

- *APOE ε4* carriers (>60 years of age) have higher parenchymal and vascular Aβ load[1,2]
- When exposed to monoclonal antibodies that remove amyloid, they would experience a larger antibody-mediated shift in Aβ compared with non-carriers[3]



Aβ, amyloid beta; AD, Alzheimer's disease; APOE ε4, apolipoprotein E ε4; ARIA, amyloid-related imaging abnormalities.

1. Caselli RJ, et al. Neurosci Lett. 2010;473(3):168–171; 2. Cogswell, PM et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35; 3. Ketter N, et al. J Alzheimers Dis. 2017;57(2):557–573; 4. Filippi M, et al. JAMA Neurol. 2022;79(3):291–304.

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Pretreatment Microhemorrhage(s) Increase the Risk of ARIA

- Pre-existing imaging risk factors predictive of ARIA:[1,2]
  - **lobar microhemorrhages**
  - **intracerebral hemorrhage**
  - **superficial siderosis**
- Signals of hemosiderin deposition are **consistent with CAA**[1]
- The presence of these signals is more strongly correlated with the occurrence of ARIA **in *APOE ε4* carriers vs non-carriers**[1]

Microhemorrhages (red), intracerebral hemorrhage >10mm (blue), and superficial siderosis (green)

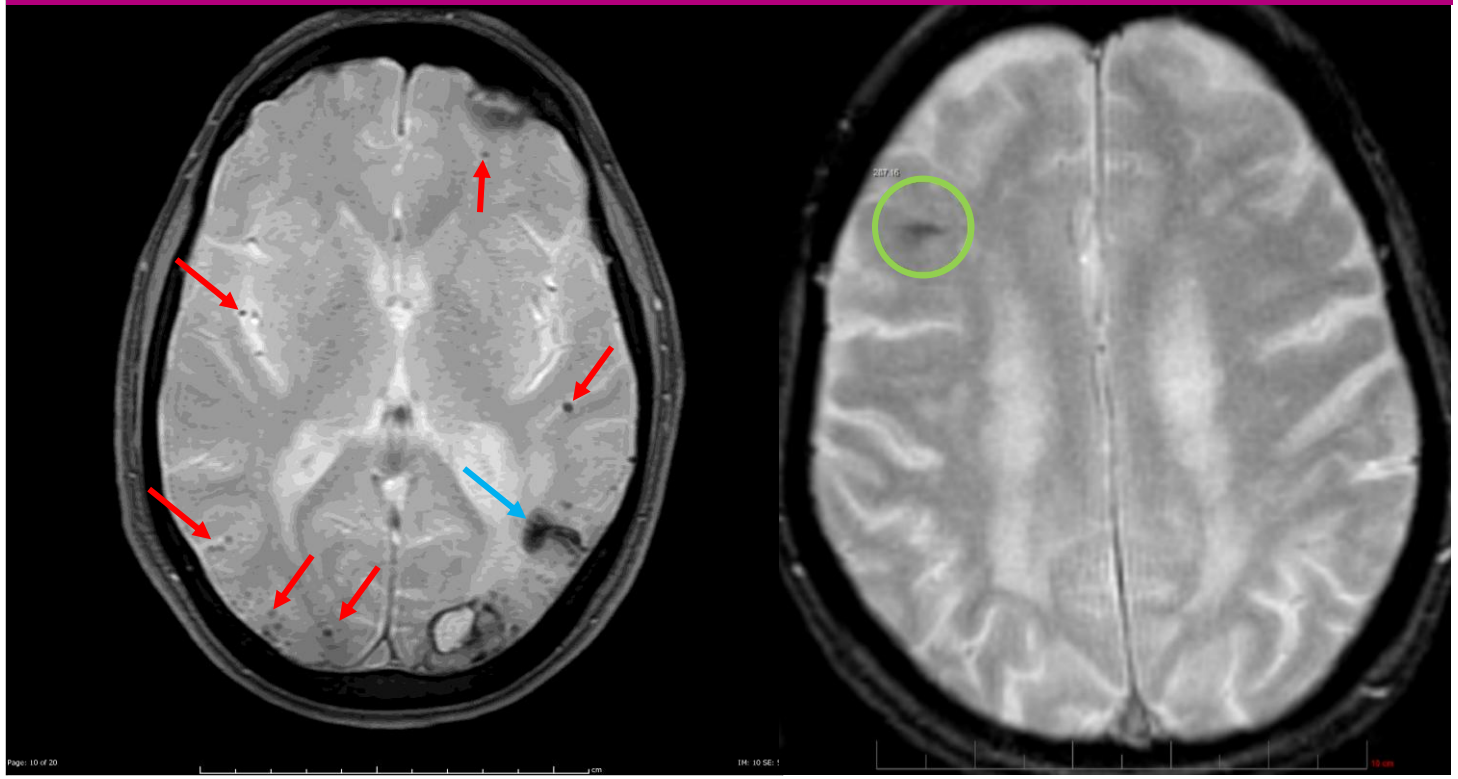

Image 1: case courtesy of Frank Gaillard, Radiopaedia.org, rID: 4561 https://doi.org/10.53347/rID-4561 (Accessed March 2024); Image 2: data on file.

APOE ε4, apolipoprotein E ε4; ARIA, amyloid-related imaging abnormalities; CAA, cerebral amyloid angiopathy.

1. Sperling RA, et al. Alzheimers Dement. 2011;7(4):367–385; 2. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35.

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Clinical Manifestations of ARIA

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Although Most Cases of ARIA Are Asymptomatic, Clinical Symptoms Can Occur

When symptoms of ARIA occur, they may include:[1–4]

Most Frequent

- Headache
- Confusion
- Dizziness
- Nausea / vomiting
- Neuropsychiatric symptoms

Less Frequent

- Fatigue
- Visual disturbance / blurred vision
- Gait disturbance

Uncommon

- Severe symptoms, eg, encephalopathy, focal neurologic symptoms, seizures
  - Requiring hospitalization and specific treatments, eg, ICU admission, EEG, corticosteroids, antiepileptics)

Serious symptoms of ARIA may occur and ARIA can be fatal

ARIA, amyloid-related imaging abnormalities; EEG, electroencephalography; ICU, intensive care unit.

1. Filippi M, et al. JAMA Neurol. 2022;79(3):291–304; 2. Sperling R, et al. Lancet Neurol. 2012;11(3):241–249; 3. Salloway S, et al. JAMA Neurol. 2022;79(1):13–21; 4. Cummings J, et al. J Prev Alzheimers Dis. 2022;9(2):221–230.

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The Typical Clinical Course of ARIA Has Been Described Based on Clinical Trial Experience

ARIA-E

Mostly occurs early in the treatment course[1–4]

- The risk decreases with increased duration of monoclonal antibodies that remove amyloid

Most cases resolve on MRI without concomitant treatment[1–8]

- Depending on the severity, treatment may continue, be interrupted, or discontinued
- Resumption of dosing following ARIA-E resolution is generally associated with a low rate of ARIA-E recurrence

Most cases are asymptomatic[1,6,8]

- Although serious and life-threatening events can occur, and these cases may require hospitalization and specific treatment (eg, corticosteroids). ARIA can be fatal

ARIA-H

ARIA-E and ARIA-H may occur concurrently[3,7,9]

- Trials have shown that ARIA-E resolves radiographically over time, whereas ARIA-H stabilizes but may remain visible on subsequent imaging

The prescribing information of monoclonal antibodies that remove amyloid should be followed for ARIA monitoring and management guidelines[10]

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; MRI, magnetic resonance imaging.

1. Filippi M, et al. JAMA Neurol. 2022;79(3):291–304; 2. Sperling R, et al. Lancet Neurol. 2012;11(3):241–249; 3. Barakos J, et al. J Prev Alzheimers Dis. 2022;9(2):211–220; 4. Honig LS, et al. Alzheimers Res Ther. 2024.10;16(1):105; 5. Ostrowitzki S, et al. Alzheimers Res Ther. 2017;9(1):95; 6. Cummings J, et al. J Prev Alzheimers Dis. 2023;10(3):362–377; 7. Salloway S, et al. JAMA Neurol. 2022;79(1):13–21; 8. Rabinovici GD, et al. J Prev Alzheimers Dis. 2025;12(5):100150; 9. Barakos J, et al. AJNR AM J Neuroradiol. 2013;34(10):1958–1965; 10. Cogswell PM, et al. AJNR Am J Neuroradiol. 2025;46(1):24–32.

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Diagnosing ARIA

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Surveillance MRIs Can Be Used to Monitor for ARIA in Patients Treated With Monoclonal Antibodies That Remove Amyloid

- **The risk of ARIA** is increased **with the use of monoclonal antibodies that remove amyloid** in patients with AD[1,2]
- In these cases, **surveillance MRIs can be used to monitor for ARIA[2]**

Detection of ARIA requires:

- Familiarity with the imaging abnormalities on MRI
- Acquisition of specific MRI sequences, which allows detection of these abnormalities

AD, Alzheimer's disease; ARIA, amyloid-related imaging abnormalities; MRI, magnetic resonance imaging.

1. Sperling RA, et al. Alzheimers Dement. 2011;7(4):367–385; 2. Filippi M, et al. JAMA Neurol. 2022;79(3):291–304.

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Recommended MRI Protocols for Baseline Imaging and Detection of ARIA

3T scanner (recommended) 1.5T scanner (minimal)[1,2]	High field strength scanners have greater sensitivity but limited availability. The use of 1.5T is endorsed as a minimum standard[2]
Slice thickness:[2] ≤5 mm	Thinner slices increase resolution but should be balanced against the loss in signal-to-noise ratio[2]
T2* GRE TE[2] ≥20 ms (20 ms at 3T, 30 ms at 1.5T)	Longer TE increases sensitivity to detection[2]
2D T2* GRE or SWI (for ARIA-H)[2,3]	To identify superficial siderosis and microhemorrhages (ARIA-H) T2* GRE and SWI are MRI sequences used to improve the detection and visualization of microhemorrhages[2]
T2-FLAIR (for ARIA-E)[2]	To monitor brain edema or sulcal effusion (ARIA-E)[3]
Diffusion-weighted imaging[3]	Recommended for differential diagnosis[3]

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; GRE, gradient-recalled echo; MRI, magnetic resonance imaging; T2-FLAIR, T2-weighted fluid-attenuated inversion recovery; TE, echo time; SWI, susceptibility-weighted imaging.

1. Cogswell PM, et al. AJNR Am J Neuroradiol. 2025;46(1):24–32; 2. Sperling RA, et al. Alzheimers Dement. 2011;7(4):367–385; 3. Barakos J, et al. J Prev Alzheimers Dis. 2022;9(2):211–220.

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MRI Is Essential for the Diagnosis of ARIA

ARIA-E are **undetectable on conventional T2 sequences**[1]

CT would not be expected to detect milder forms of ARIA-E and may lead to **misdiagnosis as stroke** or other conditions.*,[1] A stroke misdiagnosis may result in the administration of thrombolytic therapy, which may increase the risk of intracerebral hemorrhage in patients with ARIA[2]

CT is insensitive to the detection of microhemorrhages and siderosis (ARIA-H)[1]

*Confirm with the neuroradiologist
ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; CT, computed tomography.

1. Barakos J, et al. J Prev Alzheimers Dis. 2022;9(2):211–220; 2. Reish NJ, et al. N Engl J Med. 2023;388(5):478–479.

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Importance of Baseline MRI

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Obtaining a Baseline MRI Is Essential Prior to Initiating Treatment With Monoclonal Antibodies That Remove Amyloid

For the **differential diagnosis of AD**[1,2]

To **individualize treatment benefit/risk decisions**[1,2]

- Pre-existing CAA is a risk factor for intracerebral hemorrhage. MRI findings indicating CAA include evidence of prior intracerebral hemorrhage, cerebral microhemorrhage, and cortical superficial siderosis

To serve as a **reference for future MRI comparisons**[1,2]

- A baseline scan is needed to grade ARIA severity and therefore required for ARIA management

AD, Alzheimer's disease; ARIA, amyloid-related imaging abnormalities; CAA, cerebral amyloid angiopathy; MRI, magnetic resonance imaging.

1. Cummings J, et al. J Prev Alzheimers Dis. 2023;10(3):362–377; 2. Rabinovici GD, et al. J Prev Alzheimers Dis 2025;12(5):100150.

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What to Look for in a Baseline MRI Prior to Initiating Monoclonal Antibodies That Remove Amyloid

Have any of the following imaging markers been identified on MRI?

- Microhemorrhages (defined as ≤10 mm at the greatest diameter)
- Intracerebral hemorrhage (>10 mm at the greatest diameter)
- Superficial siderosis
- Vasogenic edema
- Lacunar infarcts or stroke
- Severe subcortical hyperintensities
- Evidence of ABRA
- Evidence of CAA-ri
- Other major intracranial pathologies

ABRA, amyloid-beta-related angiitis; CAA-ri, cerebral amyloid angiopathy-related inflammation; MRI, magnetic resonance imaging.

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

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Potential Interpretation Pitfalls and Differential Diagnosis

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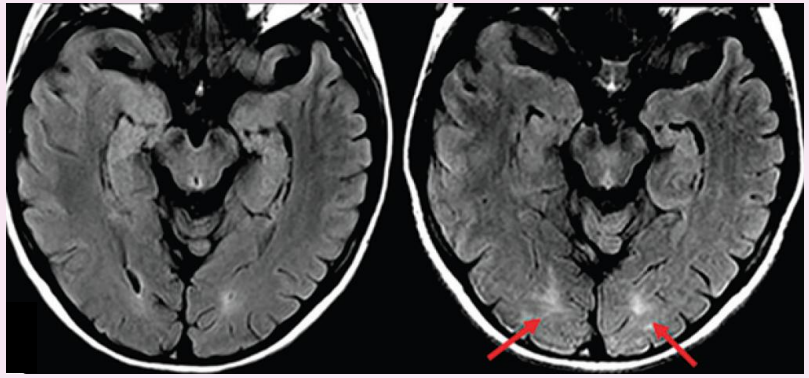
Potential Interpretation Pitfalls of MRI When Detecting ARIA-E

If a patient is imaged on different scanners, it may be difficult to distinguish true ARIA-E vs technical variation[1]

Vendor 1: Time-Point 1 | **Vendor 2: Time-Point 2**



T2-FLAIR hyperintense signal in the bilateral occipital white matter that may be mistaken for subtle ARIA-E, which appears to be new from the prior examination on Vendor 1

Figure reproduced with permission from Cogswell et al (2022).[1]

- White matter signal may differ with scan technique and field strength, such as the use of 3D vs 2D FLAIR[1]
- Shading artifacts and scanner or sequence variability may make the identification and interpretation of ARIA-E vs artifacts difficult[1]
- Axial T2-FLAIR images from 2 time points, with the 2 scans performed on different vendor scanners[1]
- Repeat imaging of the participant on Vendor 1 showed that the apparent abnormality was resolved[1]

ARIA-E can be identified using T2-weighted FLAIR sequences, but can be entirely obscured with T2-weighted imaging[2]

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; T2-FLAIR, T2-weighted fluid-attenuated inversion recovery.

1. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35; 2. Sperling RA, et al. Alzheimers Dement. 2011;7(4):367–385.

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Potential Interpretation Pitfalls of MRI When Detecting ARIA-H

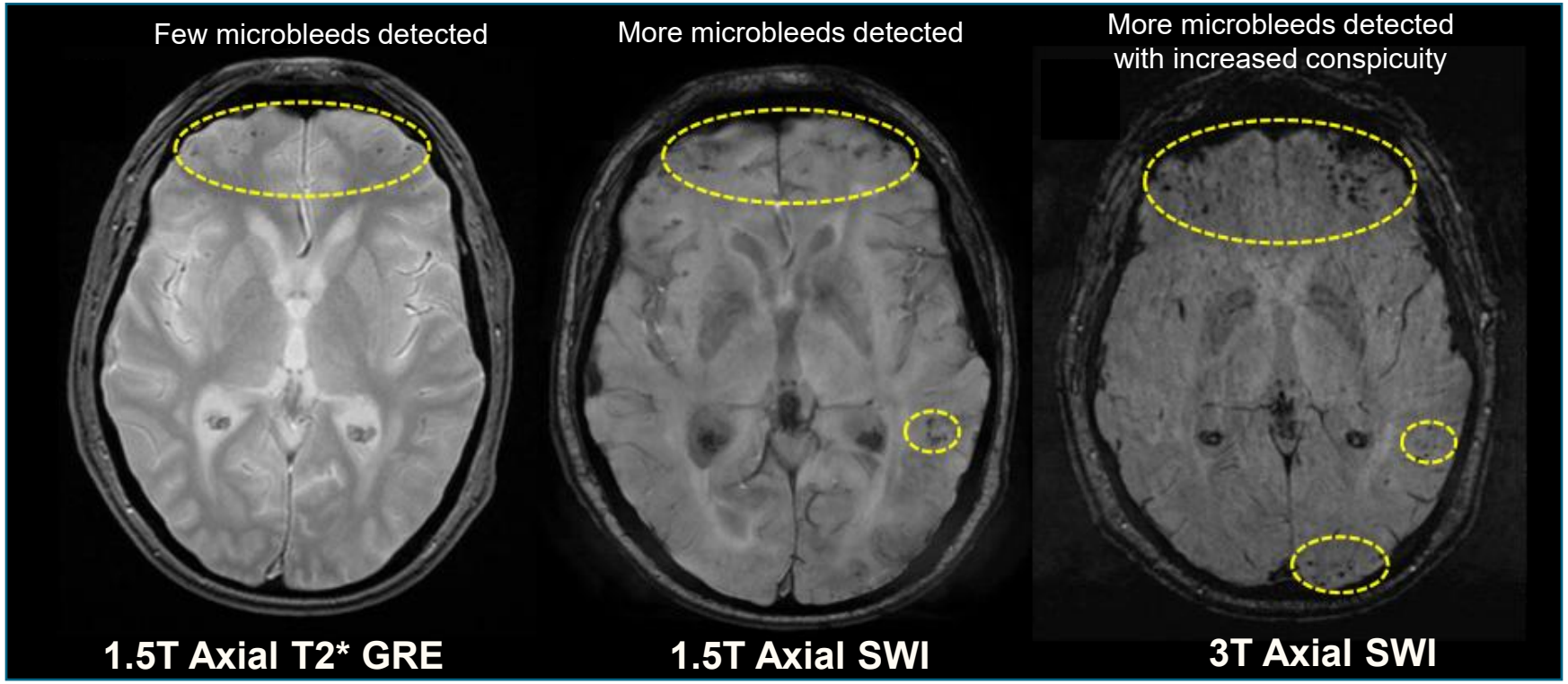

Image of a patient with spontaneous intracerebral hemorrhage. Figure reproduced with permission from Puy et al (2021).[1]

SWI is a more sensitive technique for detection of microhemorrhages than T2* GRE images[2]

ARIA, amyloid-related imaging abnormalities; ARIA-H, ARIA-hemosiderin/hemorrhage; GRE, gradient-recalled echo; MRI, magnetic resonance imaging; SWI, susceptibility-weighted imaging.

1. Puy L, et al. J Neurol Neurosurg Psychiatry 2021;92:598–607; 2. Sperling RA, et al. Alzheimers Dement. 2011;7(4):367–385.

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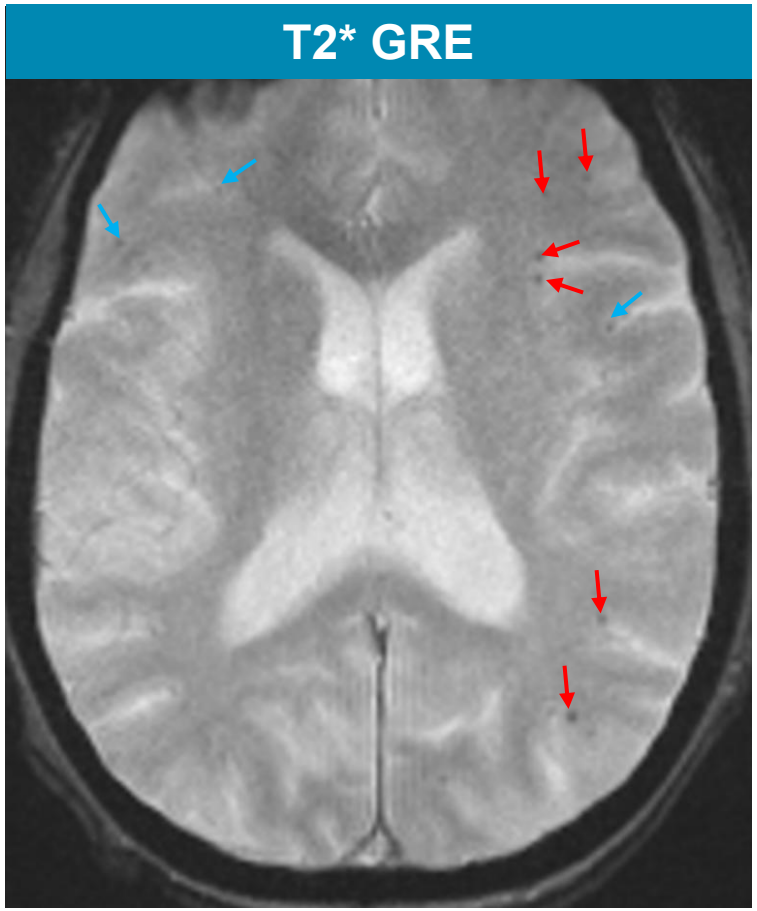
ARIA-H Microhemorrhages Can Mimic Vascular Structures on MRI

Differentiating between microhemorrhages and flow voids

- Partial volume artifact
- Motion
- Compare with T2 sequence and attempt to identify the corresponding flow void



- Microhemorrhages: red arrow
- Thru-plane vessels: blue arrow

Thru-plane vessels can mimic microhemorrhages, and in-plane vessels can mimic siderosis

Data on file.

ARIA, amyloid-related imaging abnormalities; ARIA-H, ARIA-hemosiderin/hemorrhage; GRE, gradient-recalled echo.

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MRI Is Key for the Differential Diagnosis of ARIA

ARIA are suspected

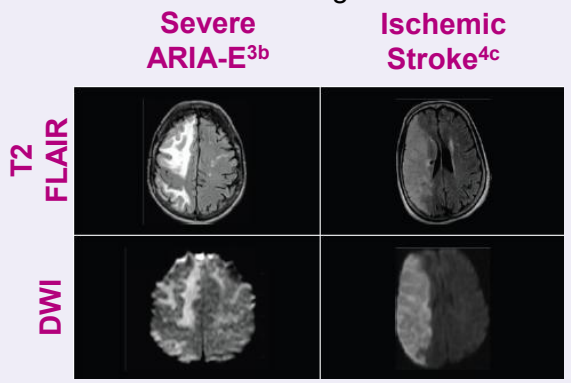
Order MRI sequences needed to detect ARIA (minimum T2 FLAIR, T2* GRE, and DWI)

- **ARIA-E** → 2D or 3D T2 FLAIR
- **ARIA-H** → T2* GRE[a] or SWI
- **Differential diagnosis** → Other tests may be needed to confirm the differential diagnosis

Stroke

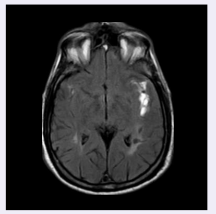
DWI

Ischemic stroke may mimic ARIA-E edema. DWI sequences can support differential diagnosis[2]



SAH

SAH may mimic ARIA-E effusion[2,5d]



Other

Eg, PRES, infection[2]

ARIA should be considered the likely cause of the abnormal imaging findings in patients receiving monoclonal antibodies that remove amyloid. Inaccurate differential diagnosis of stroke may result in the administration of thrombolytic therapy, which may increase the risk of intracerebral hemorrhage in patients with ARIA.[6] Vasculitis and intracerebral hemorrhage have also been observed with thrombolytic therapy in patients with CAA in the absence of monoclonal antibodies that remove amyloid.[7–9]

[a] GRE must be performed with appropriate TE: 3T, TE 15–20 ms; 1.5T, 25–35 ms; [b] Figure adapted from Cogswell (2022);[3] [c] Case courtesy of Balachandran G, Radiopaedia.org, rID: 107048;[4] [d] Case courtesy of Abdrabou A, Radiopaedia.org, rID: 22738.[5]
ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin hemorrhage; CAA, cerebral amyloid angiopathy; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; GRE, gradient-recalled echo; MRI, magnetic resonance imaging; PRES, posterior reversible encephalopathy syndrome; SAH, subarachnoid hemorrhage; SWI, susceptibility-weighted imaging.

1. Cogswell PM, et al. AJNR Am J Neuroradiol. 2025;46(1):24–32; 2. Barakos J, et al. AJNR AM J Neuroradiol. 2013;34(10):1958–1965; 3. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35;
4. Balachandran G. Radiopaedia.org. https://doi.org/10.53347/rID-10704 (Accessed April 2025); 5. Abdrabou A. Radiopaedia.org. https://doi.org/10.53347/rID-22738 (Accessed April 2025); 6. Reish NJ, et al. N Engl J Med. 2023;388(5):478–479;
7. Sabbagh M, van Dyck CH. N Engl J Med. 2023;388(5):480; 8. Schwab P, et al. Arthritis Rheum. 2003;49(3):421–427; 9. Felling RJ, et al. J Neurol Transl Neurosci. 2014;2(10):1034.

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Differential Diagnosis: Acute Ischemic Stroke

T2-Weighted Axial FLAIR: Parenchymal Edema

Severe ARIA-E[1a] | Right MCA . Ischemic Stroke[2]

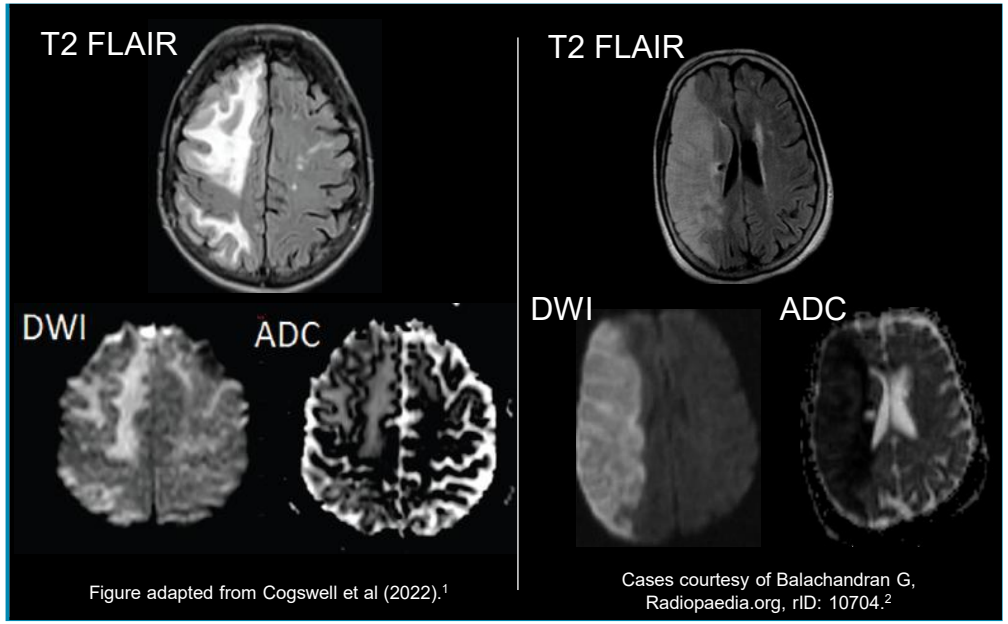

Figure adapted from Cogswell et al (2022).[1]

Cases courtesy of Balachandran G, Radiopaedia.org, rID: 10704.[2]

- Parenchymal FLAIR hyperintensity of ARIA-E edema may be mimicked by ischemic stroke[3]
- Diffusion-weighted imaging (DWI) is needed to differentiate between ARIA-E and ischemic stroke[3]
- Signs and symptoms of ischemic stroke include acute onset, hemiparesis, dysphasia or dysarthria, facial paresis, paresthesia, eye movement abnormalities, and visual field defects[4]
- Knowledge of whether a patient is receiving a monoclonal antibody that removes amyloid can aid in diagnosing ARIA[3]

[a] Hyperintense signal on DWI is confirmed to be T2 shinethrough on the ADC map, differentiating ARIA-E from acute ischemia or other cause of cytotoxic edema.

ADC, apparent diffusion coefficient; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; DWI, diffusion-weighted imaging; MCA, middle cerebral artery; T2-FLAIR: T2-weighted fluid-attenuated inversion recovery.

1. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35; 2. Balachandran G, Radiopaedia.org, rID: 10704 https://doi.org/10.53347/rID-10704 (Accessed March 2025); 3. Barakos, J et al. AJNR AM J Neuroradiol. 2013;34(10):1958–1965; 4. Yew KS, et al. Am Fam Physician 2015;91(8):528–536.

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Differential Diagnosis: Subarachnoid Hemorrhage

T2 Axial FLAIR. Effusion

Moderate ARIA-E[1] | Subarachnoid Hemorrhage[2]

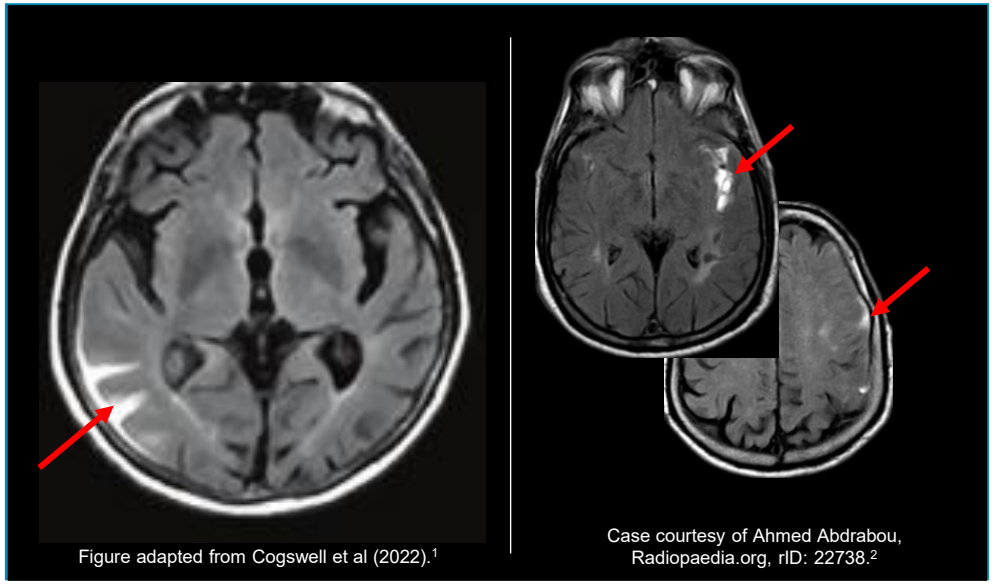

Figure adapted from Cogswell et al (2022).[1]

Case courtesy of Ahmed Abdrabou, Radiopaedia.org, rID: 22738.[2]

- Leptomeningeal FLAIR hyperintensity of ARIA-E effusion may be mimicked by SAH[3]
- Differentiating ARIA and SAH requires a systematic clinical and diagnostic approach[3]
- Subarachnoid hemorrhage typically presents with a number of signs and symptoms: severe headache accompanied by nausea or vomiting[4]
- Decreased level of consciousness, neck stiffness, and focal neurological signs can also be present[4]

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; FLAIR, fluid-attenuated inversion recovery; SAH, subarachnoid hemorrhage.

1. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35; 2. Abdrabou A. Radiopaedia.org https://doi.org/10.53347/rID-22738 (Accessed March 2025); 3. Barakos, J et al. AJNR AM J Neuroradiol. 2013;34(10):1958–1965; 4. Tetsuka S, Matsumoto E. BMC Neurol. 2016;16(1):196.

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Differential Diagnosis: Posterior Reversible Encephalopathy Syndrome (PRES)

T2-Weighted FLAIR Edema

Moderate ARIA-E[1] | PRES[2]

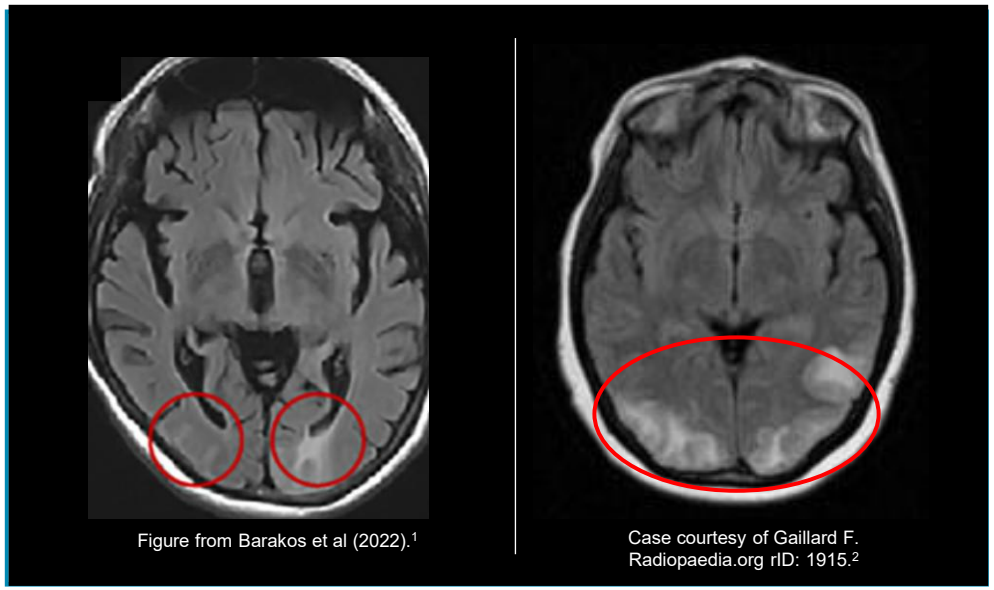

Figure from Barakos et al (2022).[1]

Case courtesy of Gaillard F. Radiopaedia.org rID: 1915.[2]

- PRES could resemble ARIA-E on imaging[3]
- PRES frequently develops from cytotoxic medication or disorders such as preeclampsia, sepsis, renal disease, or autoimmune disorders[4]
- Signs of PRES:[4]
  - Encephalopathy, epileptic seizures, visual disturbances or hallucinations, and focal neurological deficits
- Less specific signs include:[4]
  - Headache, nausea, vomiting
- In this case, clinical history is **important for differentiation**

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; FLAIR, fluid-attenuated inversion recovery; PRES, posterior reversible encephalopathy syndrome.

1. Barakos J, et al. J Prev Alzheimers Dis. 2022;9(2):211–220; 2. Gaillard F, et al. Radiopaedia.org rID1915. https://doi.org/10.53347/rID-1915 (Accessed March 2025); 3. Barakos, J et al. AJNR AM J Neuroradiol. 2013;34(10):1958–1965;
4. Fischer M, Schmutzhard E. J Neurol. 2017;264(8):1608–1616.

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Determining the Radiographic Severity of ARIA

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Grading Scale for Determining Radiographic Severity of ARIA

ARIA-E, ARIA-H microhemorrhage, and ARIA-H superficial siderosis are each categorized by radiographic severity (mild to severe) based on the following criteria:

	Mild	Moderate	Severe
ARIA-E New sulcal and/or cortical/ subcortical FLAIR hyperintensity	1 location <5 cm	1 location 5–10 cm OR >1 location each <10 cm	1 or more location >10 cm
ARIA-H New superficial siderosis	1 focal area	2 focal areas	>2 focal areas
ARIA-H Number of new microhemorrhages	≤4	5–9	≥10

ARIA is graded on basis of treatment-emergent events. For ARIA-H, this count includes cumulative new microhemorrhages or regions of siderosis compared with baseline, pretreatment examination

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

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

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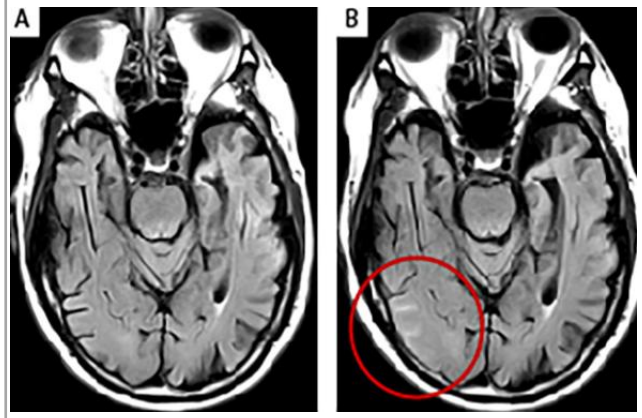
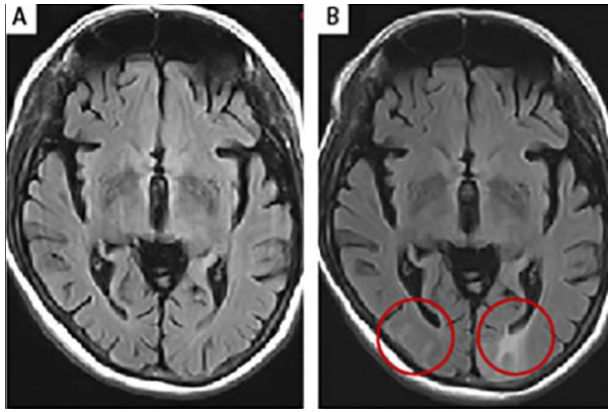
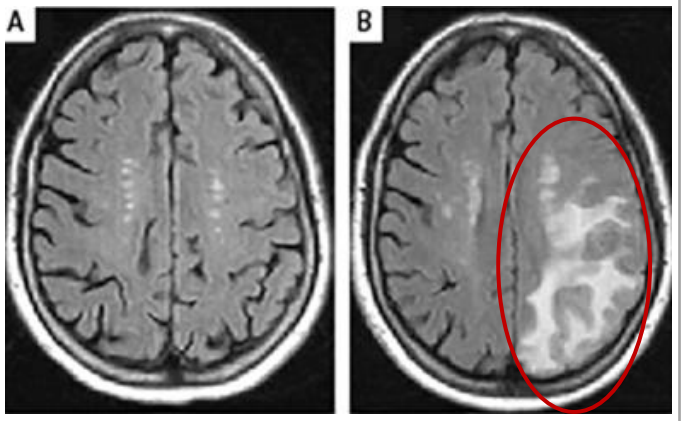
Grading Scale for Determining Radiographic Severity of ARIA-E

	Mild	Moderate	Severe
ARIA-E[1] Sulcal and/or cortical/ subcortical FLAIR hyperintensity	1 location <5 cm  Baseline Post-treatment	1 location 5–10 cm OR >1 location each <10 cm  Baseline Post-treatment	1 or more location >10 cm  Baseline Post-treatment

Figures from Barakos et al (2022).[2]

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

1. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35; 2. Barakos J, et al. J Prev Alzheimers Dis. 2022;9(2):211–220.

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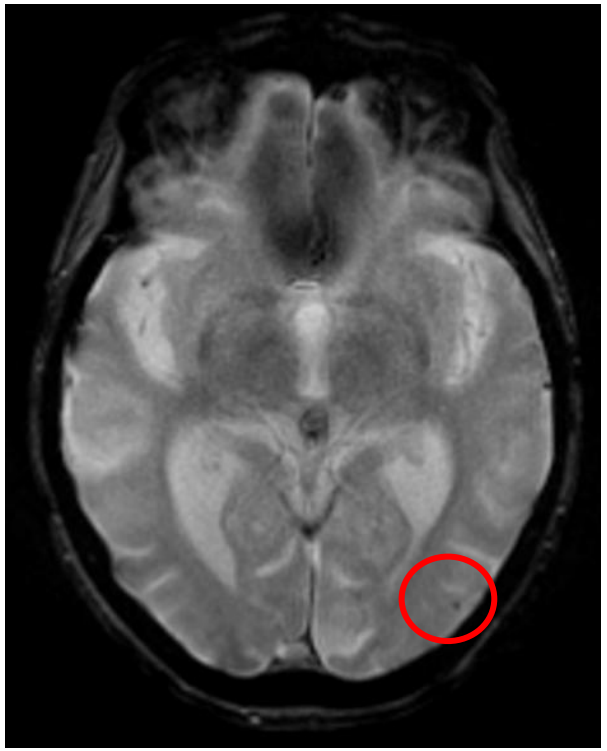
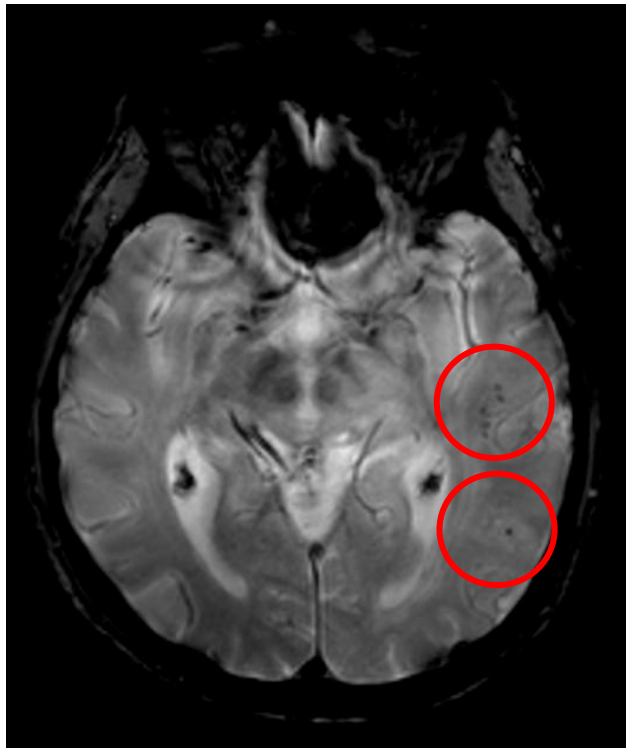
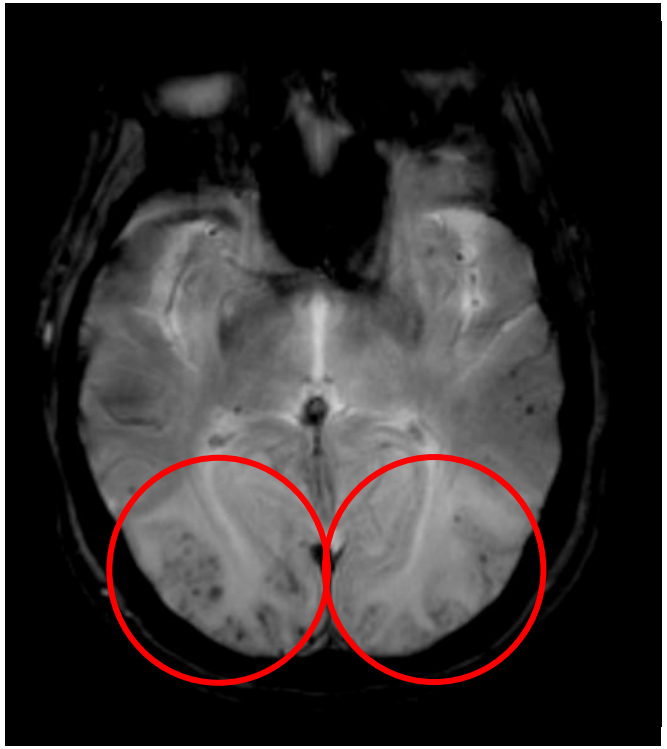
Grading Scale for Determining Radiographic Severity of ARIA-H: Microhemorrhages

T2* GRE	Mild	Moderate	Severe
ARIA-H Number of new microhemorrhages	≤4	5–9	≥10







MRI images: data on file.

ARIA, amyloid-related imaging abnormalities; ARIA-H, ARIA-hemosiderin/hemorrhage; GRE, gradient-recalled echo: MRI, magnetic resonance imaging.

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

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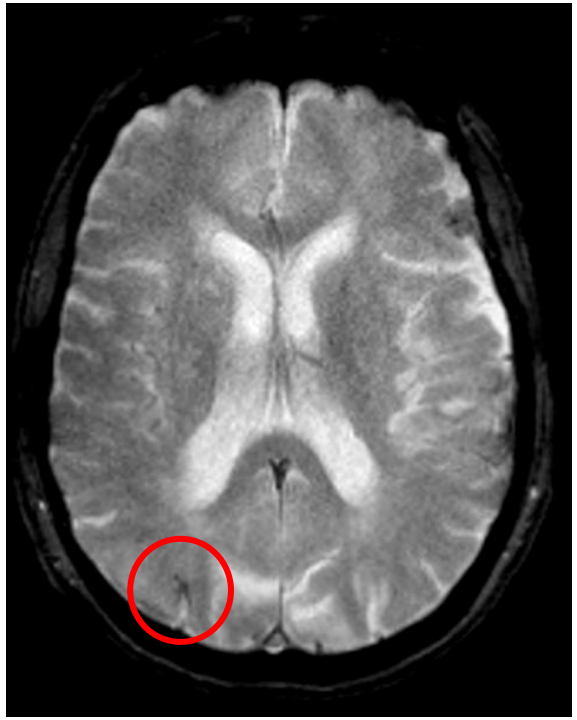
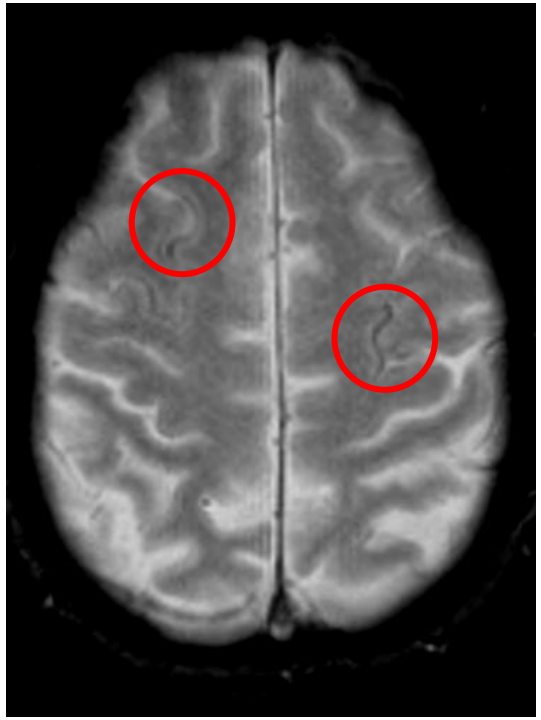
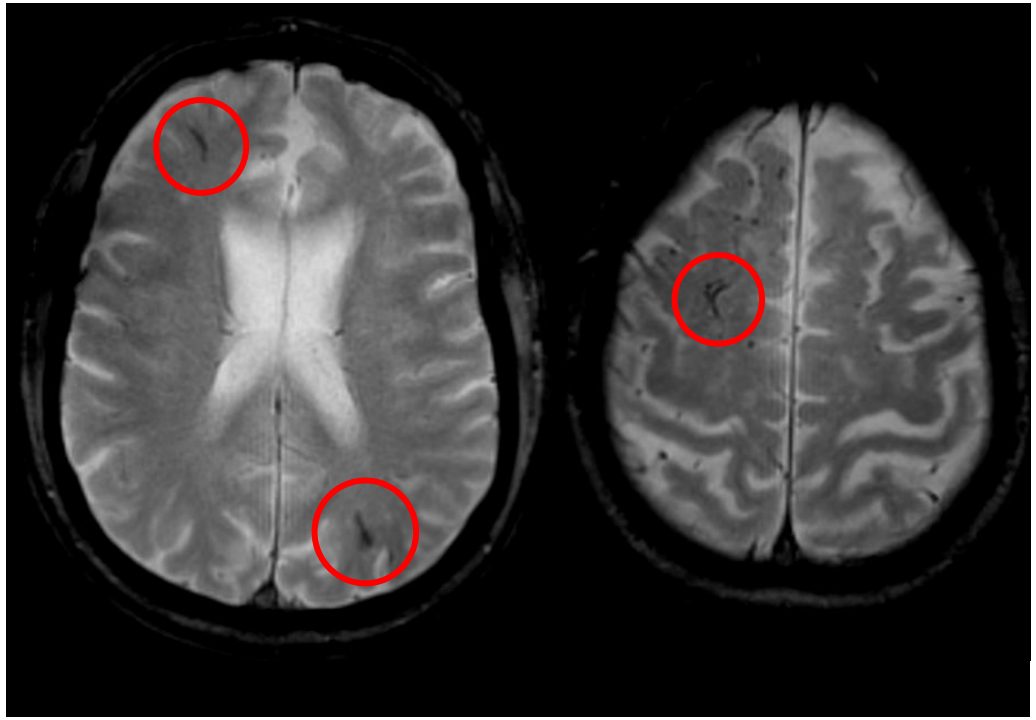
Grading Scale for Determining Radiographic Severity of ARIA-H: Superficial Siderosis

T2* GRE	Mild	Moderate	Severe
ARIA-H Superficial siderosis	1 focal area	2 focal areas	>2 focal areas







MRI images: data on file.

ARIA, amyloid-related imaging abnormalities; ARIA-H, ARIA-hemosiderin/hemorrhage; GRE, gradient-recalled echo; MRI, magnetic resonance imaging.

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

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Management of ARIA

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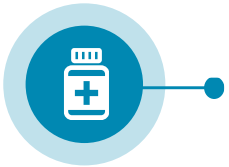
Management of ARIA (1/2)



The prescribing information of monoclonal antibodies that remove amyloid should be followed for ARIA monitoring and management guidelines

ARIA and associated symptoms should be discussed with patients and care partners before treatment initiation, including the importance of MRI monitoring and seeking urgent evaluation in the case of ARIA clinical symptoms[1]

MRI should be used to assess for ARIA symptoms where possible; CT scans can be deficient for detecting radiographic findings, particularly ARIA-H, owing to its relatively low spatial definition and resolution vs MRI[2]

ARIA, amyloid-related imaging abnormalities; ARIA-H, ARIA-hemosiderin/hemorrhage; CT, computed tomography; MRI, magnetic resonance imaging.

1. Cummings J, et al. J Prev Alzheimers Dis. 2022;9(2):221–230; 2. Barakos J, et al. J Prev Alzheimers Dis. 2022;9(2):211–220.

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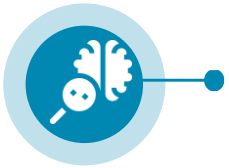
Management of ARIA (2/2)

ARIA are most frequently detected on routine surveillance MRIs in patients who are clinically asymptomatic, highlighting the need for monitoring early in the course of therapy[1]

In cases of severe or serious ARIA-E or ARIA-H, the neurologic status should be monitored closely, the prescribing information of monoclonal antibodies should be followed for recommendations on treatment interruptions, and, if deemed clinically appropriate, high-dose corticosteroids could be considered[2]



In those with neurologic symptoms, appropriate imaging is needed to support differential diagnosis and management[2]

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; MRI, magnetic resonance imaging.

1. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35; 2. Cummings J, et al. J Prev Alzheimers Dis. 2022;9(2):221–230.

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To access a growing repository of educational resources on ARIA, please scan the QR code or access the platform by the following link: www.understandingARIA.com

This information is intended for healthcare professionals only.

ARIA, amyloid-related imaging abnormalities.

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