Cerebral Amyloid Angiopathy (CAA) and Amyloid-Related Imaging Abnormalities (ARIA)

This content is intended for healthcare professionals only for educational and informational purposes and does not substitute for sound medical judgment or clinical decision-making in the context of medical treatment

Eisai hhc human health care

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Contents

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

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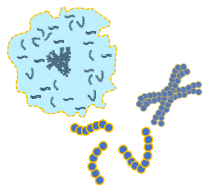
Introducing CAA

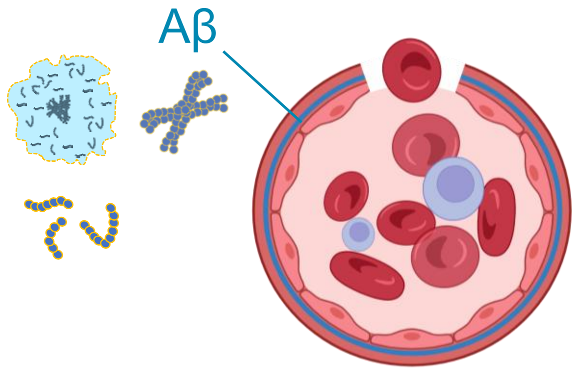
Alzheimer's Disease (AD) and Cerebral Amyloid Angiopathy (CAA) Have Overlapping Pathologies

Deposition of Aβ



CAA

Deposition of Aβ in **blood vessels** results in CAA, which leads to gradual vessel stiffening and vessel wall fragility, causing hemorrhagic or ischemic brain injury

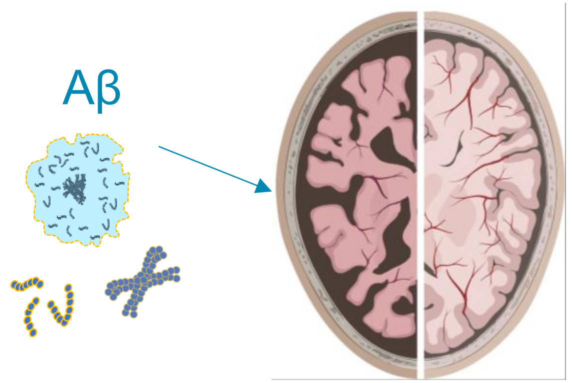


CAA and AD have overlapping pathologies

CAA might contribute to the pathogenesis of AD by affecting perivascular drainage, a major route of Aβ clearance from the brain

AD

In AD, deposition of Aβ in the **brain parenchyma** triggers downstream processes, which mediate loss of neurons



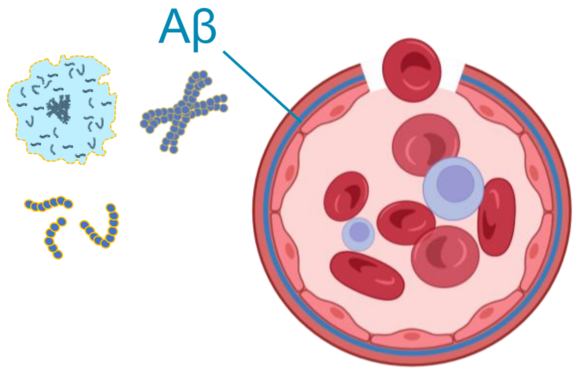
Red blood cell | Lymphocyte | Aβ species (plaque, fibril, oligomer)

Aβ, amyloid beta; AD, Alzheimer's disease; CAA, cerebral amyloid angiopathy.
Hampel H, et al. Brain 2023;146(11):4414–4424.

Alzheimer's Disease (AD) and Cerebral Amyloid Angiopathy (CAA) Have Overlapping Pathologies

CAA

Deposition of Aβ in **blood vessels** results in CAA, which leads to gradual vessel stiffening and vessel wall fragility, causing hemorrhagic or ischemic brain injury[1]



CAA is an age-related cerebrovascular disorder characterized by the accumulation of Aβ within the leptomeninges and within small- and medium-sized cerebral blood vessels[2]

Pathological CAA refers to the underlying disease pathology. **Clinical CAA** refers to CAA with observable clinical symptoms in different stages and underlying MRI findings[3,4]

Aβ, amyloid beta; AD, Alzheimer's disease; CAA, cerebral amyloid angiopathy.

1. Hampel H, et al. Brain 2023;146(11):4414–4424; 2. Kuhn J, Sharman T. Cerebral amyloid angiopathy. 2022 Jun 6. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan; 3. Koemans EA, et al. Lancet Neurol. 2023;22(7):632–642; 4. Charidimou A, et al. Lancet Neurol. 2022;21(8):714–725.

Red blood cell
Lymphocyte
Aβ species (plaque, fibril, oligomer)

What Is the Estimated Prevalence of CAA Pathology?

Prevalence in Cognitively Normal Elderly Individuals[1]

~30%

Prevalence in Patients With AD[2]

CAA is almost ubiquitous in AD neuropathology[2]

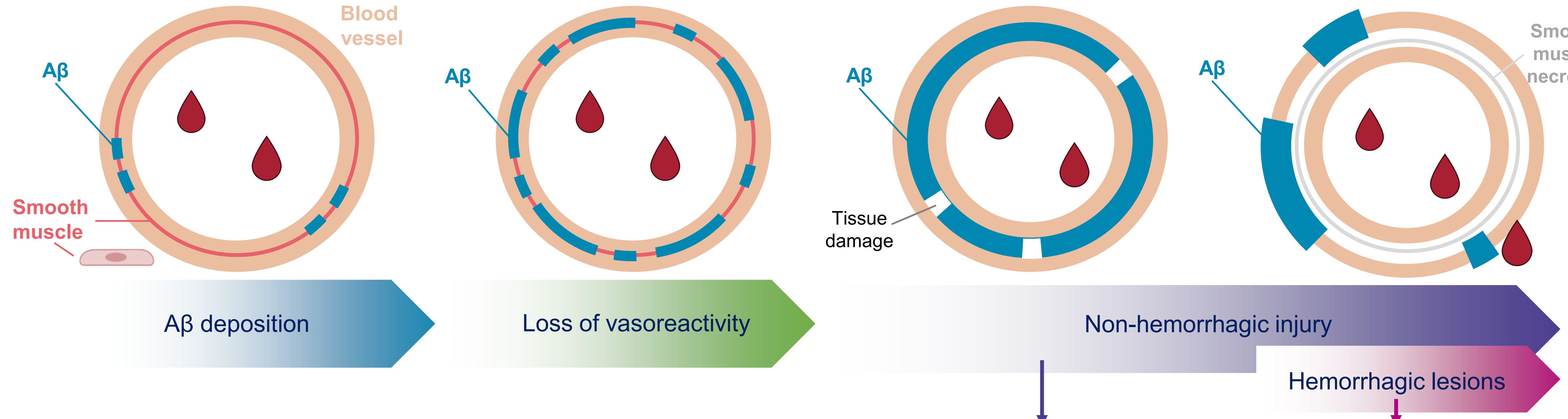
Sporadic CAA is uncommon in people <60 years and very rare in those <50 years[3]

AD, Alzheimer's disease; CAA, cerebral amyloid angiopathy.

1. Jäkel L, et al. Alzheimers Dement. 2022;18(1):10–28; 2. Thomas DX, et al, Sci Rep. 2020;10(1):14579; 3. Kuhn J, Sharman T. Cerebral amyloid angiopathy. 2022 Jun 6. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan.

CAA Pathological Changes Occur Decades Before Clinical Symptoms Appear

Years before first hemorrhagic lesion:	Stage 1	Stage 2 (mild CAA)	Stage 3 (moderate CAA)	Stage 4 (severe CAA)
	~30 years	~20 years	~10–15 years	0 years



Cognitive impairment
Lobar lacunes, microinfarcts, white matter hyperintensities, visible PVS in the centrum semiovale

Intracerebral hemorrhage, **cerebral microbleeds**, cortical **superficial siderosis** or **convexity subarachnoid hemorrhage**, and *transient focal neurological episodes*

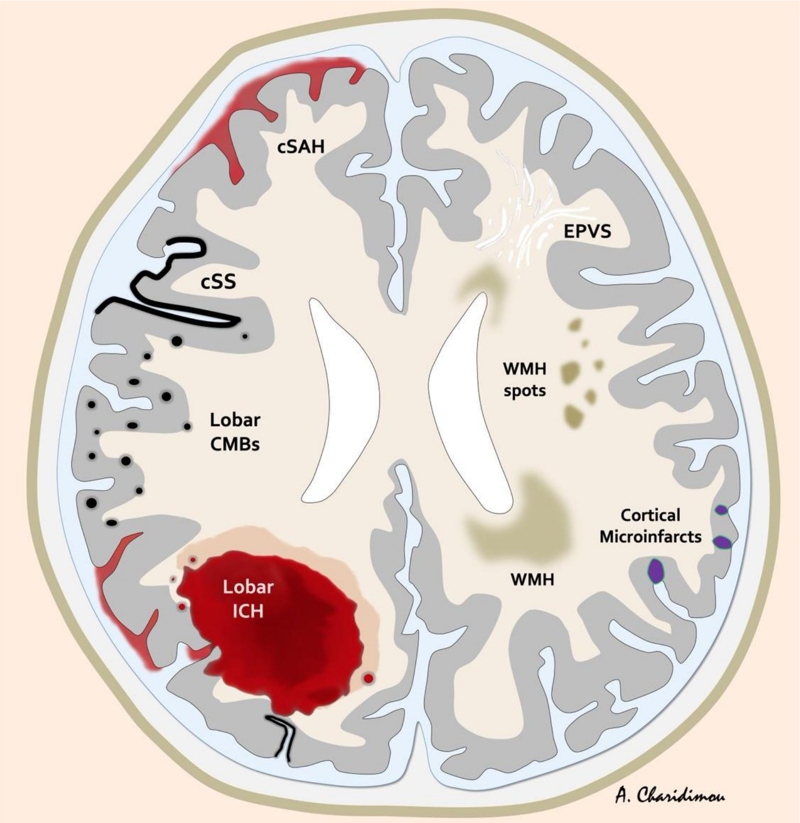
Figure adapted with permission from: Koemans EA, et al. Lancet Neurol 2023;22(7):632–642.
Aβ, amyloid beta; CAA, cerebral amyloid angiopathy; PVS, perivascular space.

Koemans EA, et al. Lancet Neurol. 2023;22(7):632–642.

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



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

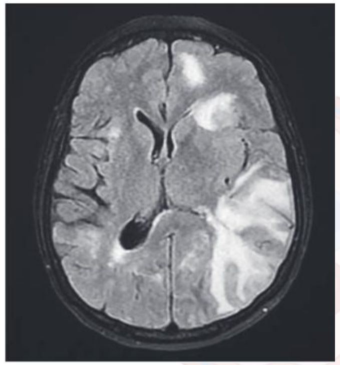
Aβ, amyloid beta; CAA, cerebral amyloid angiopathy; CMB, cerebral microbleed; cSAH, convexity subarachnoid hemorrhage; cSS, cortical superficial siderosis; EPVS, enlarged perivascular spaces; ICH, intracerebral hemorrhage; MRI, magnetic resonance imaging; WMH, white matter hyperintensities.

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

Inflammatory CAA is a rare complication of CAA

Inflammatory CAA

- CAA-related inflammation (CAA-ri)
- Aβ-related angiitis (ABRA)



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

- Inflammatory CAA is a rare complication of CAA, thought to be driven by a spontaneous autoimmune response to the deposited Aβ in the vasculature[1–3]
- There are two subtypes of inflammatory CAA, with shared clinical and radiographical presentation that can occur together, but with characteristic neuropathology:[1]
  - **CAA-related inflammation (CAA-ri):** Perivascular inflammatory response to Aβ in blood vessels
  - **Aβ-related angiitis (ABRA):** Transmural inflammation with vasculitis in response to Aβ in blood vessels
- It is a potentially reversible condition responsive to immunosuppressive therapies[1,4]

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

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

The Link Between CAA and ARIA

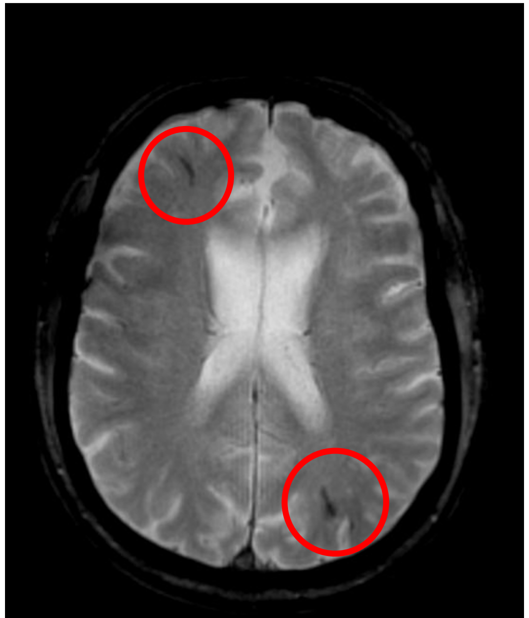
What Is ARIA?

- Amyloid-related imaging abnormalities (**ARIA**) were first reported in 2009 in clinical trials of monoclonal antibodies that remove amyloid[1,2]
- ARIA imaging findings can occur with or without clinical manifestations[3]
- There is an increased risk of ARIA with monoclonal antibodies that remove amyloid. ARIA can occur spontaneously, in AD or CAA, in the absence of monoclonal antibodies that remove amyloid[4a]

ARIA-Edema/Effusion (ARIA-E)

Eisai internal MRI images.

ARIA-Hemosiderin/Hemorrhage (ARIA-H)



Eisai internal MRI images.

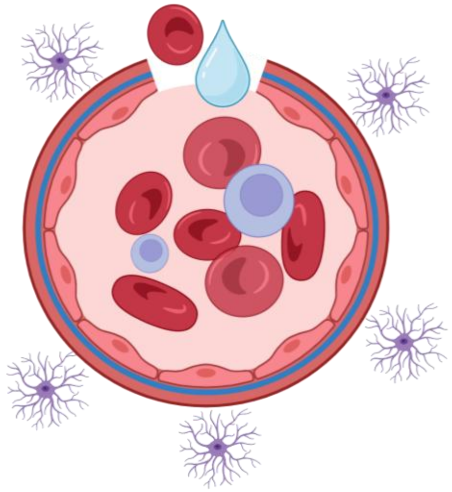
[a] The FDA and the Alzheimer's Association Research Roundtable Workgroup defining publication recognizes that ARIA can occur spontaneously as part of the natural history of AD or CAA in the absence of anti-amyloid treatments.[4,5] Cogswell et al.[6] define ARIA as occurring only in the setting of monoclonal antibodies that remove amyloid.

AD, Alzheimer's disease; ARIA, amyloid-related imaging abnormalities; ARIA-E, amyloid-related imaging abnormalities-edema/effusion; ARIA-H, amyloid-related imaging abnormalities-hemosiderin/hemorrhage; CAA, cerebral amyloid angiography; FDA, US Food and Drug Administration; MRI, magnetic resonance imaging.

1. Salloway S, et al. Neurology 2009;73(24):2061–2070; 2. Black RS, et al. Alzheimer Dis Assoc Disord. 2010;24(2):198–203; 3. Filippi M, et al. JAMA Neurol. 2022;79(3):291–304; 4. Sperling RA, et al. Alzheimers Dement. 2011;7(4):367–385; 5. US Food and Drug Administration. Eisai Inc. Briefing Document. Published Jun 9, 2023. https://www.fda.gov/media/169264/download (Accessed July 2025); 6 Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35.

What Is the Connection Between ARIA and CAA in the Setting of Monoclonal Antibodies That Remove Amyloid?

CAA

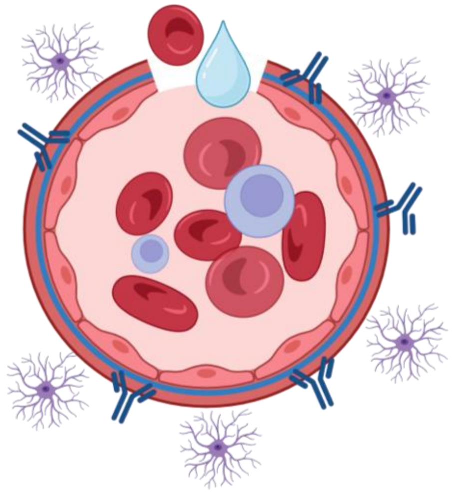


Initiation of monoclonal antibodies that remove amyloid

Mobilization of amyloid in cerebral blood vessel walls (**CAA**) as a result of microglial phagocytosis of amyloid in the perivascular spaces

Transient increased permeability to fluid (vasogenic edema, **ARIA-E**) or blood products (**ARIA-H**)

ARIA



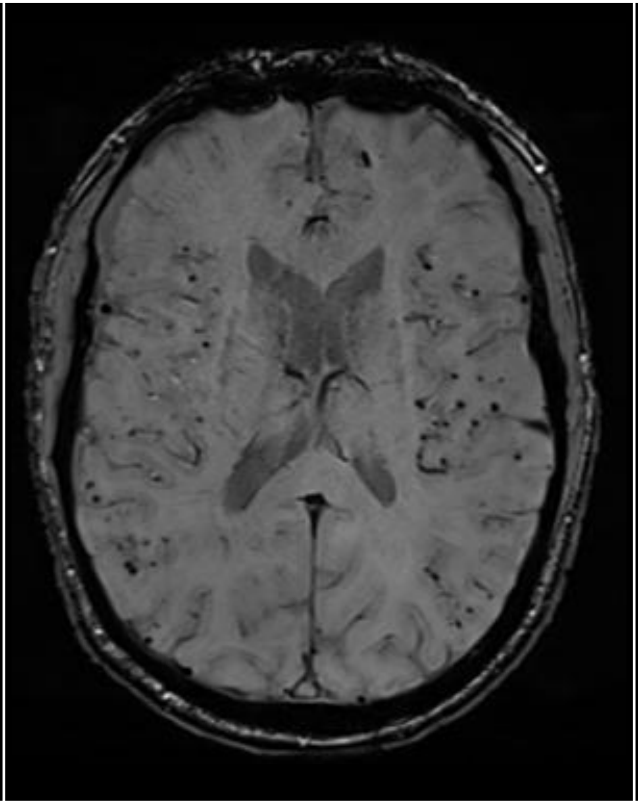
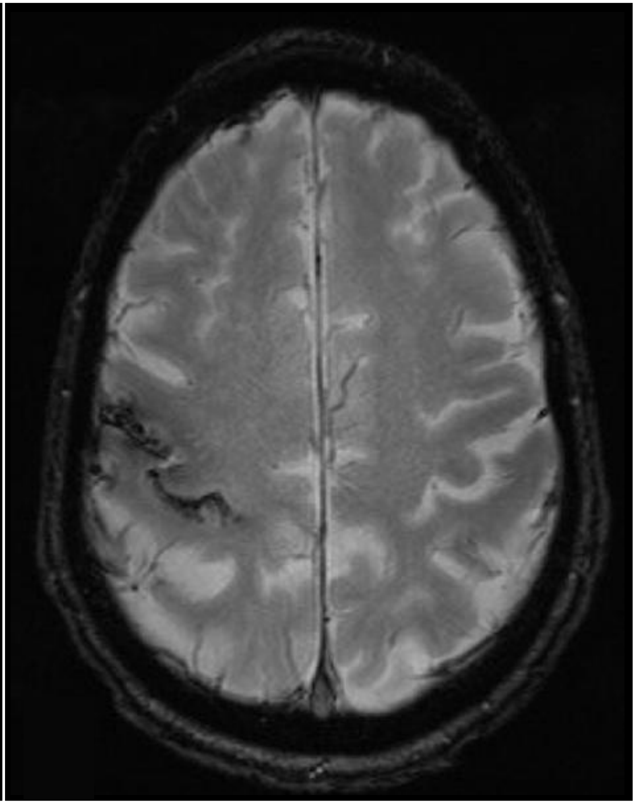
ARIA is a consequence of the mobilization of amyloid in cerebral blood vessel walls (CAA)

Aβ, amyloid beta; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; CAA, cerebral amyloid angiopathy.

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

MRI Findings of CAA and ARIA

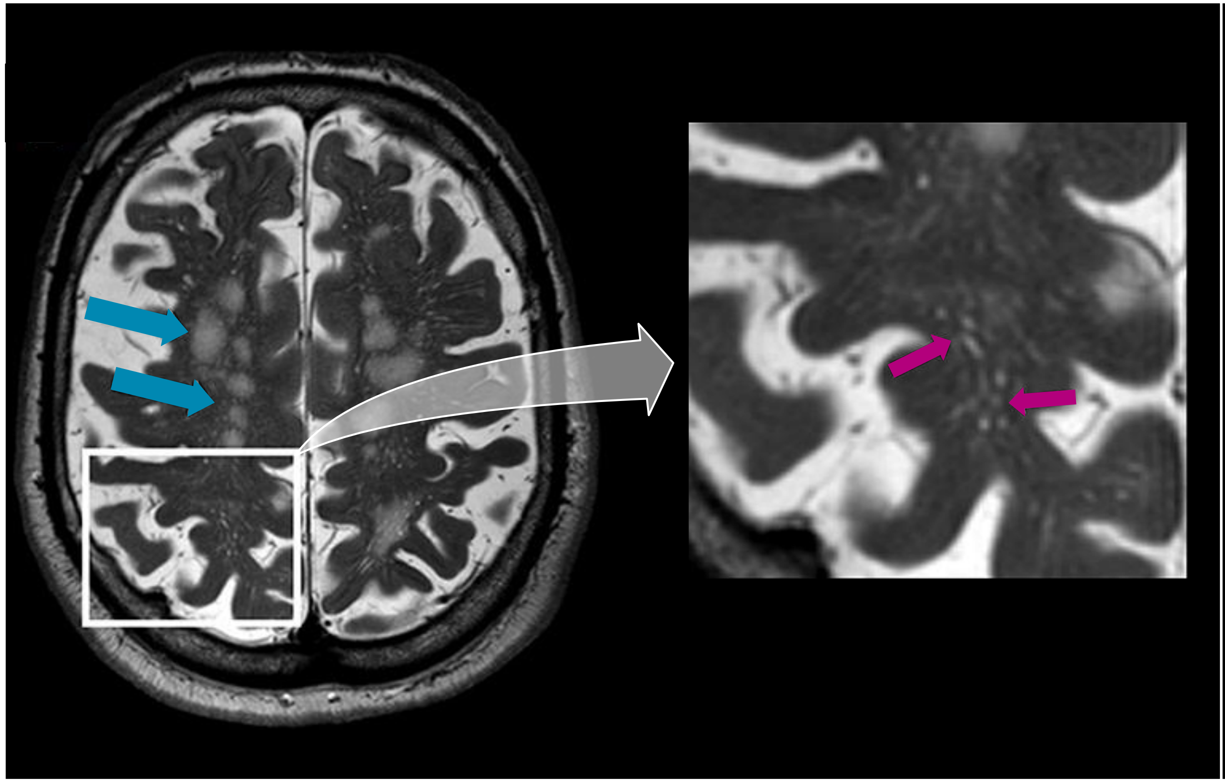
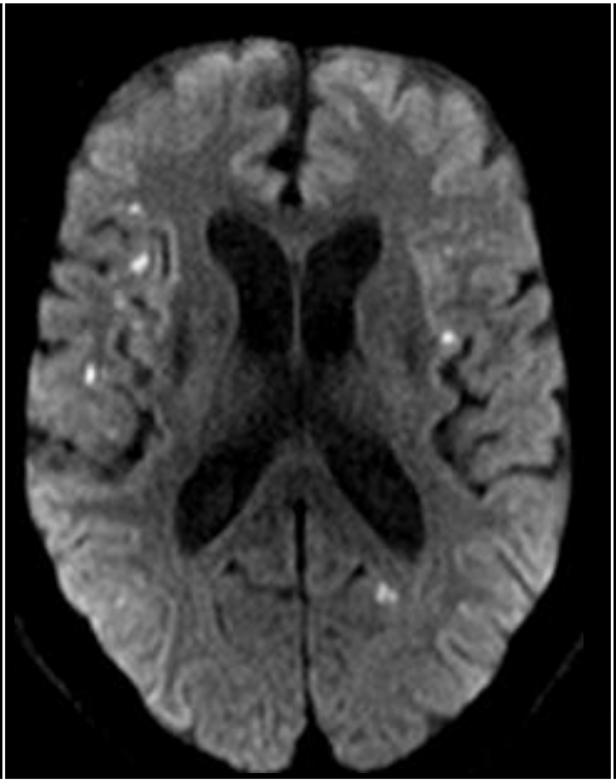
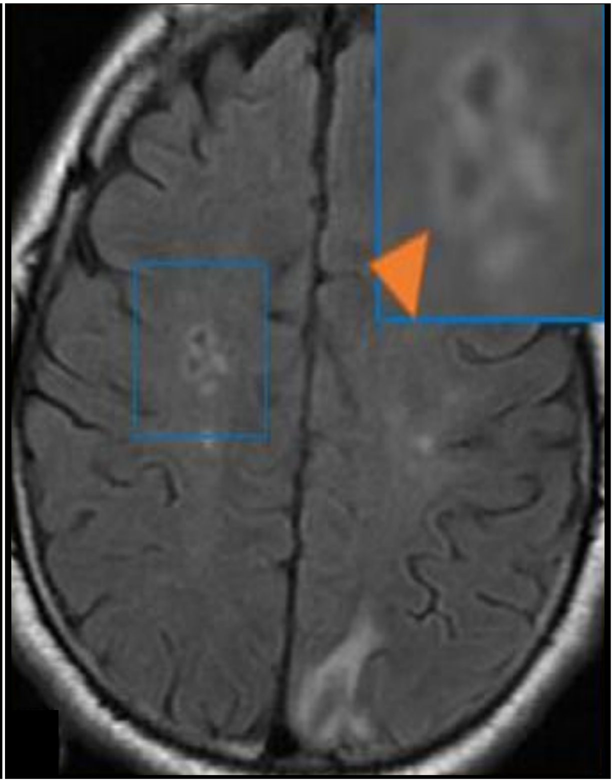
MRI Can Identify **Hemorrhagic** Lesions Associated With CAA

Lobar ICH[1] *Non-Contrast CT Scan*	**Cerebral Microhemorrhages**[2] *Susceptibility-Weighted MRI*	**Superficial Siderosis**[3] *T2* GRE*
		

CAA, cerebral amyloid angiopathy; CT, computerized tomography; GRE, gradient recalled echo; ICH, intracerebral hemorrhage; MRI, magnetic resonance imaging.

1. Case courtesy of Mark Rodrigues, Radiopaedia.org, rID: 58532. 2018. https://radiopaedia.org/cases/lobar-intracerebral-haemorrhage-4?embed_domain=staging.radpair.com&lang=us (Accessed March 2025); 2. Case courtesy of Frank Gaillard, Radiopaedia.org, rID: 46082. 2016. https://radiopaedia.org/cases/cerebral-amyloid-angiopathy-12?lang=gb (Accessed March 2025); 3. Image used with permission from Andersen NH, et al. BMC Neurol. 2023;23(1):252. (CC-BY 4.0: http://creativecommons.org/licenses/by/4.0/).

MRI Can Identify **Non-Hemorrhagic** Lesions Associated With CAA

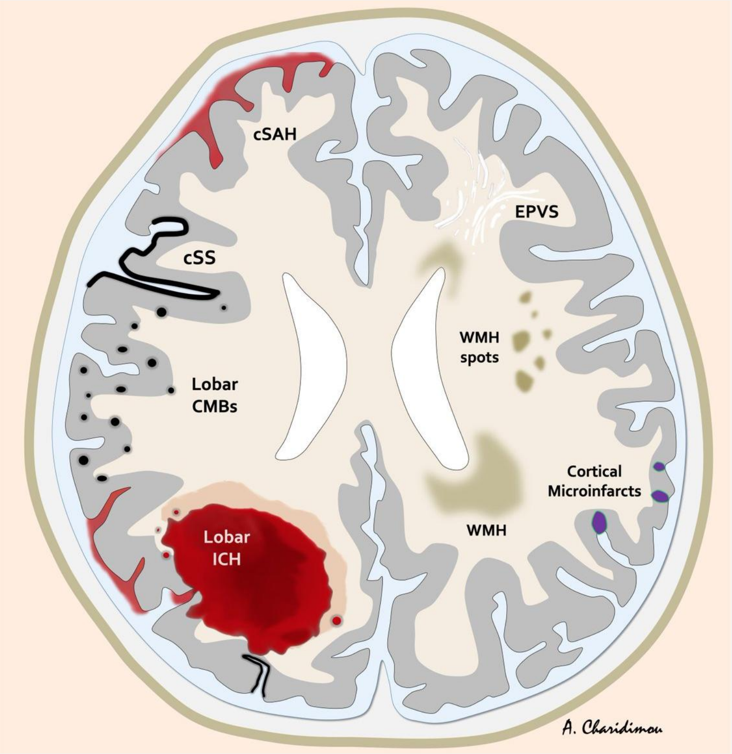
White Matter Hyperintensities (Blue Arrows) and Enlarged Perivascular Spaces (Pink Arrows)[1] *T2-Weighted Axial MRI*	**Cerebral Microinfarct[2]** *Diffusion-Weighted MRI*	**Lobar Lacunes[3]** *T2-Weighted FLAIR MRI*
		

CAA, cerebral amyloid angiopathy; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

1. Image adapted from Huhndorf M, et al. Front Neurol. 2023;14:1146737. (CC-BY-4.0: https://creativecommons.org/licenses/by/4.0/); 2. Case courtesy of Francis Deng, Radiopaedia.org, rID: 167371. 2023. https://radiopaedia.org/cases/amyloid-beta-related-angiitis?embed_domain=external.radpair.comfavicon.icofavicon.ico&lang=us (Accessed: March 2025); 3. Image used with permission from Das AS, et al. Stroke Vasc Neurol. 2023;8(1):26–33. (CC-BY-NC 4.0: http://creativecommons.org/licenses/by-nc/4.0/).

Clinical CAA Is Diagnosed Based on Clinical Presentation and MRI Features

Boston Criteria 2.0 for Probable CAA Diagnosis (in Persons ≥50 Years)



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

Clinical Presentation

Spontaneous ICH, transient focal neurological episodes, cognitive impairment, or dementia (does not imply CAA as a cause/contributor)

MRI Features Presentation

- ≥2 lobar hemorrhagic lesions on T2* sequences: cerebral microbleeds, cerebral superficial siderosis, intracerebral hemorrhage, or convexity subarachnoid hemorrhage

OR

- One lobar hemorrhagic lesion plus 1 white matter feature (severe perivascular spaces in the centrum semiovale or white matter hyperintensities in a multispot pattern)

Absence of:

- Any deep hemorrhagic lesions (ie, intracerebral hemorrhage or cerebral microbleeds)
- Other cause of hemorrhagic lesions
- Cerebellar hemorrhages

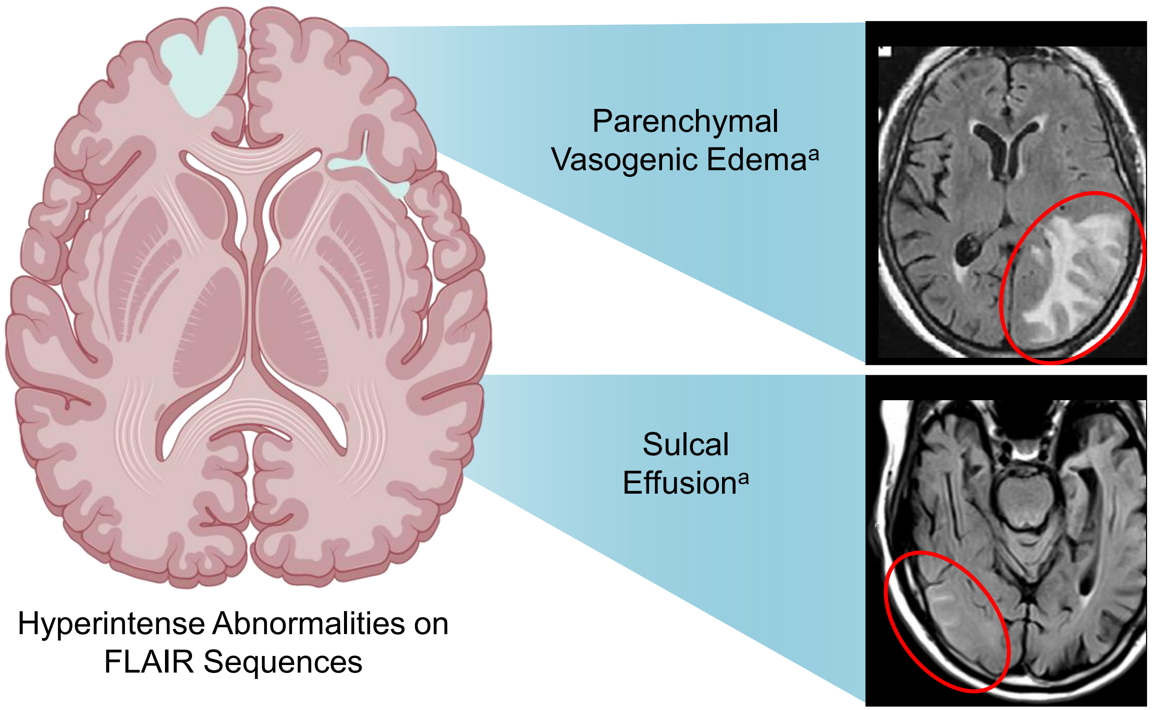
Definitive diagnosis remains reliant on post-mortem examination

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.

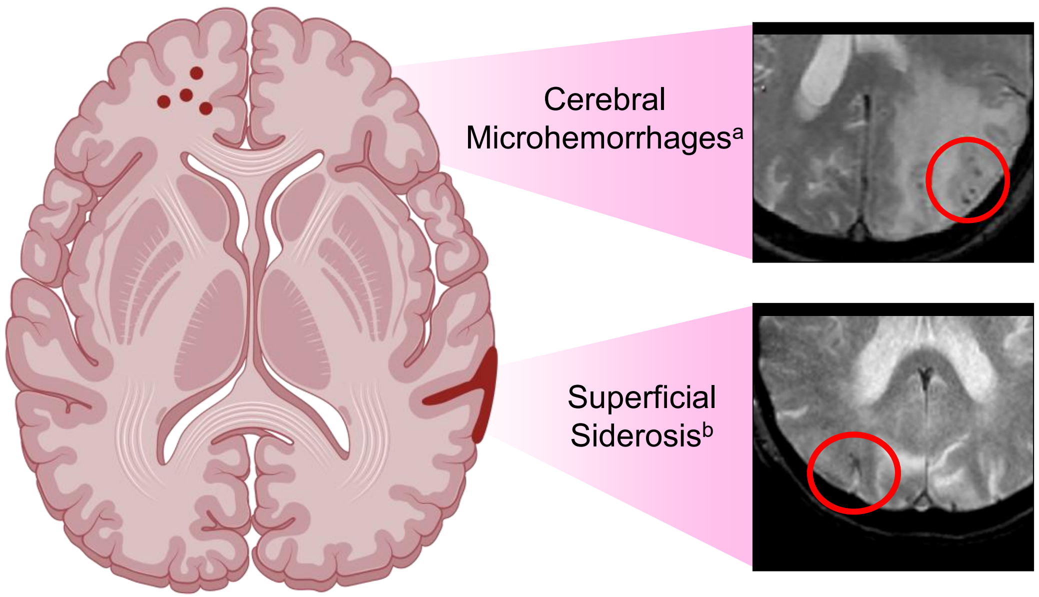
There Are 2 Subtypes of ARIA: ARIA-E and ARIA-H

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.

[a] MRI images reproduced from Barakos J, et al. 2022[1] (CC BY 4.0 http://creativecommons.org/licenses/by/4.0/); [b] MRI image data on file.

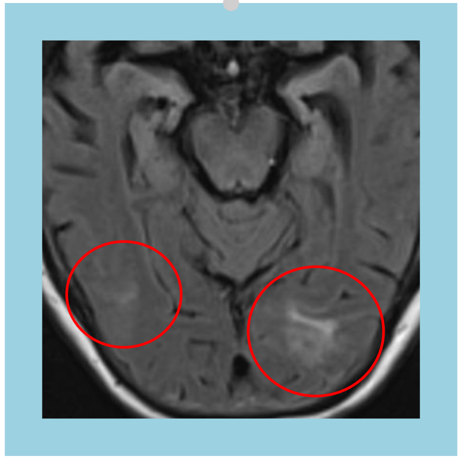
ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H: ARIA-hemosiderin/hemorrhage; FLAIR, fluid-attenuated inversion recovery; GRE, gradient recalled echo; MRI, magnetic resonance imaging.

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.

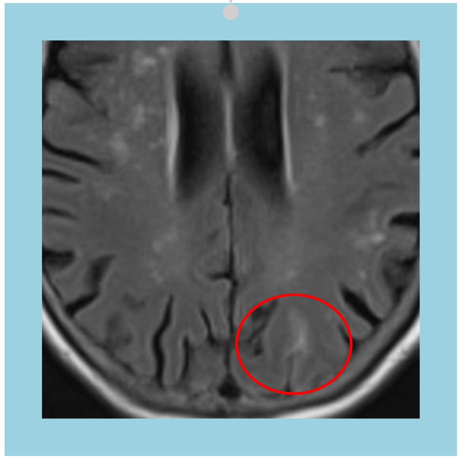
ARIA Is Diagnosed Based on MRI Findings

In most cases, ARIA is asymptomatic. Surveillance MRIs can be used to monitor for ARIA in patients receiving monoclonal antibodies that remove amyloid. Detection of ARIA requires acquisition of specific MRI sequences and familiarity with the imaging abnormalities[1]

ARIA-E is identified on T2-FLAIR sequences as:

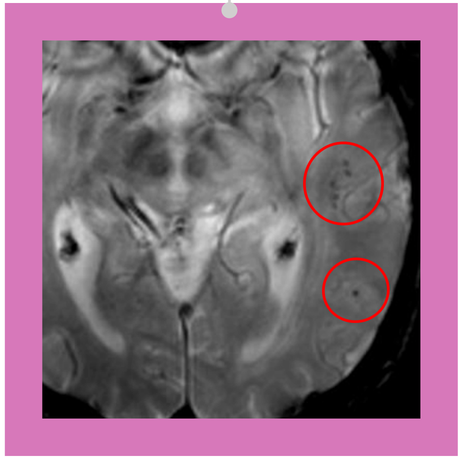


Parenchymal signal abnormalities (ARIA-E edema)

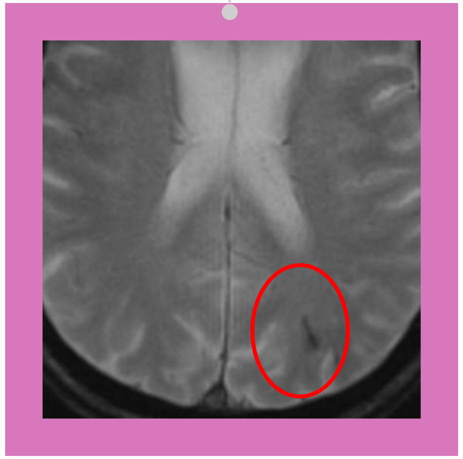


Sulcal FLAIR hyperintensities (ARIA-E effusion)

ARIA-H is identified on T2* GRE or SWI sequences as:



Microhemorrhages



Superficial siderosis

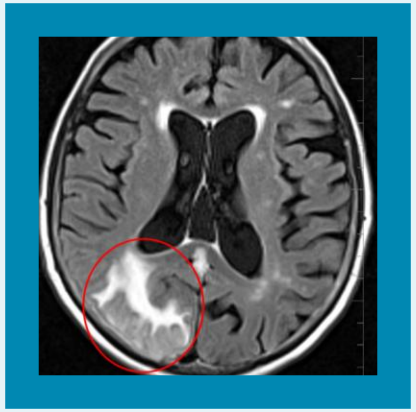
Eisai internal MRI images.

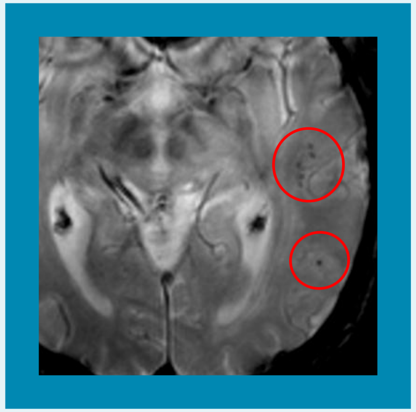
ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; FLAIR, fluid-attenuated inversion recovery; GRE, gradient recalled echo; MRI, magnetic resonance imaging; SWI, susceptibility-weighted imaging.

Filippi M, et al. JAMA Neurol. 2022;79(3):291–304.

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



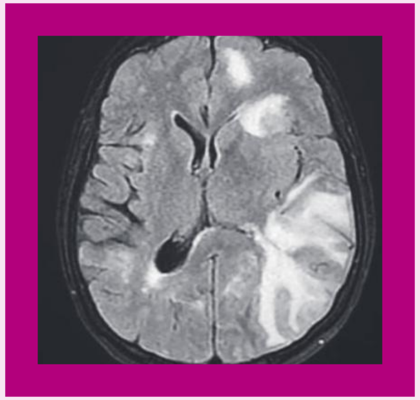


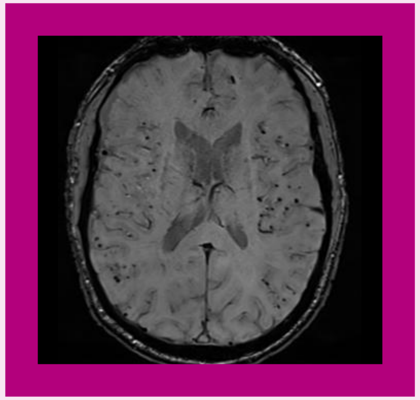
ARIA-E edema

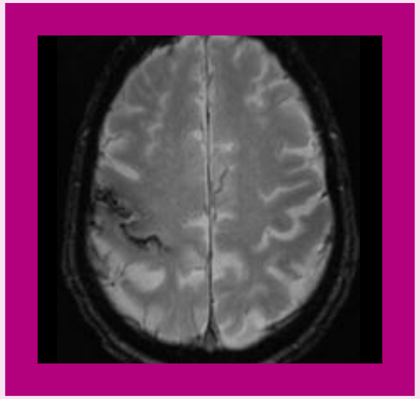
ARIA-H (microhemorrhages)

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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ARIA and CAA in the Setting of Monoclonal Antibodies That Remove Amyloid

There Are 3 Key Known Risk Factors for ARIA

Treatment with monoclonal antibodies that remove amyloid[1,2]

There is an increased risk of ARIA with monoclonal antibodies that remove amyloid[2]

APOE ε4 carrier status[1–3]

The presence of an APOE ε4 allele is a shared risk factor for both ARIA and CAA[3,4]

Pre-treatment microhemorrhages[2,3]

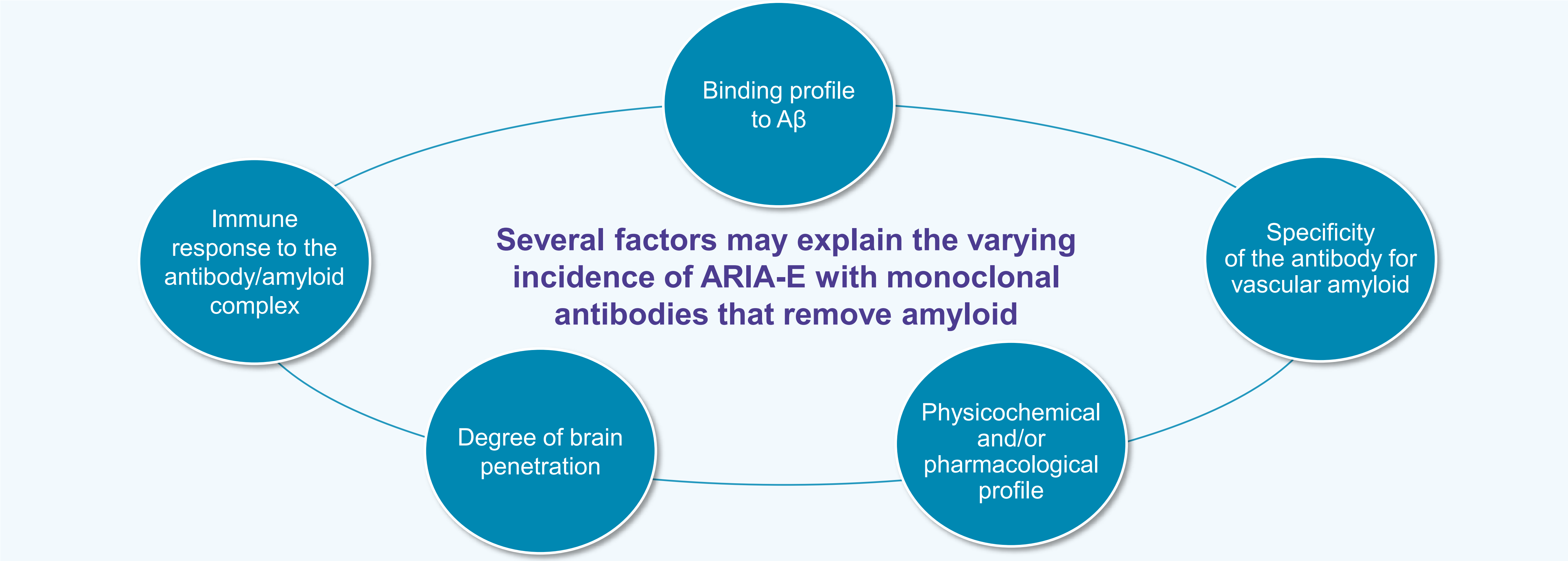
Pre-treatment microhemorrhages are a marker of CAA and a risk factor for ARIA[2]

APOE, apolipoprotein E; 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; 3. Filippi M, et al. JAMA Neurol. 2022;79(3):291–304; 4. Charidimou A, et al. Brain 2017;140(7):1829–1850.

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



Aβ, amyloid beta; APOE, apolipoprotein E; 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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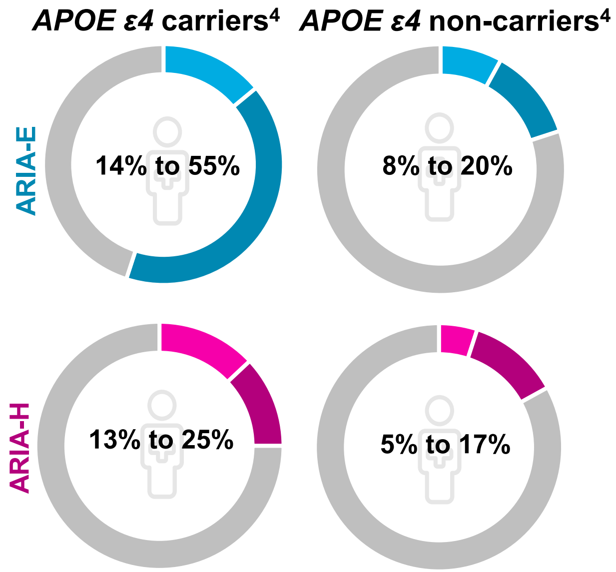
APOE ε4 Genotype Is a Risk Factor for Both CAA and ARIA

APOE ε4 is associated with **earlier and greater Aβ deposition** in plaques and vessels, and **impaired Aβ clearance** from the brain, resulting in higher perivascular accumulation of Aβ and subsequent CAA, **loss of blood-brain barrier integrity** and **increased cerebrovascular leakiness**, and **microglia-mediated neuroinflammation**[1–3]

The *APOE ε4* allele is a risk factor for CAA Type 1, and for CAA-related inflammation

The presence of 1 or more *APOE ε4* alleles is a risk factor for ARIA-E and ARIA-H

In trials of monoclonal antibodies that remove amyloid plaque in patients with AD:



Aβ, amyloid beta; AD, Alzheimer's disease; APOE, apolipoprotein E; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; CAA, cerebral amyloid angiopathy.

1. Greenberg SM, et al. Nat Rev Neurol. 2020;16(1):30–42; 2. Yamazaki Y, et al. Nat Rev Neurol. 2019;15(9):501–518; 3. Tai LM, et al. Acta Neuropathol. 2016;131(5):709–723; 4. Filippi M, et al. JAMA Neurology 2022;79(3):291–304.

Pre-Treatment Microhemorrhage(s) Are a Risk Factor for ARIA

Pre-treatment MRI findings of **hemosiderin deposition** (lobar microhemorrhages, intracerebral hemorrhage, and superficial siderosis) are:

- **Risk factors** predictive of ARIA[1,2]
- **Consistent with CAA**[1]
- Strongly correlated with the occurrence of ARIA **in *APOE ε4* carriers**[1]

Microhemorrhages (Red), Intracerebral Hemorrhage >10 mm (Blue) and Superficial Siderosis (Green)

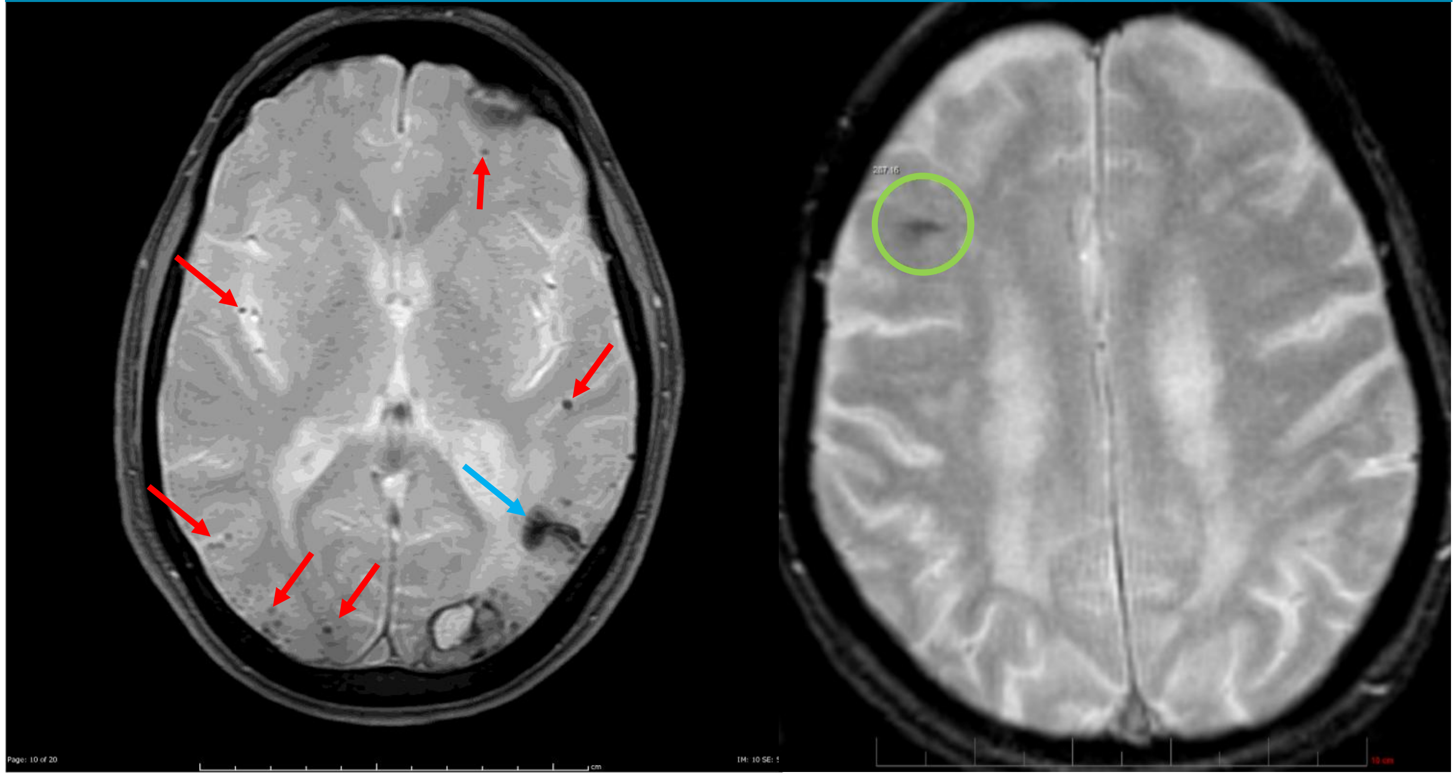


Image on the left: case courtesy of Frank Gaillard, Radiopaedia.org, rID: 4561 https://doi.org/10.53347/rID-4561 (Accessed March 2024); image on the right: data on file.

APOE, apolipoprotein E; 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.

MRI Markers of CAA Should Be Identified Prior to Initiating Monoclonal Antibodies That Remove Amyloid to Assess ARIA Risk

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

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

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

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Summary

Summary: CAA and ARIA

CAA is the accumulation of amyloid in cerebral blood vessel walls, leading to a weakened vasculature and thereby creating a risk for ICH[1]

CAA occurs sporadically in cognitively normal elderly individuals (estimated prevalence: ~30%) and is almost ubiquitous in AD[2]

Spontaneous ARIA or ARIA associated with monoclonal antibodies that remove amyloid are associated with CAA and share clinical, pathophysiological, and imaging features[3,4]

Aquiring a screening MRI for evidence of CAA (microhemorrhage, siderosis, prior ICH, or vasogenic edema) is essential to assess individual patient risk for ARIA prior to administration of monoclonal antibodies that remove amyloid[5]

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

1. Jäkel L, et al. Alzheimers Dement. 2022;18(1):10–28; 2. Thomas DX, et al. Sci Rep. 2020;10(1):14579; 3. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35; 4. Roytman M, et al. AJR Am J Roentgenol. 2023;220(4):562–574;
5. Cummings J, et al. J Prev Alzheimers Dis. 2023;10(3):362–377.

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.