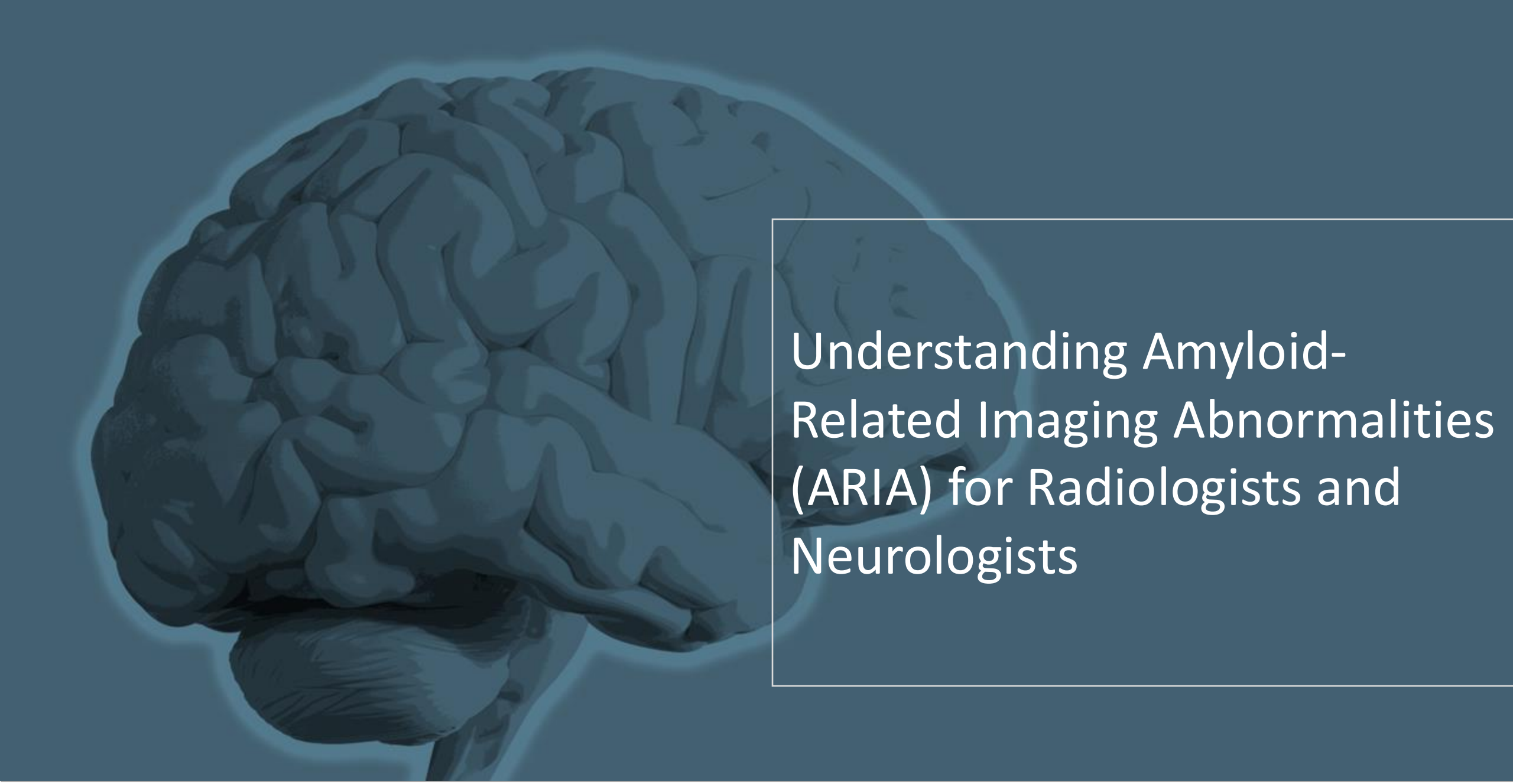
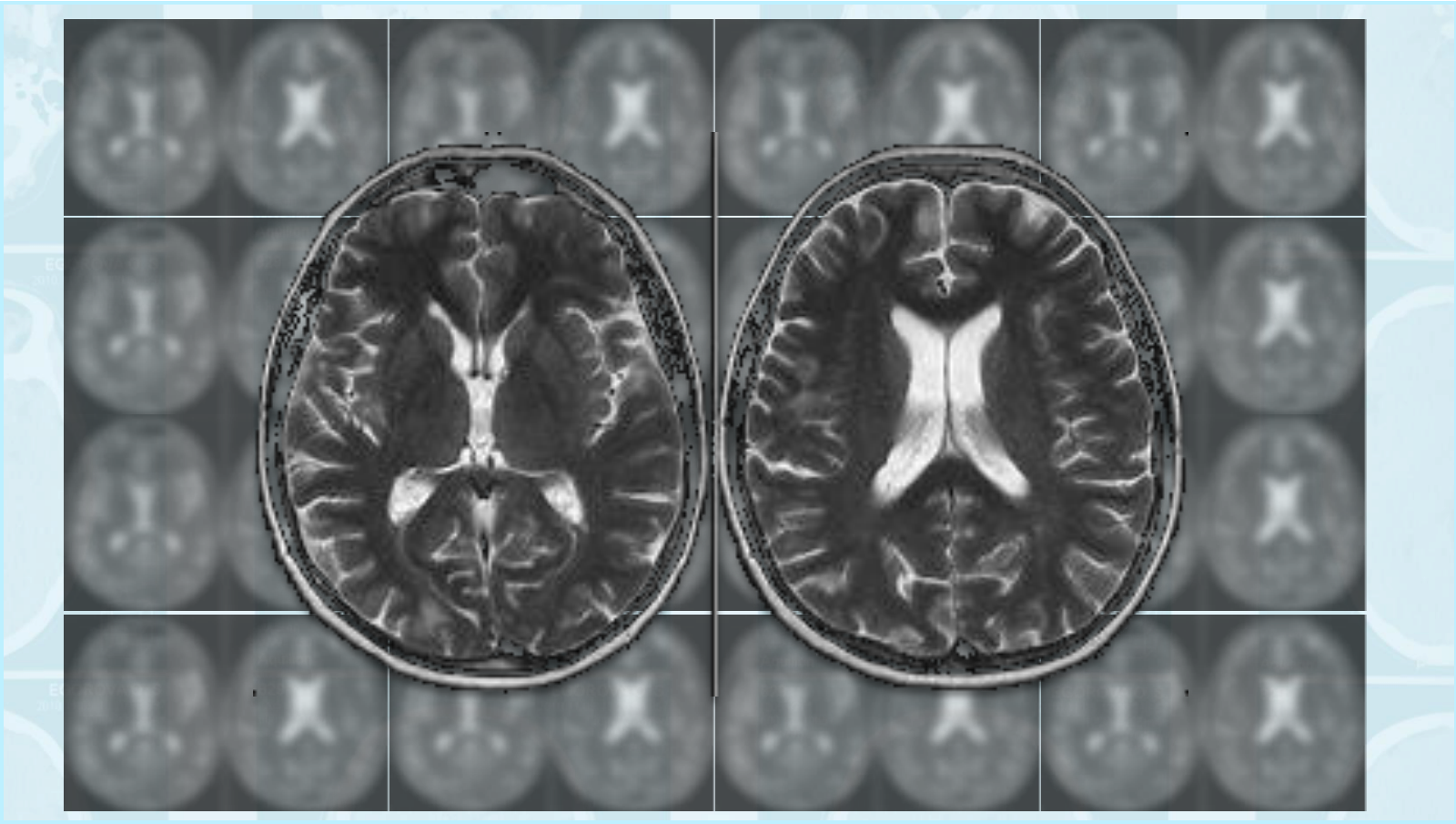


Understanding Amyloid-Related Imaging Abnormalities (ARIA) for Radiologists and Neurologists

Eisai hhc human health care

Outline



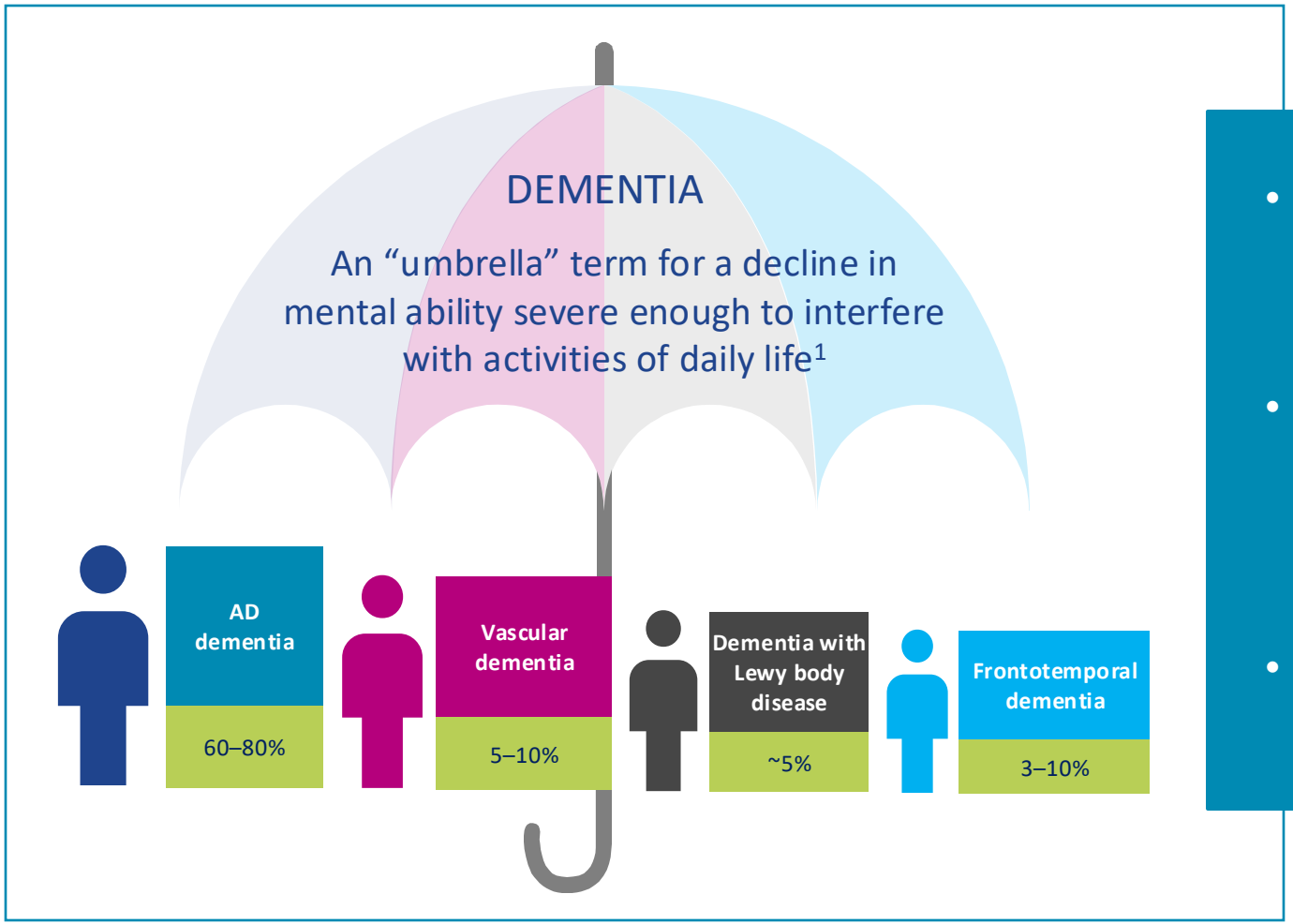
- Introducing ARIA
- Pathophysiology
- Deeper focus on ARIA
- Clinical manifestation of ARIA
- Diagnosis of ARIA
- Management of ARIA

ARIA, amyloid-related imaging abnormalities

Introducing ARIA

ARIA, amyloid-related imaging abnormalities

Introduction to Alzheimer's disease

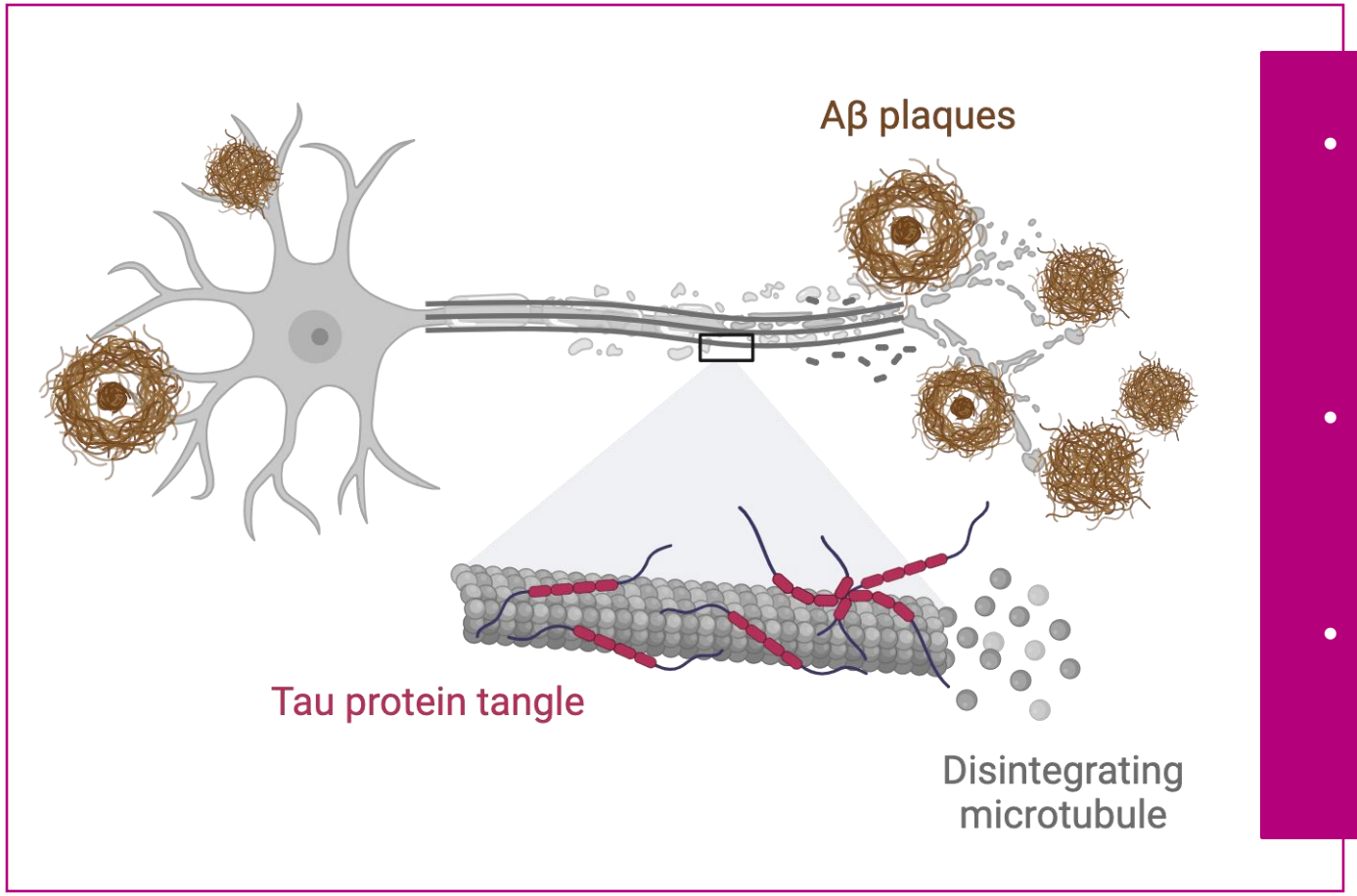


- Dementia is a **clinical syndrome**—a group of symptoms—that has several causes.[1]
- **AD** is a neurodegenerative disease **defined by Aβ and tau pathologies** that results in dementia.[2,3]
- **AD is the most common cause of dementia.**[1]

Aβ, amyloid beta; AD, Alzheimer's disease

1. Alzheimer's Association. 2023 Alzheimer's disease facts and figures. Alzheimers Dement. 2023;19:1598–1695; 2. Hyman BT, et al. Alzheimers Dement. 2012;8:1–13; 3. Dubois B, et al. Lancet Neurol. 2021;20:484–496

The two pathological hallmarks of AD are amyloid plaques and neurofibrillary tangles



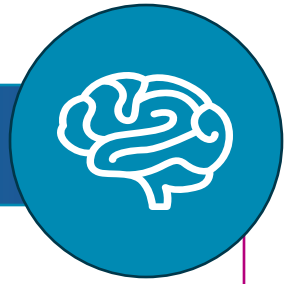
- **Amyloid-beta (Aβ) plaques accumulate at the earliest stage of disease and, along with tau neurofibrillary tangles, are a hallmark of AD.[1,2]**
- In addition to plaques and tangles, inflammation, synaptic degeneration, and irreversible neuronal loss occur.[1,2]
- Neurodegeneration and the level of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

Aβ, amyloid beta; AD, Alzheimer's disease

1. Serrano-Pozo A et al. *Cold Spring Harb Perspect Med*. 2011;1:a006189. 2. Jack CR et al. *Alzheimers Dement*. 2018;14:535–562. 3. Horie K et al. *Brain*. 2021;144:515–527.

Cerebral amyloid angiopathy (CAA) presentation and cerebral amyloid angiopathy-related inflammation (CAA-ri)

What is CAA?



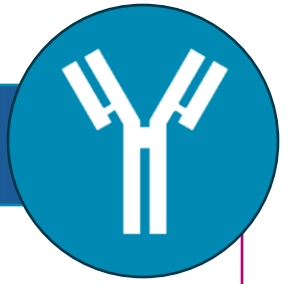
CAA is a type of cerebrovascular disorder characterized by the accumulation of Aβ peptide within the leptomeninges and small/medium-sized cerebral blood vessels in patients with or without AD symptoms.[1]

CAA shows some overlap with AD pathology and is prevalent in 80% of patients with AD.[2]

CAA presentation

Aβ deposition results in fragile vessels that may present with microhemorrhages, superficial hemosiderosis, or intracerebral hemorrhage (macrohemorrhage).[1]

CAA-ri



CAA-ri (inflammatory CAA) is a rare and potentially life-threatening autoimmune response to vascular amyloid in the setting of CAA.[3]

It can be treatment-reversible, responsive to immunosuppressive therapies.[4]

Aβ, amyloid beta; AD, Alzheimer's disease; CAA, cerebral amyloid angiopathy; CAA-ri, CAA-related inflammation

1. Kuhn J, Sharman T. Cerebral Amyloid Angiopathy. 2022 Jun 6. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan. 2. Kozberg MG et al. *Int J Stroke*. 2021;16(4):356–369. doi:10.1177/1747493020974464.
3. Grasso D et al. *Radiol Case Rep*. 2021 Sep:;16(9):2514–2521. 4. Antolini L et al. *Neurology*. 2021;97:e1809–e1822.

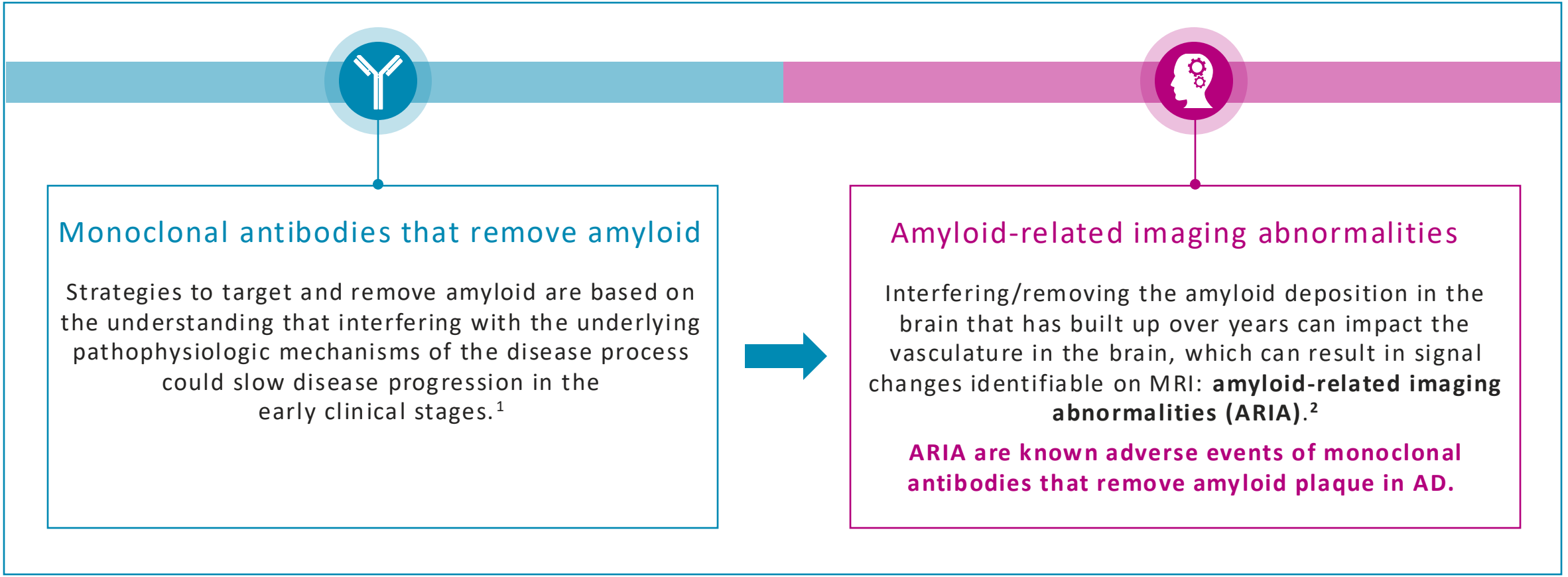
What is ARIA?

- An Alzheimer's Association workgroup defined the term **"amyloid-related imaging abnormalities" or "ARIA" in 2009** based on MRI findings observed in a small number of patients receiving monoclonal antibodies in clinical trials.
- These findings were subdivided into ARIA-E and ARIA-H[1]:
  - ARIA-E: parenchymal vasogenic edema or sulcal effusions detected on FLAIR sequences[2]
  - ARIA-H: microhemorrhages, superficial hemosiderin deposition (superficial siderosis) detected on T2* GRE sequences[3]
- ARIA is a consequence of the presence of amyloid in cerebral blood vessel walls (cerebral amyloid angiopathy [CAA]).[1] CAA can cause spontaneous ARIA in patients with AD, and the risk of ARIA is increased with monoclonal antibodies that remove amyloid plaques.[1]
- Studies have suggested that ARIA-E and ARIA-H may be caused by disruption of vessels with CAA, and the risk is increased by the clearance of Aβ from cerebral vessels, but other mechanisms are also hypothesized.[3]
- **Most cases of ARIA in patients treated with monoclonal antibodies that remove amyloid plaque are asymptomatic; however, ARIA-E may have concurrent symptoms such as headache, confusion, dizziness, and nausea and, less likely, gait disturbances, visual impairment, and rarely seizures.[4] ARIA can be serious and life-threatening and may require intervention beyond withholding treatment to address symptoms.[5]**

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

1. Sperling RA et al. *Alzheimers Dement*. 2011;7:367–385. 2. Barakos J et al. *J Prev Alzheimers Dis*. 2022;9(2):211–220. 3. Sperling RA et al. *Lancet Neurol*. 2012;11:241–249. 4. Salloway S et al. *JAMA Neurol*. 2022;79(1):13–21. 5. Cummings J et al. *J Prev Alzheimers Dis*. 2022;9:221–230.

Therapies that remove amyloid beta



AD, Alzheimer's disease; ARIA, amyloid-related imaging abnormalities; MRI, magnetic resonance imaging
1. Hampel H et al. *Mol Psychiatry*. 2021;26(10):5481–5503. 2. Sperling RA et al. *Alzheimers Dement*. 2011;7:367–385.

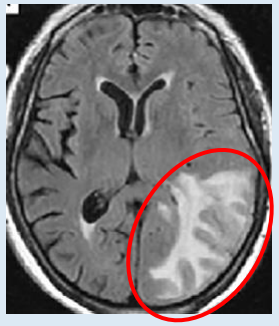
ARIA-E and ARIA-H imaging appearance

ARIA-E[1]

Interstitial vasogenic edema or sulcal effusion that manifests as parenchymal or sulcal hyperintensities

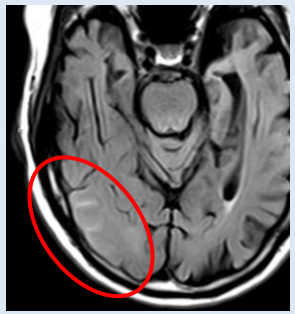
Primary MRI features

Edema



FLAIR hyperintense; parenchymal edema in left occipital-parietal lobe[a]

Effusion



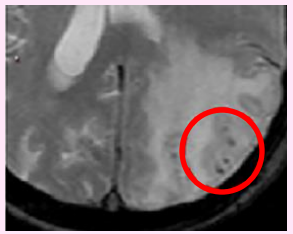
FLAIR hyperintense; increased MRI signal in sulci within right temporal-occipital lobe[a]

ARIA-H[1]

Microhemorrhages observed as hypointense hemosiderin deposition in the parenchyma or leptomeningeal/subpial space (superficial siderosis)

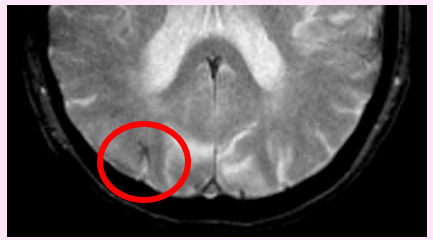
Primary MRI features

Microhemorrhage



Punctate foci of signal void on T2* GRE in an area of parenchymal edema[a]

Superficial siderosis



Superficial siderosis on T2* GRE imaging[b]

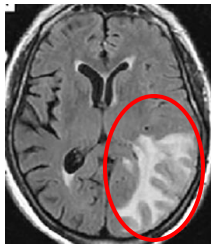
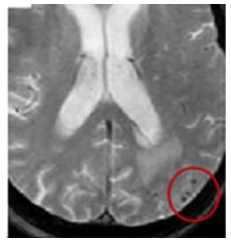
Intracerebral hemorrhage

Rare lobar intracerebral hemorrhage occurs spontaneously in AD and with monoclonal antibodies that remove amyloid, related to underlying CAA[2]

[a]Figures reproduced from Barakos et al. (2022). [b]MRI image data on file.
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
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-E and ARIA-H characteristics

ARIA is an umbrella term used to describe two types of amyloid-related imaging abnormality[1]

	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 (i.e., exudates) **Parenchyma:** vasogenic edema	**Leptomeninges:** superficial hemosiderin deposits (superficial siderosis) **Parenchyma:** microhemorrhages (typically defined as <10 mm) and intracerebral hemorrhages (macrohemorrhages; ≥10 mm)
Evaluation of severity	MRI severity scales[3] and assessment of symptoms	Number of microhemorrhages and hemosiderin deposits on MRI and assessment of symptoms
Image	 ARIA-E seen on FLAIR images demonstrating increased signal in the left hemisphere, affecting both gray and white matter[4]	 ARIA-H seen on T2* GRE MRI, revealing several microhemorrhages (<10 mm; red circle)[4]

Figures reproduced from Barakos et al. (2022).
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;7:367–385. 2. Barakos J et al. *AJNR Am J Neuroradiol*. 2013;34:1958–965. 3. Barkhof F et al. *AJNR Am J Neuroradiol*. 2013;34:1550–1555. 4. Barakos J et al. *J Prev Alzheimers Dis*. 2022;9(2):211–220.

Pathophysiology

Hypothesized pathophysiology of ARIA

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 may be thought of as a transient exacerbation of the effects of CAA**. The leakage of fluid into the parenchyma or leptomeninges could give rise to an increased signal detected on FLAIR images (ARIA-E), while leakage of red blood 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]

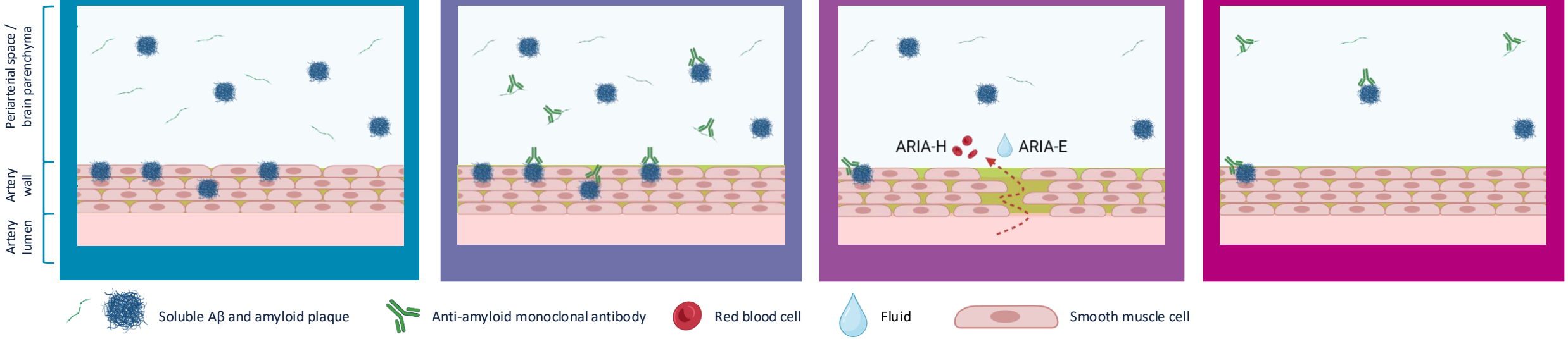


Figure created with BioRender.com.

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:E19–E35. 2. Sperling RA et al. *Alzheimers Dement*. 2011;7:367–385. 3. Sperling R et al. *Lancet Neurol.* 2012;11:241–249.

Evidence of pathophysiology

1. Preclinical studies showed vascular alterations after treatment with 3D6, a murine form of bapineuzumab.[1]

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

3. The risk of ARIA-E is dose dependent—the higher the dose, the greater the level of amyloid clearance and risk of ARIA-E occurrence.[2]

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

5. Treatment-related ARIA-E appears to occur early in the course of therapy, and the risk of ARIA-E decreases as duration of exposure increases.[3,4]

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;11:241–249. 3. Ketter N et al. *J Alzheimers Dis*. 2017;57:557–573. 4. Salloway S et al. *N Engl J Med*. 2014;370:322–333.

Commonalities in pathophysiology between CAA-ri and ARIA

While ARIA and CAA-ri are separate entities, they share a number of similarities:

Risk factors

Increased number of microbleeds and *APOE ε4* genotype

Location

CAA develops to a greater extent in cortical and leptomeningeal vessels (the locations where ARIA occur)

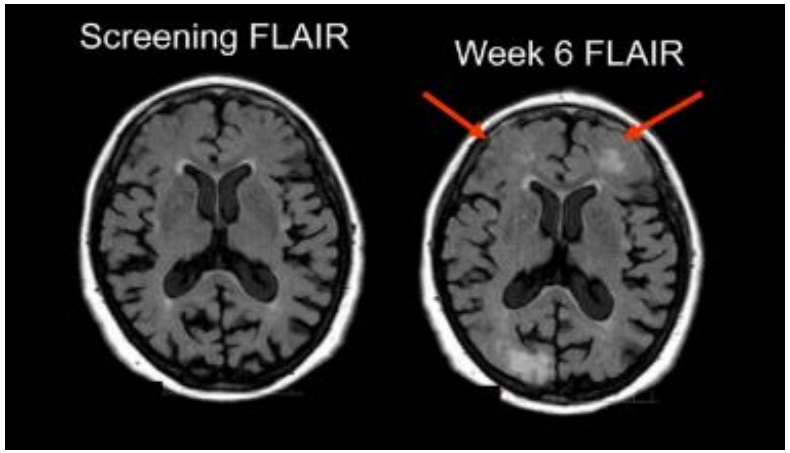
Syndrome resemblance

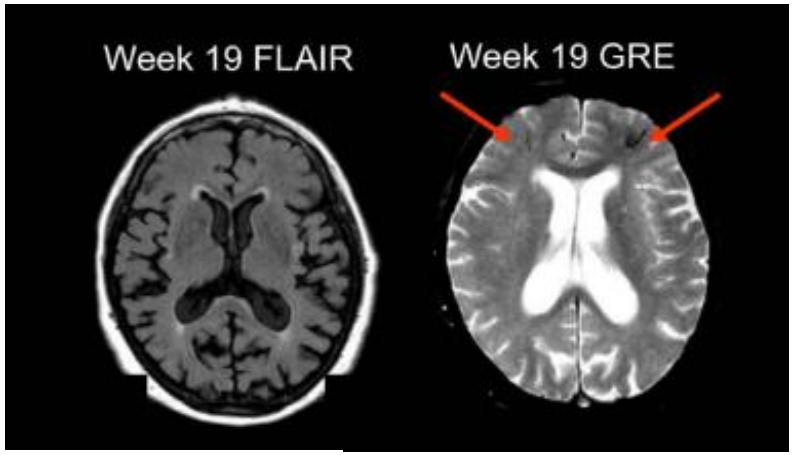
Infiltration of inflammatory cells (microglia, T cells, and Aβ-containing multinucleated cells) in CAA-ri suggests possible spontaneous anti-Aβ immunization

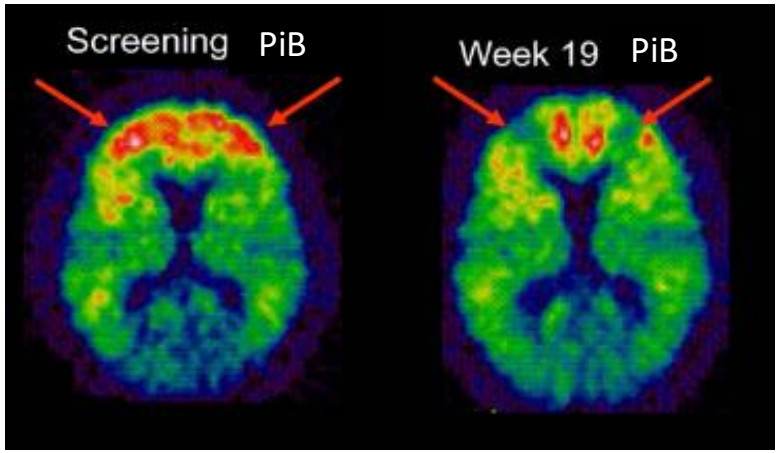
Aβ, amyloid beta; *APOE ε4*, apolipoprotein E ε4; ARIA, amyloid-related imaging abnormalities; CAA, cerebral amyloid angiopathy; CAA-ri, CAA-related inflammation

Greenberg SM et al. *Nat Rev Neurol*. 2020;16(1):30–42.

Relationship between amyloid removal with monoclonal antibodies and ARIA-E and ARIA-H







At Week 6, 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)

Baseline PiB retention is consistent with high fibrillar burden

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

Reduced PiB retention is temporally and regionally associated with ARIA-E and ARIA-H

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; PiB, Pittsburgh compound B

Sperling RA et al. *Lancet Neurol*. 2012;11:241–249.

Increased risk of ARIA-E and ARIA-H in carriers of *APOE ε4*

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

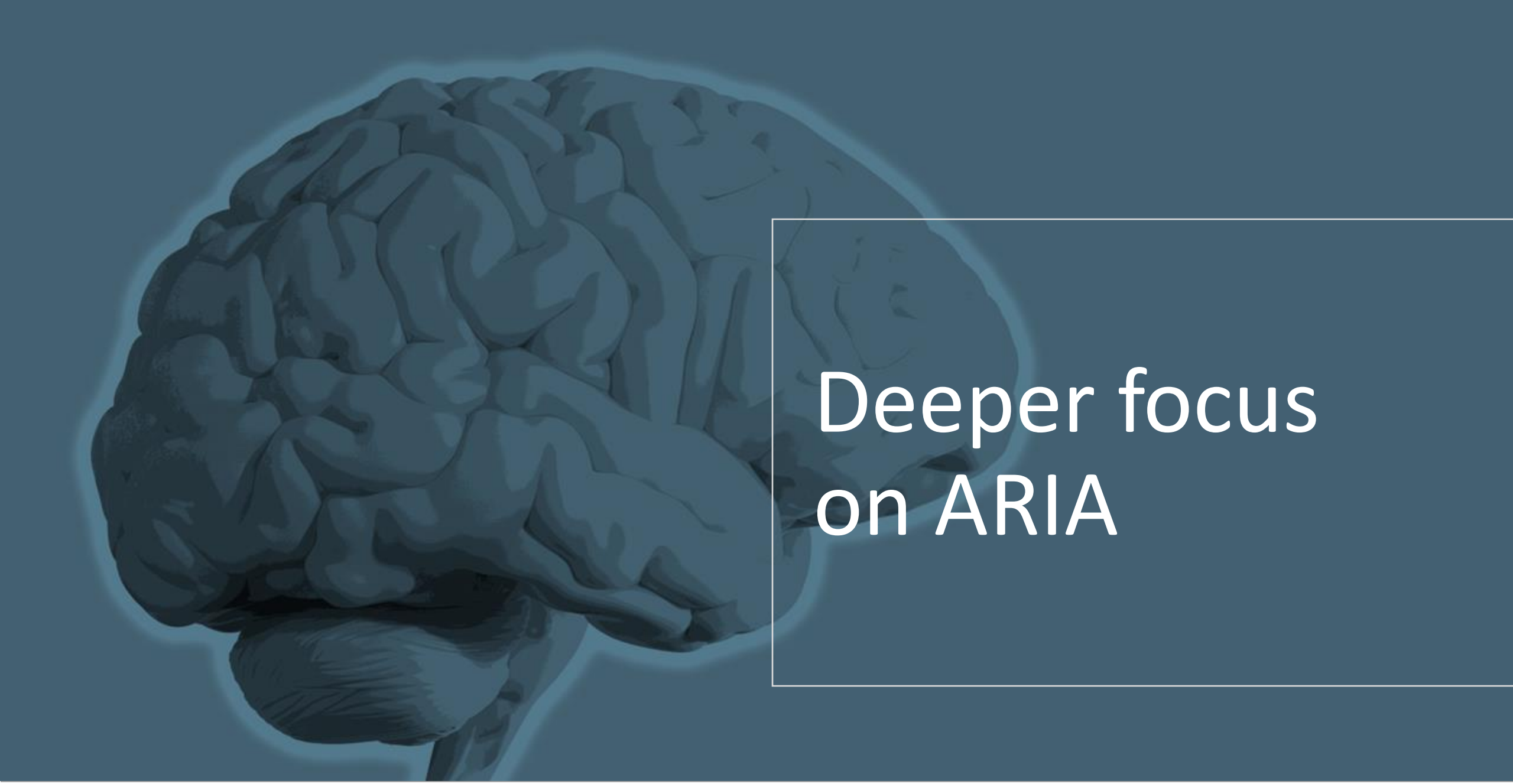
- The presence of *APOE ε4* alleles is one of the most robust known risk factors for ARIA-E[3] and a proposed risk factor for ARIA-H[4] in trials of monoclonal antibodies that remove amyloid plaque in patients with AD.

- *APOE ε4* positive carrier status is also a risk factor for spontaneously occurring ARIA-like events in microhemorrhage in the general population,[5] microhemorrhages among patients in memory clinics,[6] and CAA-ri.[7]

These findings support the hypothesis that vascular amyloid plays a key role in the induction of ARIA-E and ARIA-H.[1,2]

Aβ, amyloid beta; AD, Alzheimer's disease; *APOE ε4*, apolipoprotein E ε4; ARIA, amyloid-related imaging abnormalities; ARIA-E: ARIA-edema/effusion; ARIA-H: ARIA-hemosiderin/hemorrhage; CAA-ri, cerebral amyloid angiopathy-related inflammation

1. Caselli RJ et al. *Neurosci Lett*. 2010;473:168–171. 2. Cogswell PM et al. *AJNR Am J Neuroradiol*. 2022;43(9):E19–E35. 3. Ketter N et al. *J Alzheimers Dis*. 2017;57:557–573. 4. Arrighi HM et al. *J Neurol Neurosurg Psychiatry*. 2016;87:106–112. 5. Poels MM et al. *Stroke*. 2011;42:656–661. 6. Goos JD et al. *Neurology*. 2010;74:1954–1960. 7. Kinnecom C et al. *Neurology*. 2007;68:1411–1416.



Deeper focus on ARIA

ARIA-E

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]

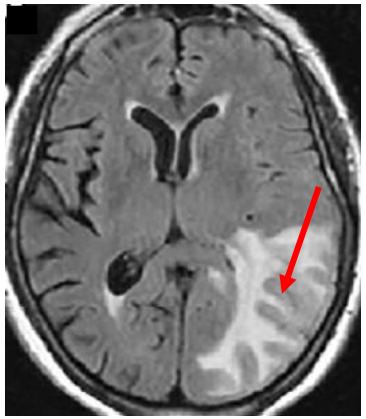


Figure from Barakos et al. (2022).[3]

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]

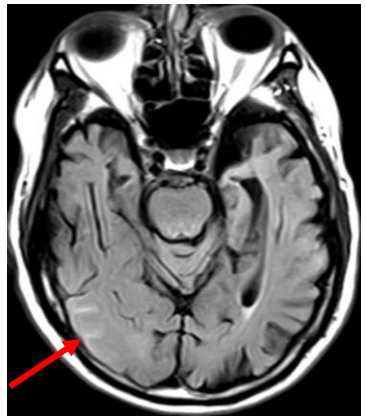


Figure from Barakos et al. (2022).[3]

Spontaneous ARIA-E has been reported to occur in the placebo arm in clinical trials.[4-7]

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

1. Barakos J et al. *AJNR Am J Neuroradiol*. 2013;34:1958–1965. 2. Sperling RA et al. *Alzheimers Dement.* 2011;7:367–385. 3. Barakos J et al. *J Prev Alzheimers Dis*. 2022;9(2):211–220.
4. Budd-Haeberlein S et al. *J Prev Alzheimers Dis*. 2022;9:197–210. 5. van Dyck C et al. *N Eng J Med*. 2023;388:9–21. 6. Ostrowitzki S et al. *Alzheimers Res Ther*. 2017;9(1):95. 7. Vandenberghe R et al. *Alzheimers Res Ther*. 2016;8:18.

ARIA-H

Microhemorrhages

- **Hypointense, focal, round, punctate lesions on T2* GRE MRI sequences** (typically defined by a cutoff of **<10 mm**)[1]
- Small deposits of iron in hemosiderin in the brain **parenchyma**[2]
- Thought to represent residua of a small leakage of blood from a vessel into **adjacent tissue**[2]
- The baseline prevalence of microhemorrhages is estimated to be 15.3%[3]
  - This prevalence increases with age: ~17% in people aged 60–69 years, ~29% in people aged 70–79 years, and ~36% in people aged 80–97 years[3]
- **Less commonly, macrohemorrhages (≥10 mm) can also occur**[1]

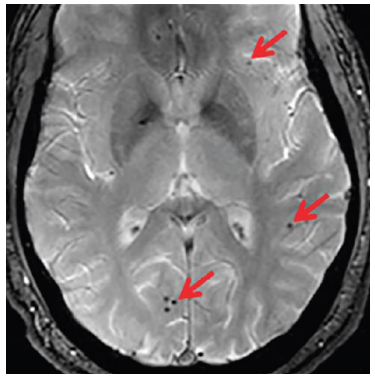


Figure from Cogswell et al. (2022).[4]

Superficial siderosis

- **Curvilinear low intensities on T2* GRE MRI sequences** that lie adjacent to the surface of the brain[2]
- Attributed to the deposition of iron in the form of **hemosiderin** and is thought to represent residua of leakage of blood from a vessel into the **adjacent subarachnoid space or the periadventitial compartment**[1]
- The baseline prevalence of superficial siderosis is estimated to be 0.21% in those aged 50–69 years and 1.43% in those >69 years[5]

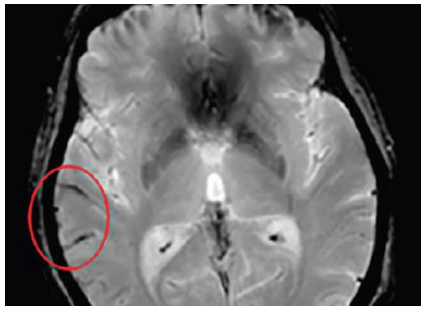


Figure from Cogswell et al. (2022).[4]

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

1. Barakos J et al. *AJNR Am J Neuroradiol*. 2013;34:1958–1965. 2. Sperling RA et al. *Alzheimers Dement.* 2011;7:367–385. 3. Poels MM et al. *Stroke*. 2010;41:S103–S106.
4. Cogswell PM et al. *AJNR Am J Neuroradiol*. 2022;43(9):E19–E35. 5. Pichler M et al. *Stroke*. 2017;48:3210–3214.

Clinical manifestations of ARIA

Clinical manifestations of ARIA

- In most cases, ARIA are **asymptomatic**.[1] Moreover, most cases **occur early** in the treatment course. The incidence **decreases with increased duration** of exposure.[1,2]

- The most commonly reported symptoms of ARIA-E are transient and nonspecific and include **headache, confusion, dizziness, nausea, and neuropsychiatric symptoms; less frequent symptoms include fatigue, visual impairment, blurred vision, and gait disturbance.**[1,3]

- Infrequently, severe symptoms occur (e.g., encephalopathy, focal neurologic symptoms, seizures), requiring hospitalization and specific treatments (e.g., intensive care unit admission, electroencephalography, corticosteroids, antiepileptics).[1,4] **ARIA can be serious and life-threatening.**[4]

ARIA, amyloid-related imaging abnormalities; ARIA-E: ARIA-edema/effusion

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

ARIA experience from clinical trials

- ARIA are more common in *APOE ε4* carriers.[1,2]
- Most cases of ARIA-E and ARIA-H are asymptomatic and are usually recognized as incidental ARIA on MRI during follow-up evaluation.[1,2]
- Most cases of ARIA-E occur early in the treatment course and decrease with increased duration of exposure.[1-3] ARIA-E and ARIA-H may occur concurrently.[3]
- Most cases of ARIA-E resolve completely. Depending on severity, treatment may be continued, interrupted, or discontinued.[1,4-6] Some cases may require specific treatments or even hospitalization.[6] ARIA-H stabilizes but can remain on subsequent imaging.[3,7]
- Re-dosing following resolution is generally associated with a low rate of ARIA recurrence.[4,5]

APOE ε4, apolipoprotein E ε4; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H: ARIA-hemosiderin/hemorrhage; MRI, magnetic resonance imaging

1. Sperling R et al. *Lancet Neurol*. 2012;11:241–249. 2. Filippi M et al. *JAMA Neurol.* 2022;79(3):291–304. 3. Barakos J et al. *AJNR Am J Neuroradiol*. 2013;34(10):1958–1965. 4. Ketter N et al. *J Alzheimers Dis*. 2017;57:557–573.
5. Ostrowitzki S et al. *Alzheimers Res Ther*. 2017;9:95. 6. Cummings J et al. *J Prev Alzheimers Dis*. 2022;9:221–230. 7. Salloway S et al. *JAMA Neurol*. 2022;79(1):13–21.

Diagnosis of ARIA

ARIA risk factors

Main risk factors:

***APOE ε4* carrier status[1-3]**

Pre-treatment microhemorrhage[2,3]

Treatment with monoclonal antibodies that remove amyloid[2,3]

APOE ε4, apolipoprotein E ε4; ARIA, amyloid-related imaging abnormalities

1. Filippi M et al. *JAMA Neurol*. 2022;79(3):291–304. 2. Sperling RA et al. *Alzheimers Dement*. 2011;7(4):367–385. 3. Cogswell PM et al. *AJNR Am J Neuroradiol*. 2022;43(9):E19–E35.

Recommended MRI protocols for baseline imaging and detection of ARIA

MRI protocol: standards for detection of ARIA in clinical trials

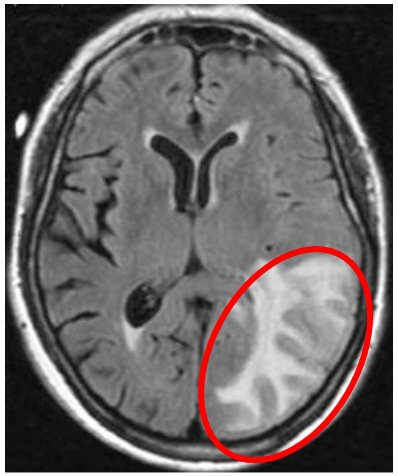


Figure adapted from Barakos et al. (2022).[3]

3T scanner (recommended) 1.5T scanner (minimal)[1,2]	High–field strength scanners have greater sensitivity but limited availability. 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 (DWI)[3]	Recommended for differential diagnosis[3]

Imaging considerations

- ARIA-E is indiscernable on conventional T2 sequences
- CT would not be expected to detect milder forms of ARIA-E and may lead to misdiagnosis, such as stroke or other conditions (confirm with the neuroradiologists)
- CT is insensitive to the detection of microhemorrhages and siderosis (ARIA-H)

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

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. Barakos J et al. *J Prev Alzheimers Dis*. 2022;9(2):211–220.

Grading scale for determining radiographic severity of ARIA

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

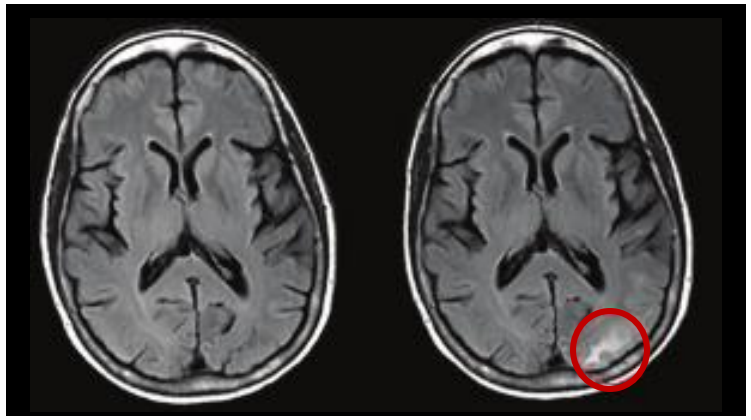
	Mild	Moderate	Severe
ARIA-E Sulcal and/or cortical/ subcortical FLAIR hyperintensity	1 location <5 cm	1 location 5–10 cm OR >1 location each <10 cm	1 or more locations each >10 cm
ARIA-H Superficial siderosis	1 focal area	2 focal areas	>2 focal areas
ARIA-H Number of new microhemorrhages	≤4	5–9	≥10

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage

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

Detection and grading of ARIA-E — parenchymal edema

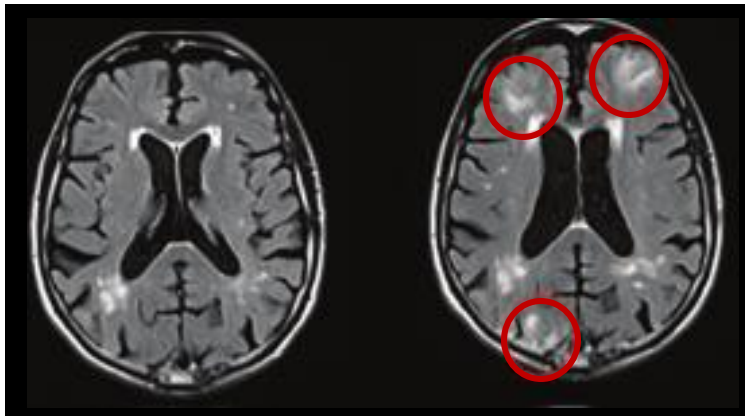
Baseline | Post-dosing



Mild ARIA-E

T2-FLAIR hyperintense signal in the left parieto-occipital subcortical white matter with mild local mass effect and sulcal effacement measuring <5 cm in the transverse dimension

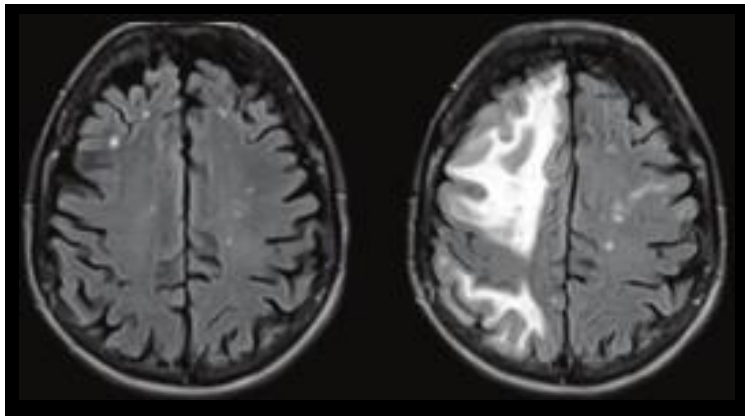
Baseline | Post-dosing



Moderate ARIA-E

New multifocal, patchy T2-FLAIR hyperintense signal in the bifrontal and right occipital subcortical white matter, each region measuring <5 cm. A single region measuring <5 cm would be classified as mild; >1 yields a moderate ARIA-E classification as long as each region is <10 cm in diameter

Baseline | Post-dosing



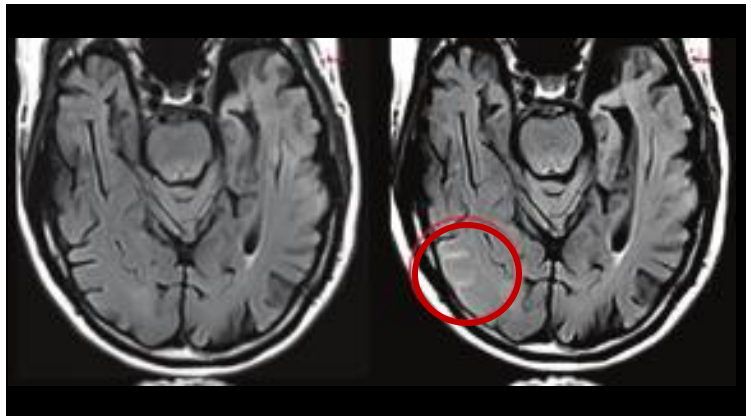
Severe ARIA-E

Development of extensive T2-FLAIR hyperintense signal throughout the right frontal and parietal lobes measuring >10 cm (measurement includes all abnormal brain – swollen with or without hyperintensity). Associated mass effect and sulcal effacement throughout much of the right cerebral hemisphere

All figures adapted from Cogswell PM et al. (2022).
Data shown from 3 different patients.
ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion, T2-FLAIR, T2-weighted fluid-attenuated inversion recovery
Cogswell PM et al. *AJNR Am J Neuroradiol*. 2022;43(9):E19–E35.

Detection and grading of ARIA-E — sulcal effusion

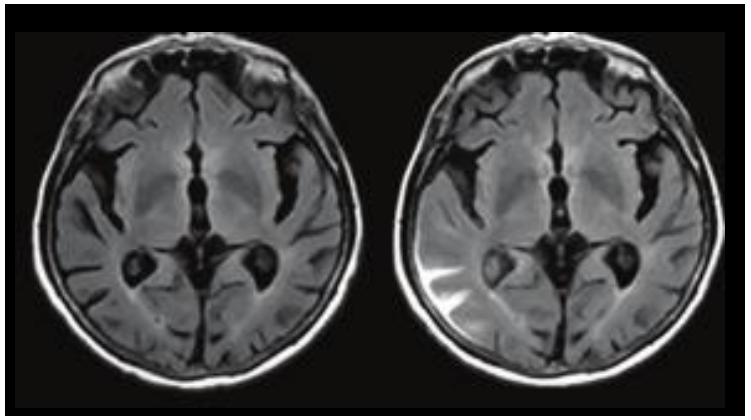
Baseline | Post-dosing



Mild ARIA-E

New sulcal T2-FLAIR hyperintense signal in the right temporal-occipital lobe measuring <5 cm in the transverse dimension

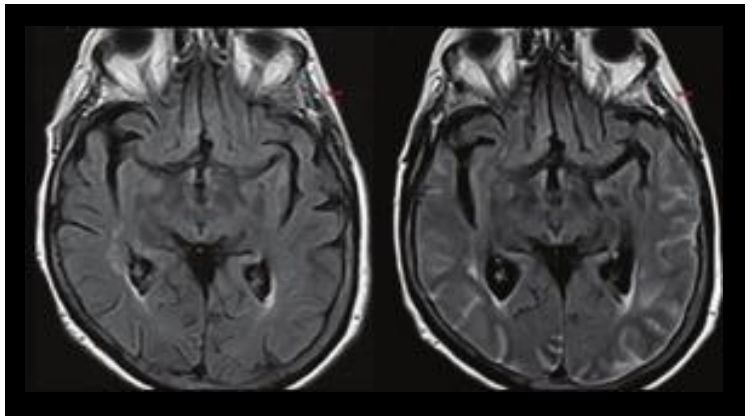
Baseline | Post-dosing



Moderate ARIA-E

New T2-FLAIR sulcal effusion involving the right posterior temporal and parietal lobes measuring 5–10 cm

Baseline | Post-dosing

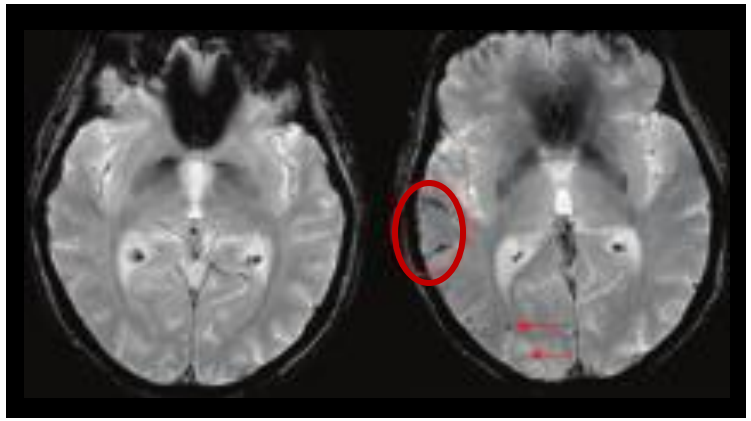


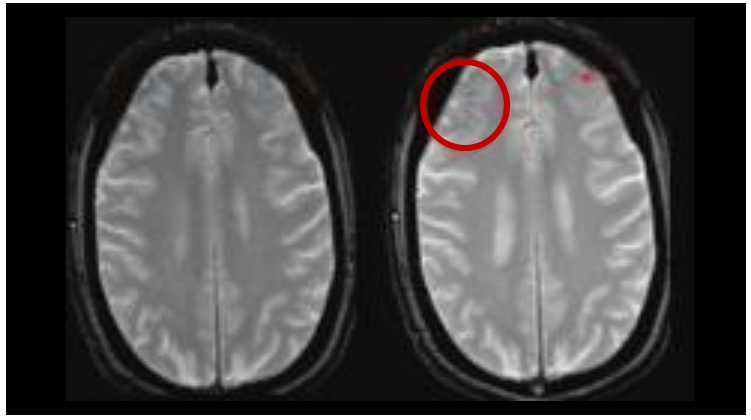
Severe ARIA-E

Extensive T2-FLAIR sulcal effusion involving the bilateral temporal and occipital lobes measuring ≥10 cm

All figures adapted from Cogswell PM et al. (2022).
Data shown from 3 different patients.
ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion, T2-FLAIR, T2-weighted fluid-attenuated inversion recovery
Cogswell PM et al. *AJNR Am J Neuroradiol*. 2022;43(9):E19–E35.

Detection and grading of ARIA-H — superficial siderosis

Baseline	Post-dosing	Axial T2* GRE imaging
		**Mild ARIA-H** Post-dosing: new right temporal superficial siderosis involves contiguous sulci when viewed over multiple slices (siderosis, red circle). This patient also had two treatment-emergent microhemorrhages in the right occipital lobe (red arrows)

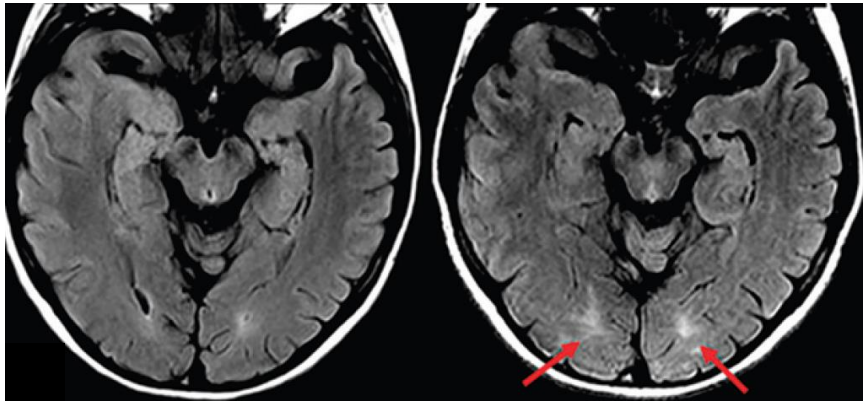
Baseline	Post-dosing	Axial T2* GRE imaging
		**Moderate ARIA-H** Two regions of treatment-emergent superficial siderosis in the right greater-than-left frontal lobes (red circle and arrow)

Figures adapted from Cogswell et al. (2022).
Data shown from 2 different patients.
ARIA, amyloid-related imaging abnormalities; ARIA-H: ARIA-hemosiderin/hemorrhage; GRE, gradient recalled echo
Cogswell PM et al. *AJNR Am J Neuroradiol*. 2022;43(9):E19–E35.

Potential MRI interpretation pitfalls when detecting ARIA-E

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

Vendor 1: Timepoint 1 **Vendor 2: Timepoint 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 vendor 1 examination

White matter signal may differ with scan technique and field strength, such as the use of 3D versus 2D FLAIR.

Shading artifacts and scanner or sequence variability may make identification and interpretation of ARIA-E versus artifacts difficult.

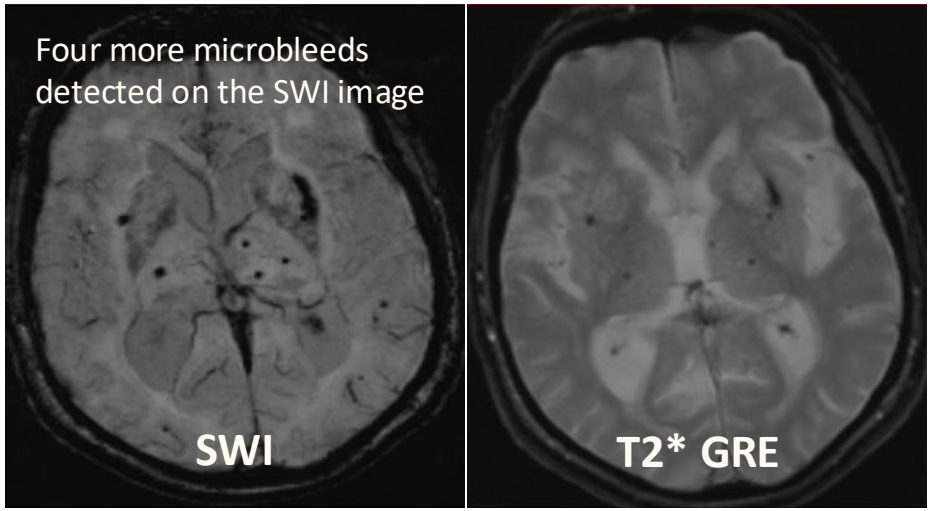
- Axial T2-FLAIR images from two timepoints, with the two scans performed on different vendor scanners.
- Repeat imaging of participant on vendor 1 scanner showed that the apparent abnormality was resolved.

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

Figure reproduced with permission from Cogswell et al. (2022).
ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; 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. Barakos J et al. *AJNR Am J Neuroradiol*. 2013;34:1958–1965.

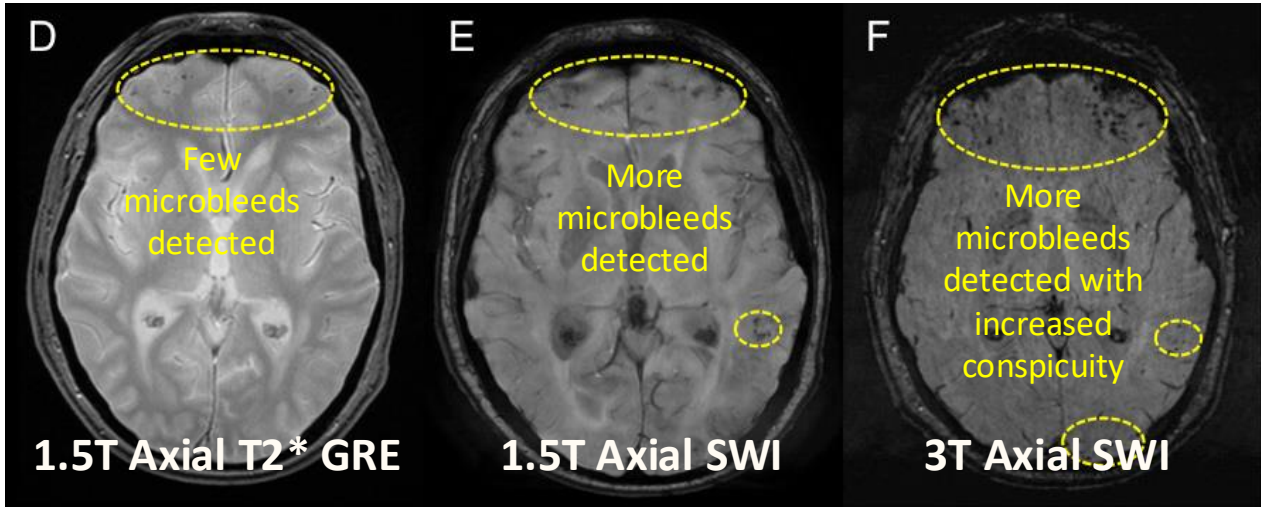
Potential MRI interpretation pitfalls when detecting ARIA-H

SWI is a more sensitive technique for detection of microhemorrhages than T2* GRE images[1]



Images acquired from the same patient on the same day.
Figure reproduced with permission from Sperling et al. (2011).

The conspicuity of microhemorrhages can be increased based on sequence and magnetic field strength[2]



Images of a patient with spontaneous intracerebral hemorrhage.
Figure reproduced with permission from Puy et al. (2021).

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. Puy L et al. *J Neurol Neurosurg Psychiatry*. 2021;92(6):598–607

Differentiating ARIA from other pathologies

ARIA-E or ARIA-H should be considered as the presumptive diagnosis when signal abnormalities on MRI are identified in patients recently exposed to monoclonal antibodies that remove amyloid plaque and in whom no evidence of any other inciting cause or underlying lesion can be found.[1]

- In a suspected ARIA case, the full clinical picture must be taken into account before a diagnosis is confirmed.[1]
- MRI is key for the diagnosis and differential diagnosis of ARIA.[2]
- CT would not be expected to detect milder forms of ARIA-edema/effusion (ARIA-E) and is insensitive to the detection of microhemorrhages and siderosis (ARIA-H).[2]
- Training should be provided to ensure reliable diagnosis of ARIA.[2]

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA- edema/effusion; ARIA-H: ARIA-hemosiderin/hemorrhage; CT, computed tomography; MRI, magnetic resonance imaging

1. Barakos J et al. *AJNR Am J Neuroradiol*. 2013;34:1958–1965. 2. Barakos J et al. *J Prev Alzheimers Dis*. 2022;9(2):211–220.

Differential diagnosis: acute ischemic stroke

T2-weighted axial FLAIR
Parenchymal edema

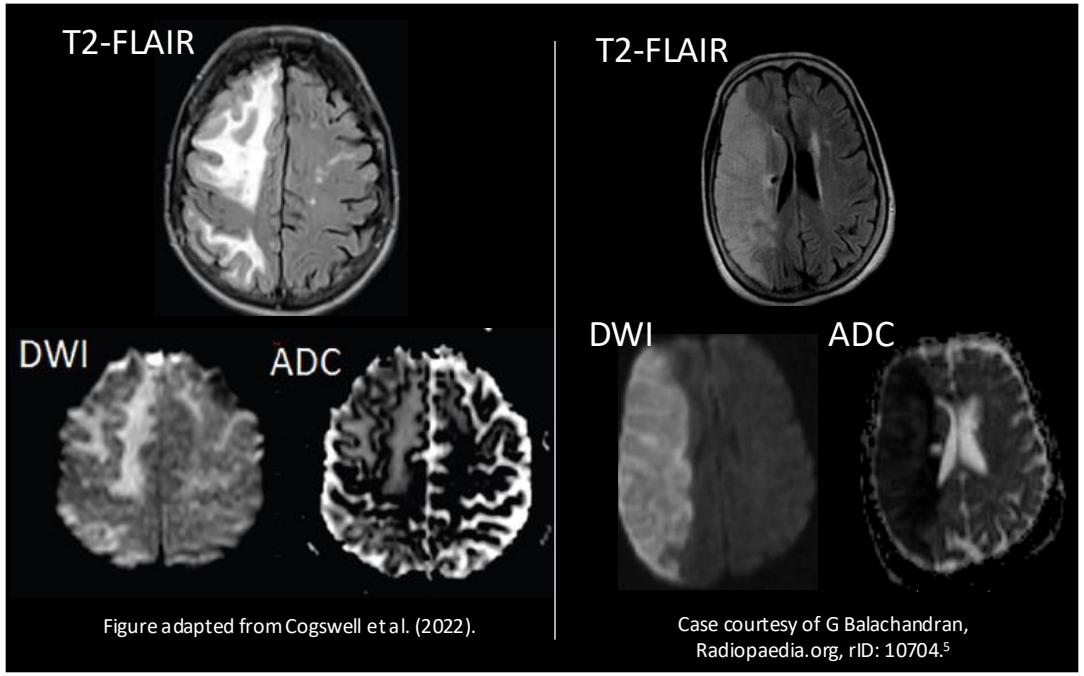


Figure adapted from Cogswell et al. (2022).

Case courtesy of G Balachandran, Radiopaedia.org, rID: 10704.[5]

Severe ARIA-E*,[1]

Right MCA ischemic stroke[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]. ARIA-E does not typically demonstrate restricted diffusion.
- Signs and symptoms of ischemic stroke include acute onset, hemiparesis, dysphasia or dysarthria, facial paresis, paresthesia, eye movement abnormalities, and visual field defects.[4]
- Knowing if a patient is on monoclonal antibodies that remove amyloid helps with determining the diagnosis of ARIA.[3]

*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; FLAIR, fluid-attenuated inversion recovery; 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. Bhuta S et al. Radiopaedia.org. https://radiopaedia.org/articles/13401. 3. Barakos J et al. *AJNR AM J Neuroradiol*. 2013;34:1958–1965. 4. Yew KS et al. *Am Fam Physician*. 2015;91(8):528–36. 5. Balachandran, G. Radiopaedia.org (Accessed on 05 Nov 2024) https://doi.org/10.53347/rID-10704

Differential diagnosis: subarachnoid hemorrhage

T2-weighted axial FLAIR
Effusion

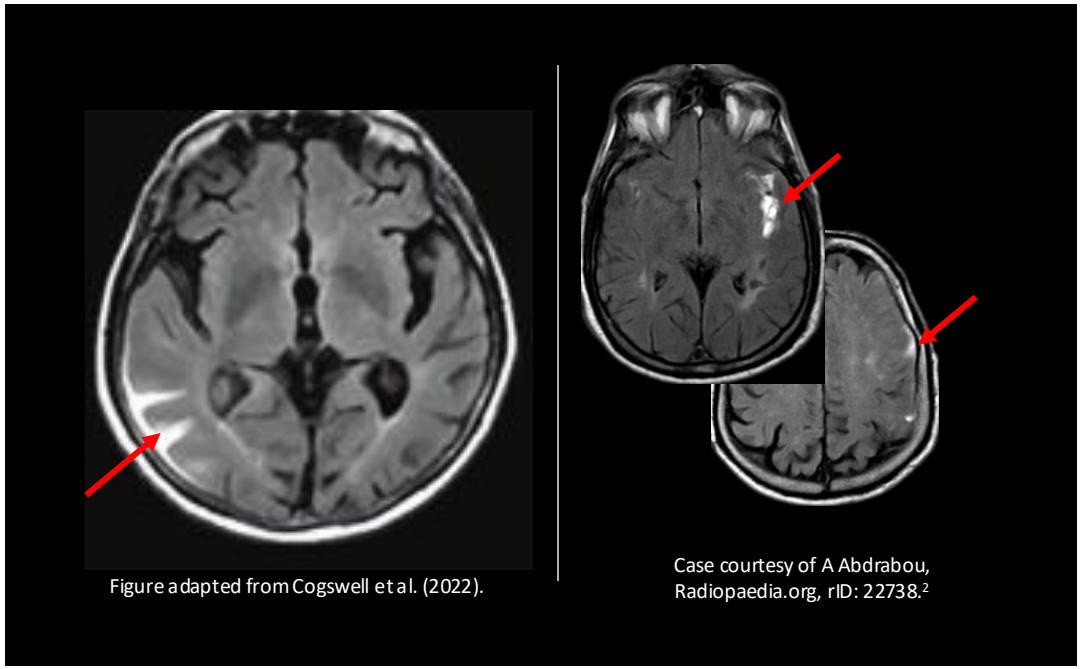


Figure adapted from Cogswell et al. (2022).

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

Moderate ARIA-E[1]

Subarachnoid hemorrhage[2]

- Leptomeningeal FLAIR hyperintensity of ARIA-E effusion may be mimicked by subarachnoid hemorrhage.[3]
- Differentiating ARIA and subarachnoid hemorrhage requires a systematic clinical and diagnostic approach.[3] Other sequences (T2* GRE/SWI), modalities (CT), and investigations may be helpful in supporting the diagnosis.
- Subarachnoid hemorrhage typically presents with a number of signs and symptoms: severe headache accompanied by nausea or vomiting.[4]
- Decreased level of consciousness and focal neurological signs can also be present.[2,4]

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; CT, computed tomography; FLAIR, fluid-attenuated inversion recovery; GRE, gradient recalled echo; SWI, susceptibility-weighted imaging

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. 3. Barakos J et al. *AJNR AM J Neuroradiol*. 2013;34:1958–1965. 4. Tetsuka S et al. *BMC Neurol*. 2016;16:196.

Differential diagnosis: posterior reversible encephalopathy syndrome (PRES)

T2-weighted axial FLAIR
Edema

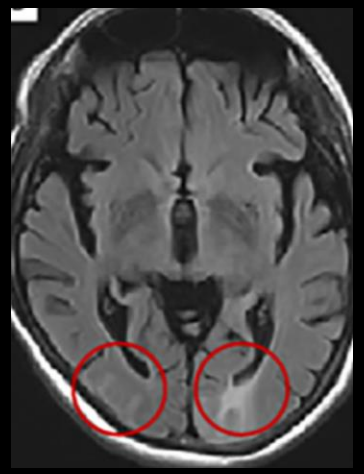
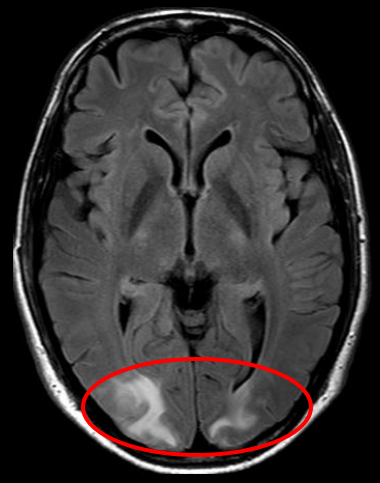


Figure from Barakos et al. (2022).



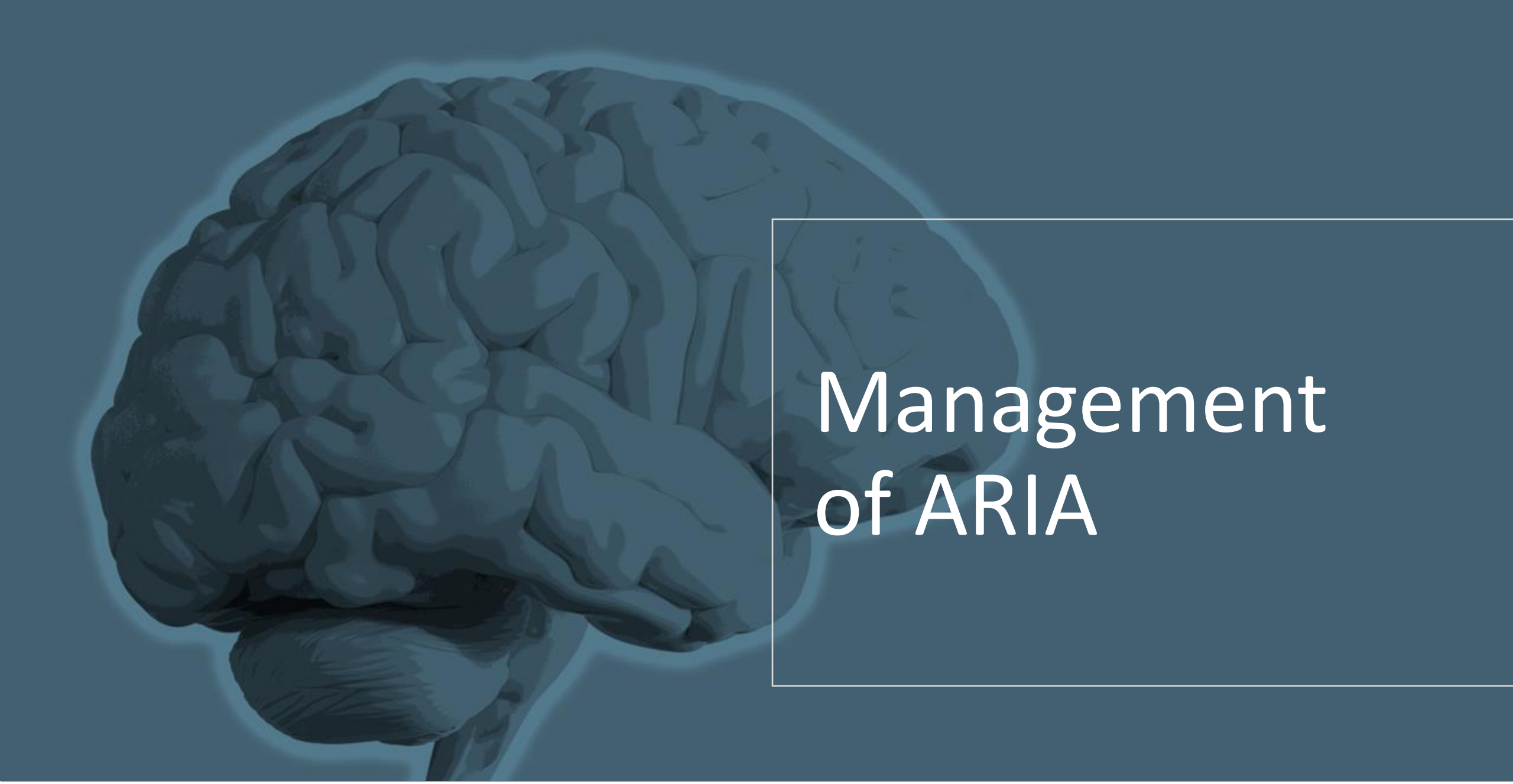
Case courtesy of Hani Makky Al Salam, Radiopaedia.org, rID: 7697.[5]

Moderate ARIA-E[3] | **PRES[4]**

- PRES could resemble ARIA-E on imaging.[1]
- PRES frequently develops from cytotoxic medication or disorders such as preeclampsia, sepsis, renal disease, and autoimmune disorders.[2]
- Signs of PRES[2]: encephalopathy, epileptic seizures, visual disturbances, and focal neurological deficits.
- Less specific signs[2]: headache, nausea, vomiting.
- In this case, clinical history, including knowledge of the patient's medication 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. *AJNR AM J Neuroradiol*. 2013;34:1958–1965. 2. Fischer M et al. *J Neurol*. 2017;264:1608–1616. 3. Barakos J et al. *J Prev Alzheimers Dis*. 2022;9(2):211–220. 4. Gaillard F et al. https://doi.org/10.53347/rID-1915. 5. Al Salam, H, Radiopaedia.org (Accessed on 05 Nov 2024) https://doi.org/10.53347/rID-7697



Management of ARIA

Management of ARIA for radiologists

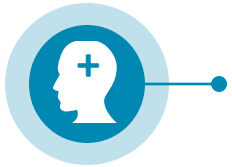
- **Diagnosis and management of ARIA** in asymptomatic and symptomatic patients is heavily **dependent on findings obtained using MRI**.
  - An integrated, organized, systematic framework for imaging diagnosis, reporting, and timely communication between radiologists and referring physicians will facilitate patient care and safety.

- **MRI should be used to assess for ARIA symptoms where possible.**
  - **CT scans can be deficient** for detecting radiographic findings, both ARIA-E and ARIA-H, owing to the lower soft tissue contrast and sensitivity for detecting small amounts of blood (microhemorrhages and siderosis) and edema.

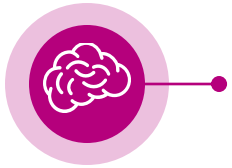
- Ensure appropriate **MRI imaging protocols** to optimize the detection of ARIA.

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

Management of ARIA for radiologists (cont'd)



- There is a need for foundational knowledge and the ability to **report standard, pre-treatment, baseline imaging features** as they will be used to **determine if patients are suitable for therapy** and if they are at an **increased risk for developing ARIA**.



- It is essential to have knowledge of the spectrum of ARIA MRI findings (as well as appropriate imaging differentials).

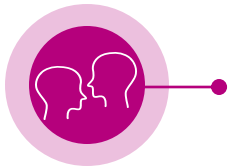
- Awareness and use of **standard grading schemes for ARIA-E and ARIA-H** in written and/or verbal communication with referring physicians would be beneficial.
  - A closed-loop system of communication would be beneficial for patient safety should a patient's MRI scan demonstrate imaging features of ARIA.

- The essential role of MRI-based decision making in the diagnosis and management of ARIA requires that **radiologists work closely with referring physicians in a multidisciplinary team**.

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

Management of ARIA for neurologists (and other HCPs)

- Refer to the **prescribing information of monoclonal antibodies** that remove amyloid for ARIA monitoring and management guidelines.



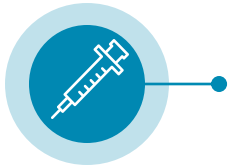
- **Discuss ARIA and associated symptoms with referring healthcare teams, patients, and care partners before treatment initiation**, including the importance of MRI monitoring and seeking urgent evaluation in the case of ARIA clinical symptoms.

- **MRI should be used to assess for ARIA symptoms where possible.**
  - **CT scans can be deficient for detecting radiographic findings**, both ARIA-E and ARIA-H, owing to the lower soft tissue contrast and sensitivity for detecting small amounts of blood (microhemorrhages and siderosis) and edema.

- **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.

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; CT, computed tomography; HCP, healthcare professional; MRI, magnetic resonance imaging

Management of ARIA for neurologists (and other HCPs) (cont'd)



- In cases of **severe or serious ARIA-E or ARIA-H, monitor neurologic status** closely. Early empiric **administration of high-dose intravenous corticosteroids** can be considered.

- In those with neurologic symptoms, **appropriate imaging is needed to support differential diagnosis and management**.

- MRI-based decision making in the diagnosis and management of ARIA requires **referring physicians to work with radiologists** to ensure that the sites where patients are referred to for **imaging have the necessary access, infrastructure, and imaging expertise for the diagnosis, communication, and monitoring of ARIA**.

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

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.ca

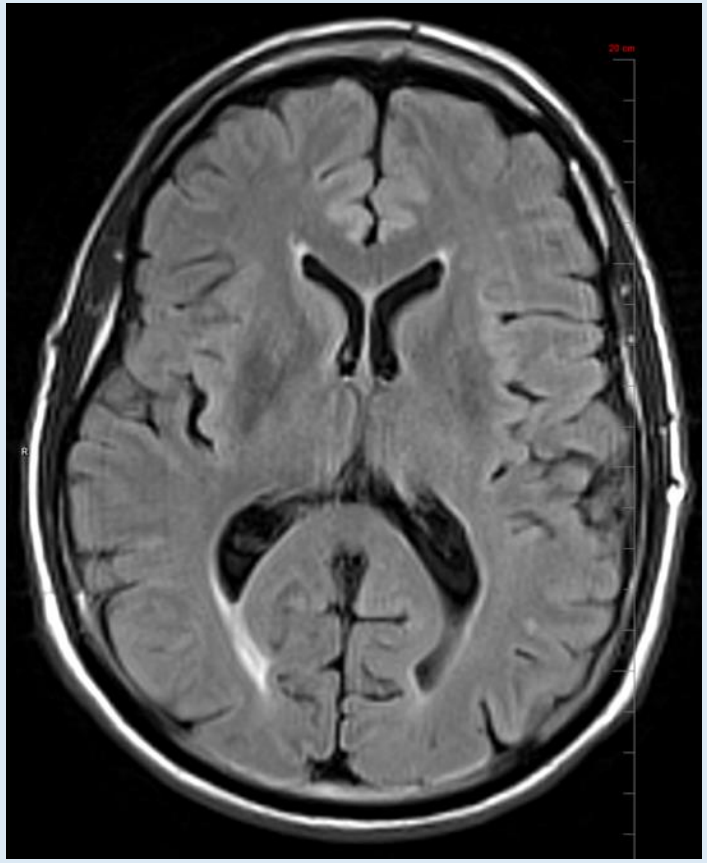
This information is intended for healthcare professionals only.

Case examples

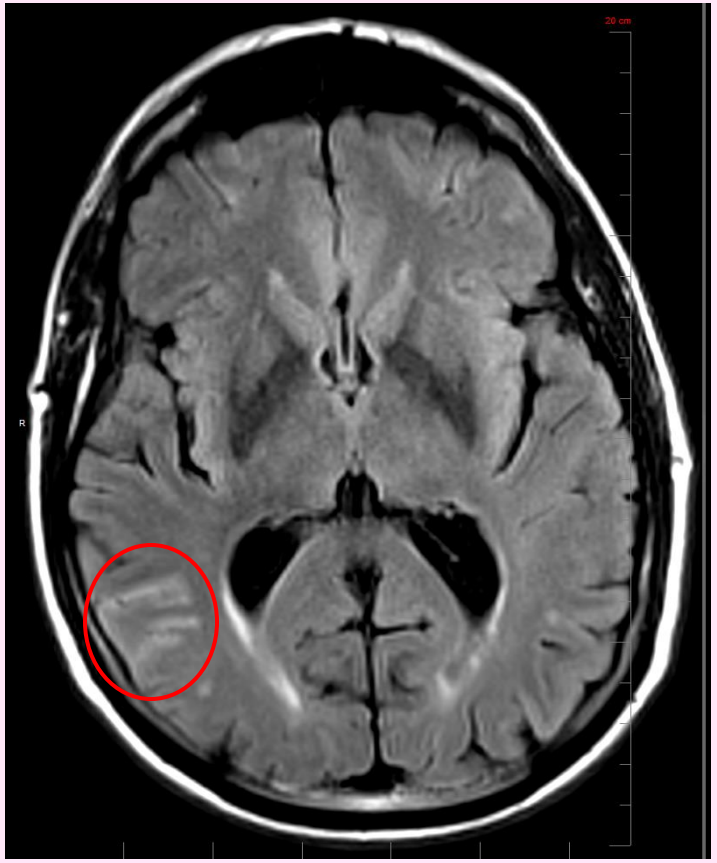
Detection of ARIA-E — parenchymal edema (mild)

1 location <5 cm
FLAIR

Baseline



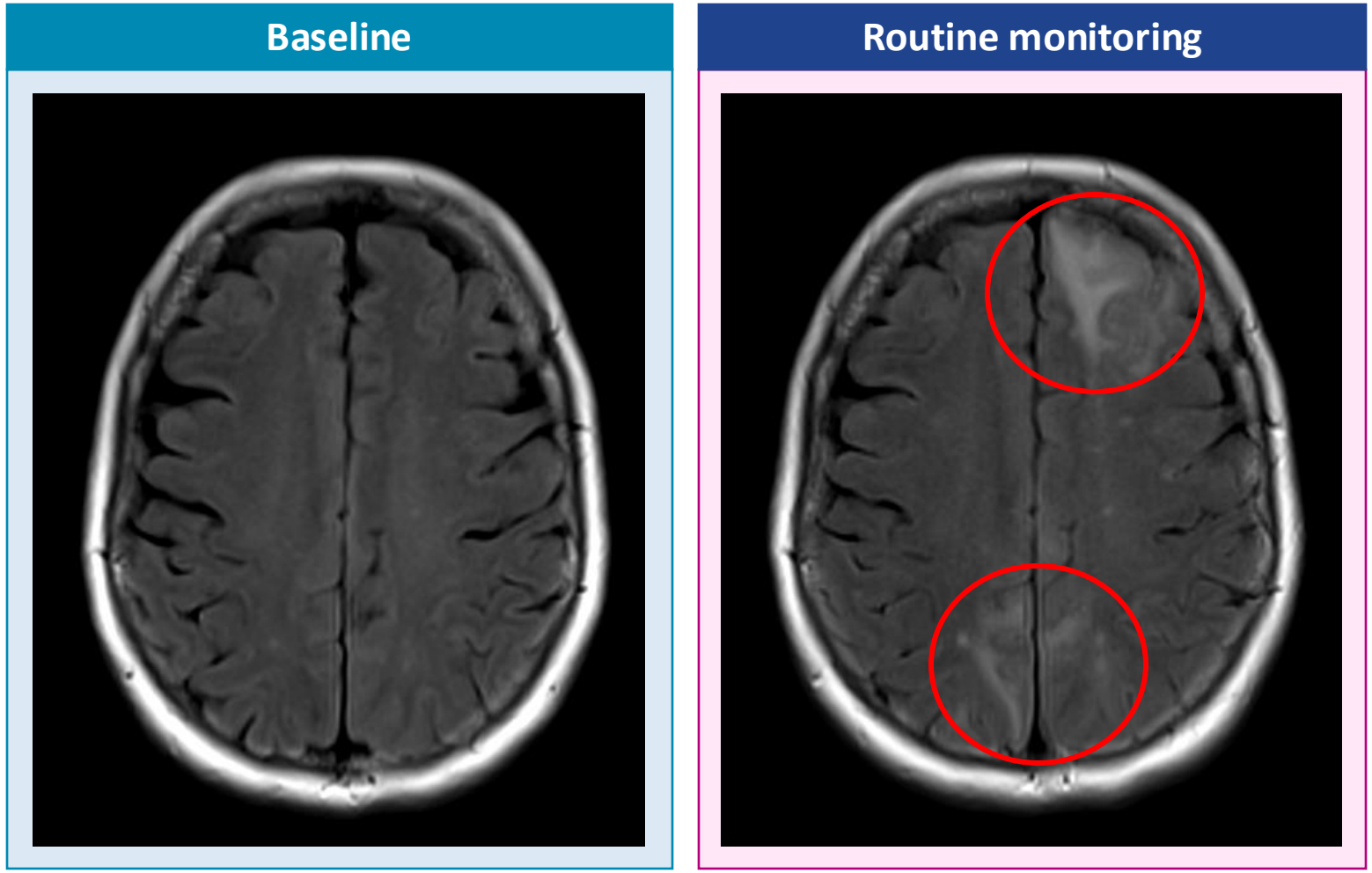
Routine monitoring



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

Detection of ARIA-E — parenchymal edema (moderate)

>1 location each <10 cm
FLAIR

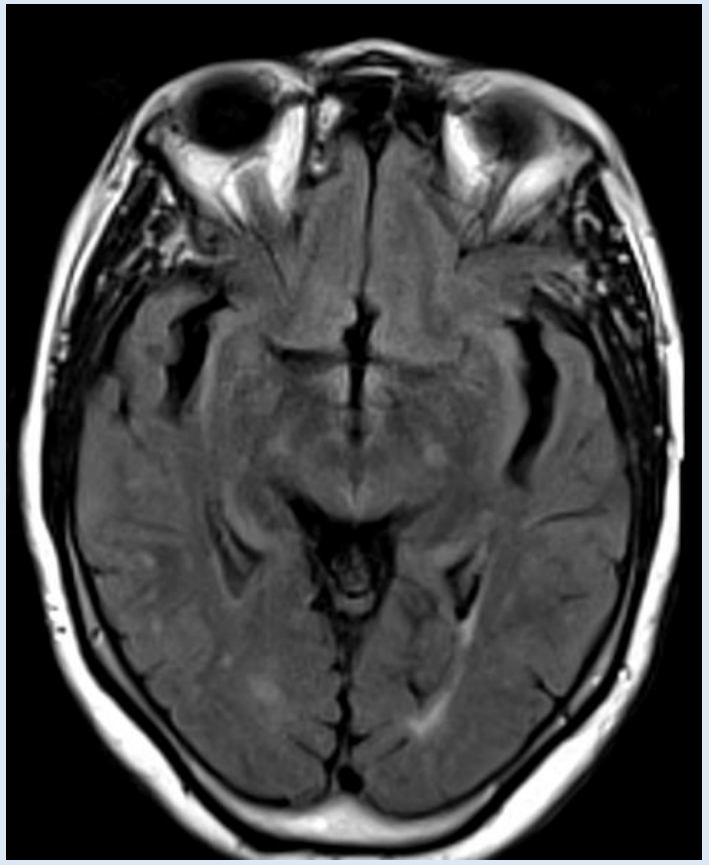


MRI images on file.
ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging

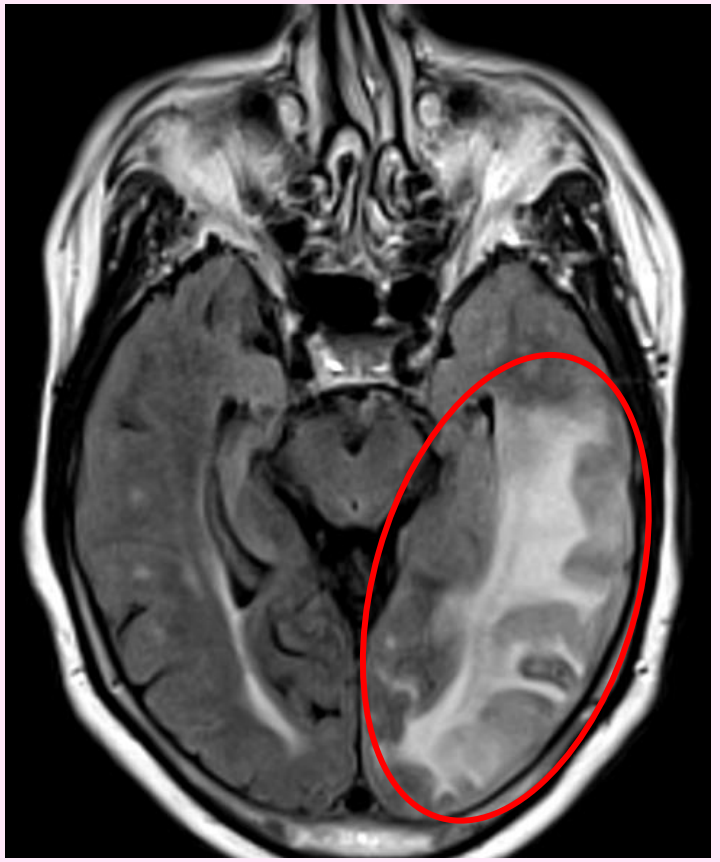
Detection of ARIA-E — parenchymal edema (severe)

1 or more locations each >10 cm
FLAIR

Baseline



Routine monitoring

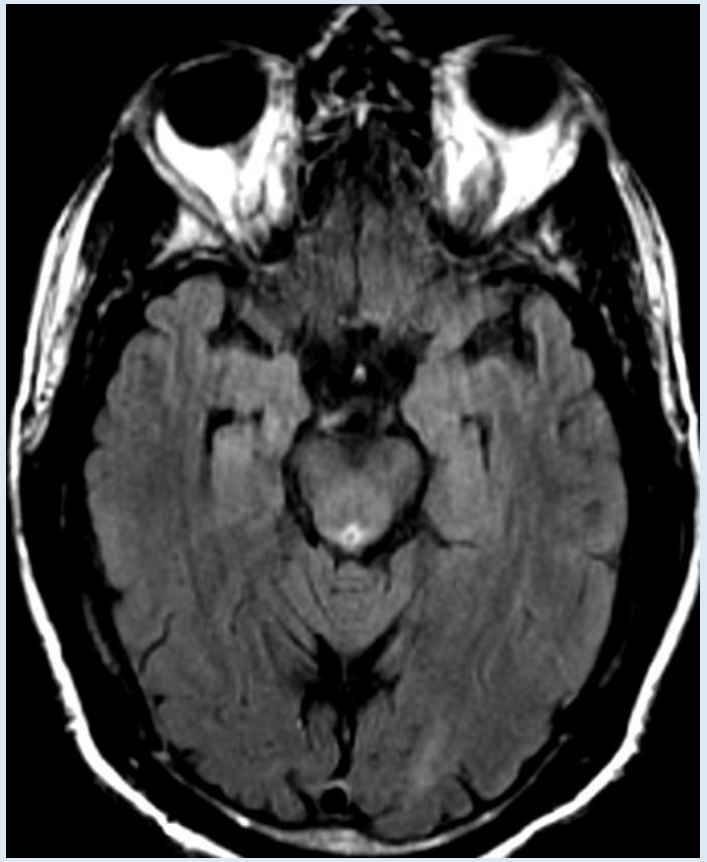


MRI images on file.
ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging

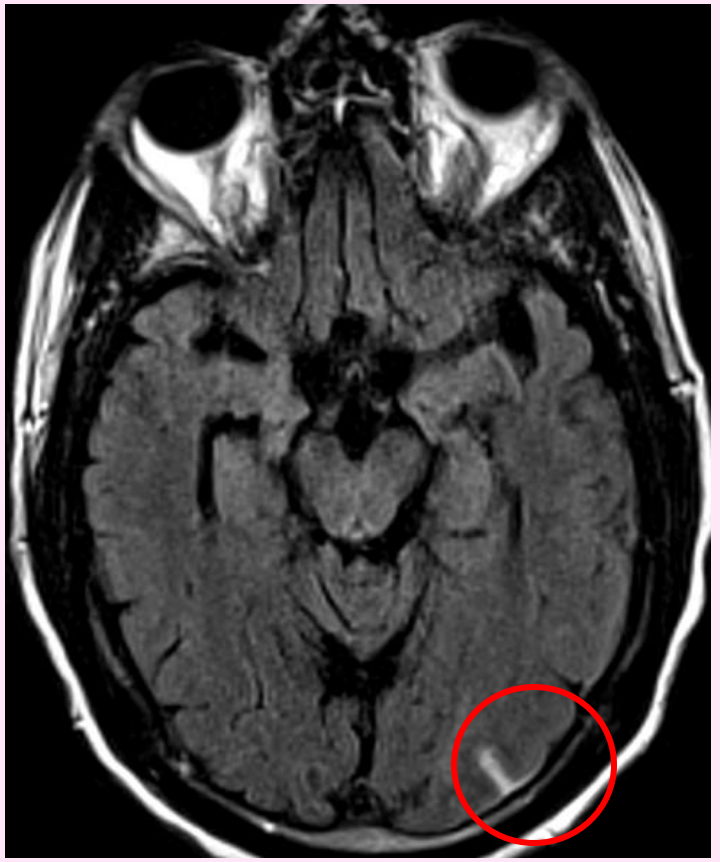
Detection of ARIA-E — sulcal effusion (mild)

1 location <5 cm
FLAIR

Baseline

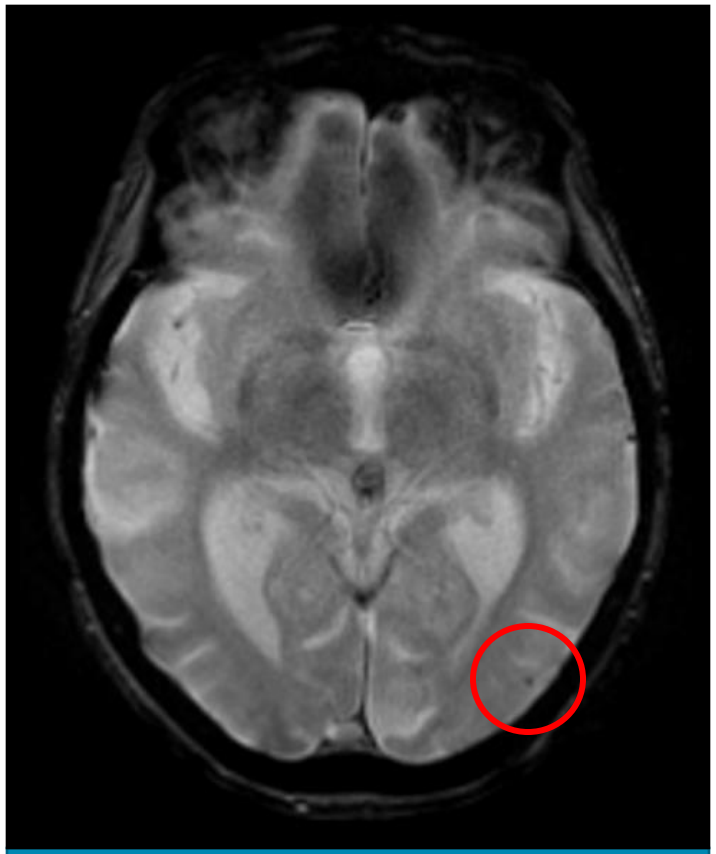


Routine monitoring

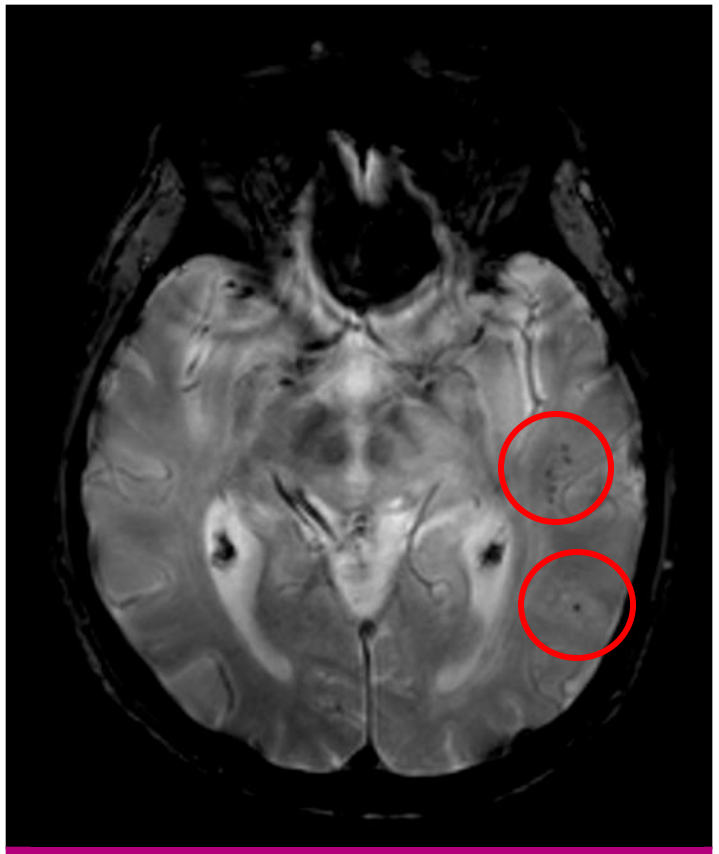


MRI images on file.
ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging

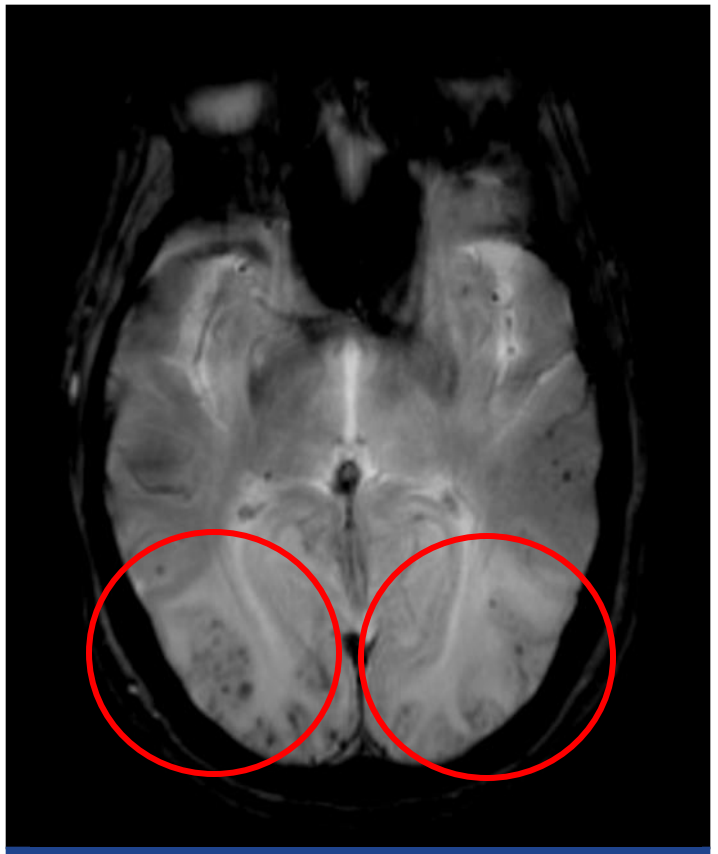
Detection of ARIA-H on T2* GRE — microhemorrhages



Mild: ≤4



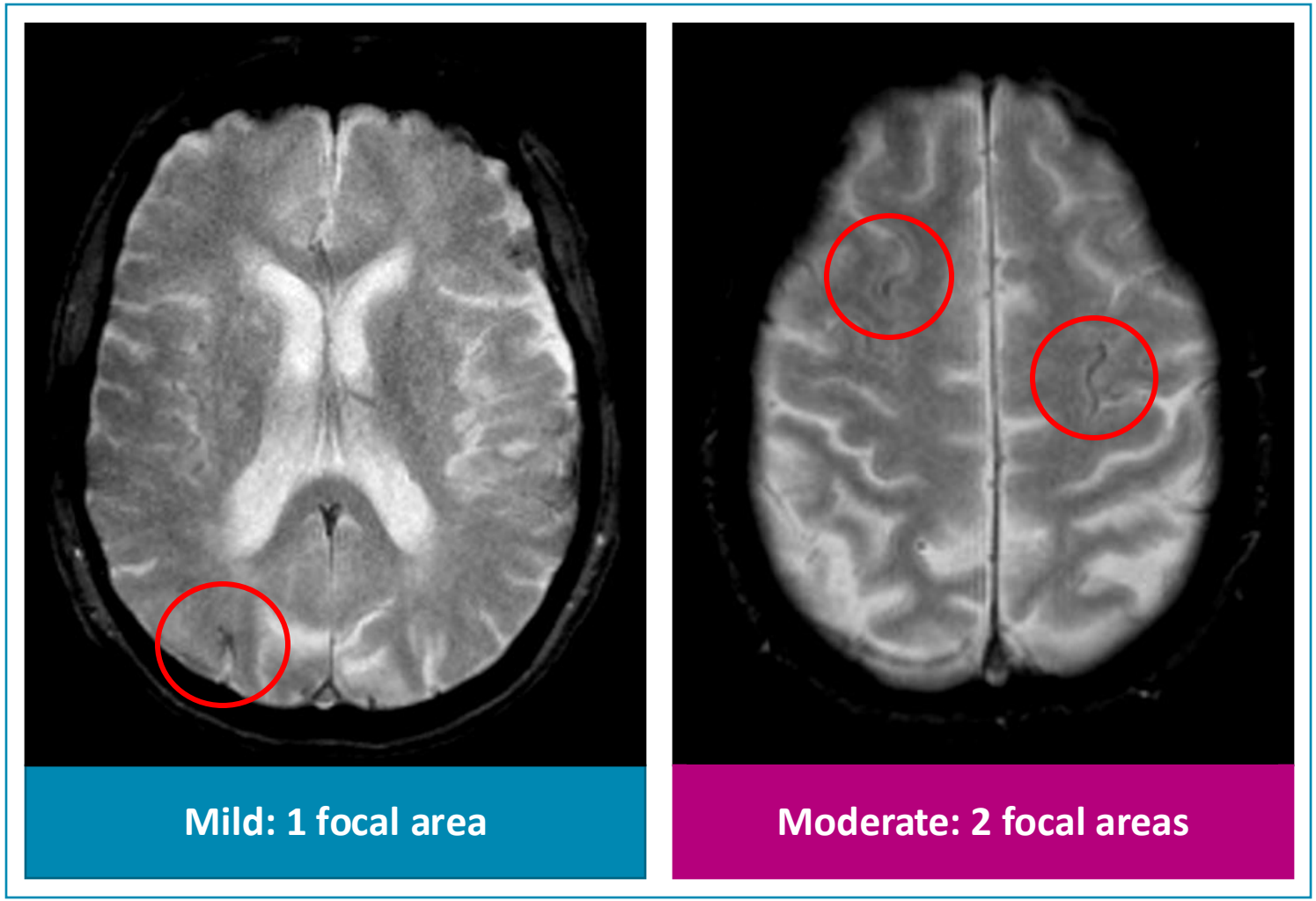
Moderate: 5–9



Severe: ≥10

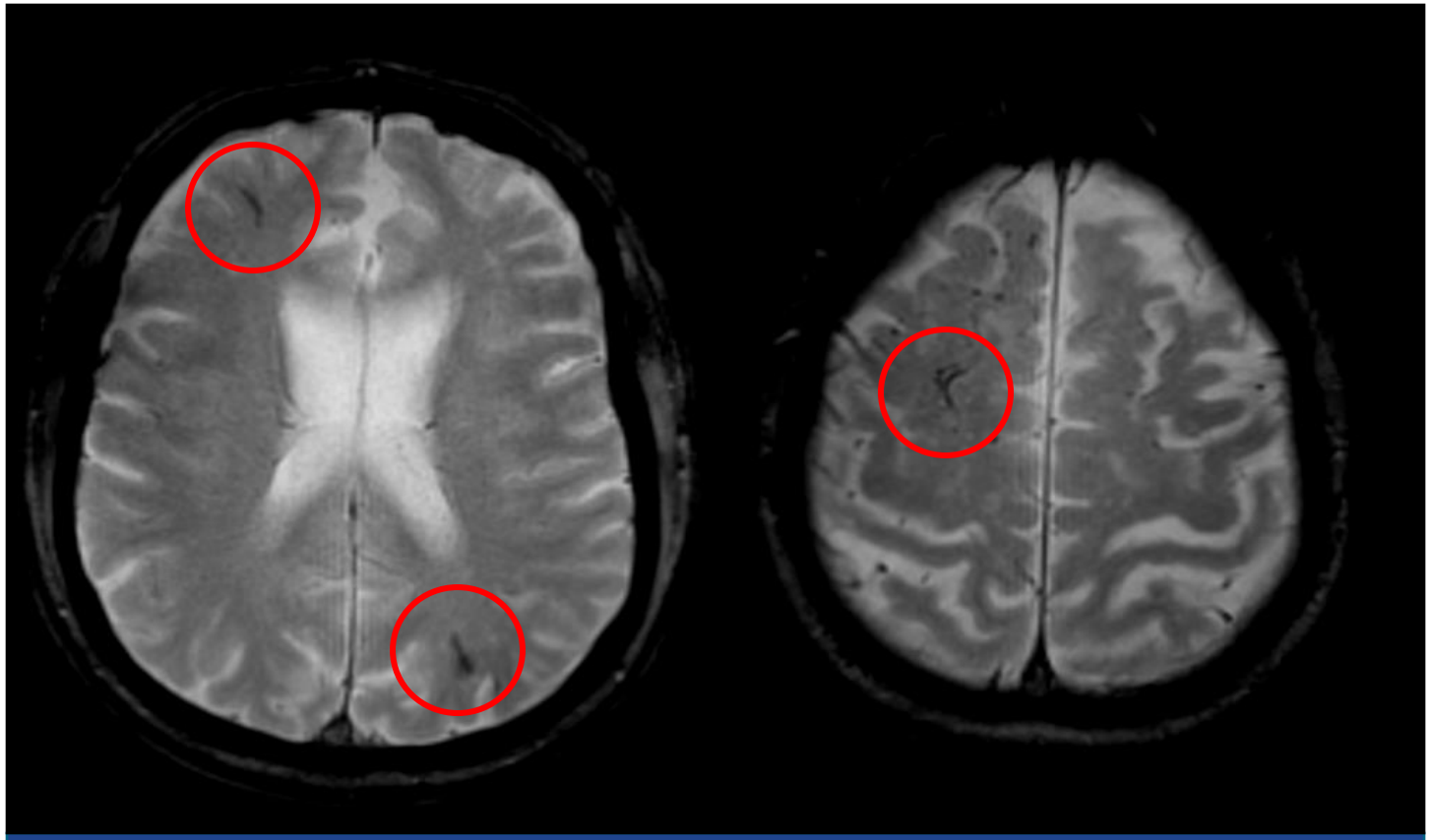
MRI images on file.
ARIA, amyloid-related imaging abnormalities; ARIA-H, ARIA-hemosiderin/hemorrhage; GRE, gradient recalled echo; MRI, magnetic resonance imaging

Detection of ARIA-H on T2* GRE — superficial siderosis



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

Detection of ARIA-H on T2* GRE — superficial siderosis

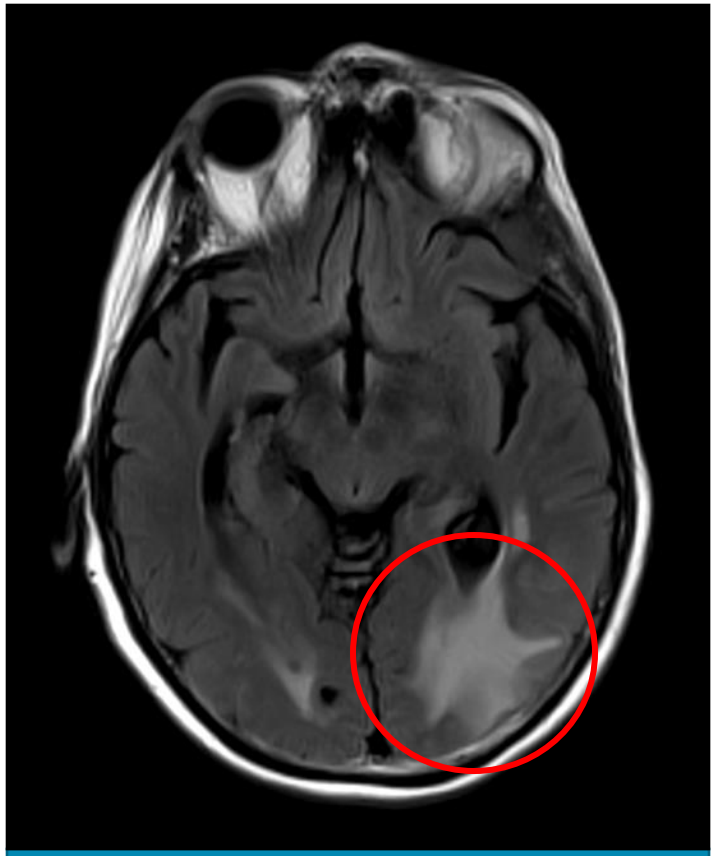


Severe: >2 focal areas

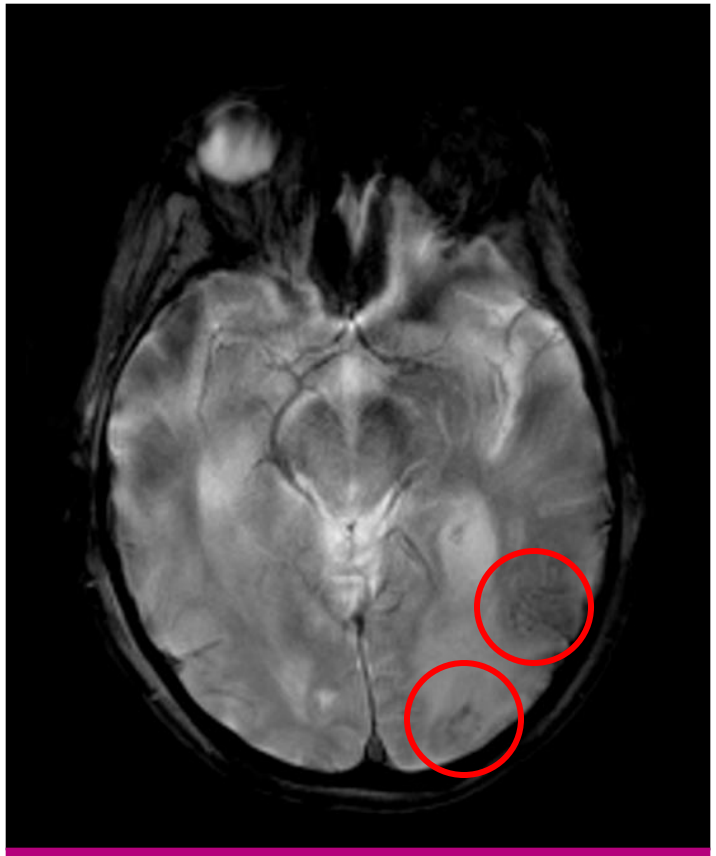
MRI images on file.
ARIA, amyloid-related imaging abnormalities; ARIA-H, ARIA-hemosiderin/hemorrhage; GRE, gradient recalled echo; MRI, magnetic resonance imaging

Detection of ARIA-E — microhemorrhages, co-occurring with ARIA-E

A leakage of heme products in the parenchyma, as a result of ARIA-E, can result in microhemorrhages (ARIA-H)[1]



ARIA-E on FLAIR



ARIA-H on T2* GRE

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