Understanding Amyloid-Related Imaging Abnormalities (ARIA)

For the Neurologist

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

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Slide outline

Introducing ARIA

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What is ARIA?

Amyloid-related imaging abnormalities (ARIA) are related to the increased permeability of amyloid-laden blood vessels to fluid or blood products that can occur spontaneously in the setting of cerebral amyloid angiopathy (CAA) and as a result of the mobilization of amyloid by monoclonal antibodies[1]

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 plaque[2,3]

MRI signals of ARIA closely parallel those of CAA[1]

Monoclonal antibodies that remove amyloid plaque are associated with an increased risk for the development of **two subtypes of ARIA:**[1,4]

- **ARIA-edema/effusion (ARIA-E)**: vasogenic edema or sulcal effusions
- **ARIA-hemosiderin (ARIA-H)**: microhemorrhages, superficial siderosis

Rare lobar intracerebral hemorrhage (also termed macrohemorrhage) occurs spontaneously in AD and with monoclonal antibodies that remove amyloid, related to underlying CAA[5]

ARIA, amyloid-related imaging abnormalities (includes ARIA-E and H); ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; CAA, cerebral amyloid angiopathy; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging

1. Sperling RA, et al. Alzheimers Dement. 2011;7:367–385; 2. Salloway S, et al. Neurology 2009;73:2061–2070; 3. Black RS, et al. Alzheimer Dis Assoc Disord 2010;24:198–203; 4`. Barakos J, et al. J Prev Alzheimers Dis. 2022;9(2):211–220; 5. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E3

Therapies that remove amyloid beta (Aβ)

Monoclonal antibodies that remove amyloid

Strategies to target and remove amyloid are based on the understanding that interfering with the underlying pathophysiologic mechanisms of the disease process could slow disease progression in the early clinical stages[1]

Amyloid-related imaging abnormalities

Interfering/removing the amyloid deposition in the brain that has built up over years can impact the vessel vasculature in the brain which can result in signal changes identifiable on MRI: **"amyloid-related imaging abnormalities or ARIA"[2]**

ARIA are known adverse events of monoclonal antibodies that remove amyloid plaque for AD

Aβ, amyloid beta; AD, Alzheimer's disease; ARIA, amyloid-related imaging abnormalities (includes ARIA-E and H); ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; 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

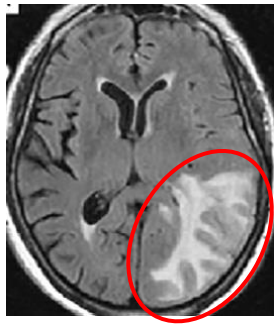
ARIA-E and ARIA-H

ARIA-E[1]

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

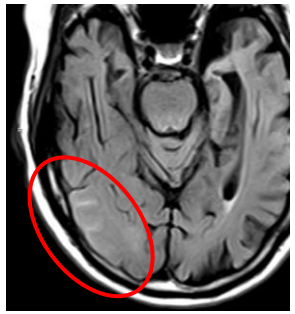
Primary MRI features

Edema



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

Effusion



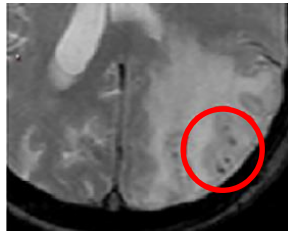
FLAIR hyperintense; increased MRI signal in sulci within right temporal-occipital lobe[a]

ARIA-H[1]

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

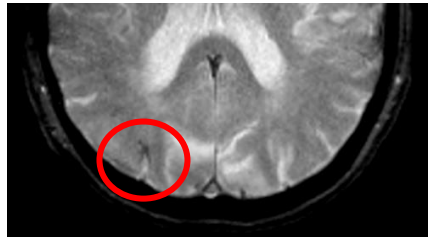
Primary MRI features

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

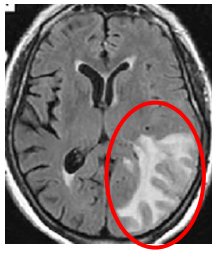
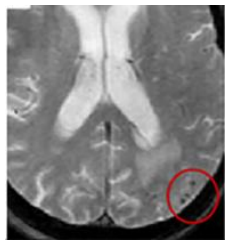
Rare lobar intracerebral hemorrhage occurs spontaneously in AD and with monoclonal antibodies that remove amyloid, related to underlying CAA[2]

Figures reproduced from [a]Barakos et al (2022); [b]MRI image data on file
ARIA, amyloid-related imaging abnormalities (includes ARIA-E and ARIA-H); ARIA-E, ARIA-edema/effusion; ARIA-H: ARIA-hemosiderin/hemorrhage; CAA, cerebral amyloid angiopathy; FLAIR, fluid-attenuated inversion recovery; GRE, gradient recalled echo; mH, microhemorrhage; MRI, magnetic resonance imaging; SWI, susceptibility weighted 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 abnormalities[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) 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
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. MRI reveals 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;7:367–85; 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 (amyloid plaques) and blood vessels (cerebral amyloid angiopathy [CAA]) contributes to Alzheimer's disease pathogenesis[1]

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

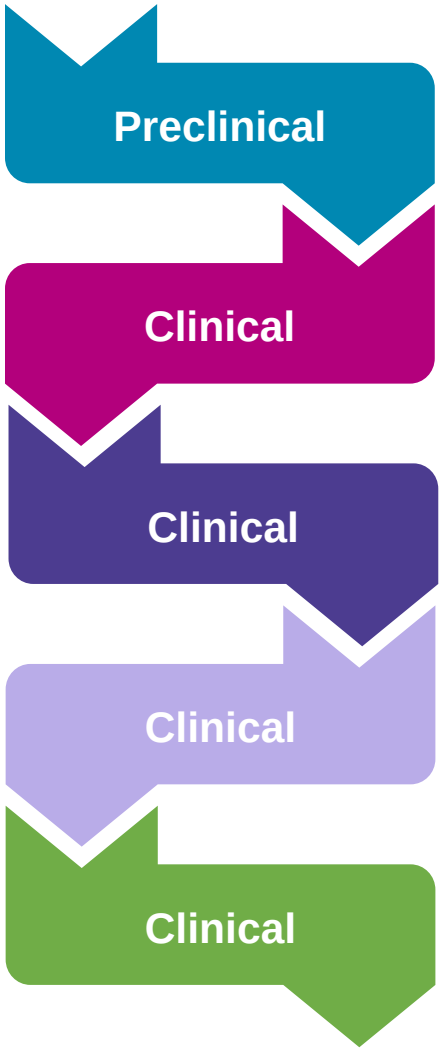
This loss of vascular integrity may be thought of as a transient exacerbation of the effects of CAA. The leakage of fluid could give rise to an increased signal detected on FLAIR images (ARIA-E), while leakage of red cells would result in ARIA-H[2,3]

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]

Aβ, amyloid beta; ARIA, amyloid-related imaging abnormalities including E and H; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; CAA, cerebral amyloid angiopathy; FLAIR, fluid-attenuated inversion recovery; GRE, gradient-recalled echo

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

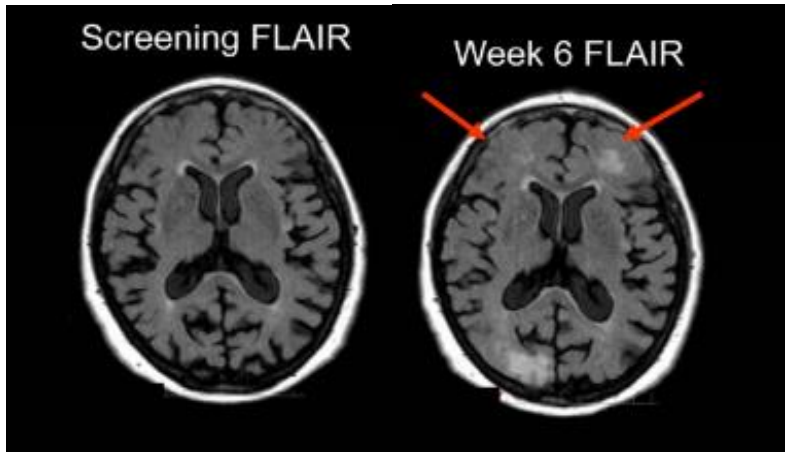
4. Reduced PiB retention on amyloid PET (which measures amyloid deposition) is both temporally and regionally associated with ARIA-E and ARIA-H[2]

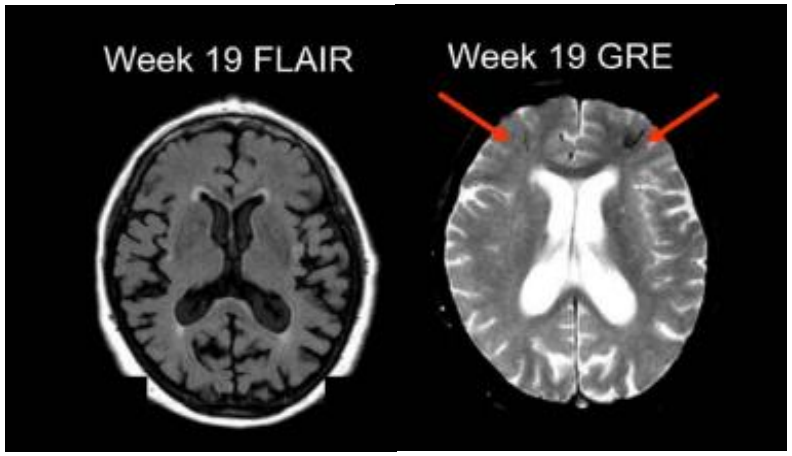
5. Treatment-related ARIA-E appears to occur early in the course of therapy, and the risk of ARIA-E decreases as duration of exposure is increased[3,4]

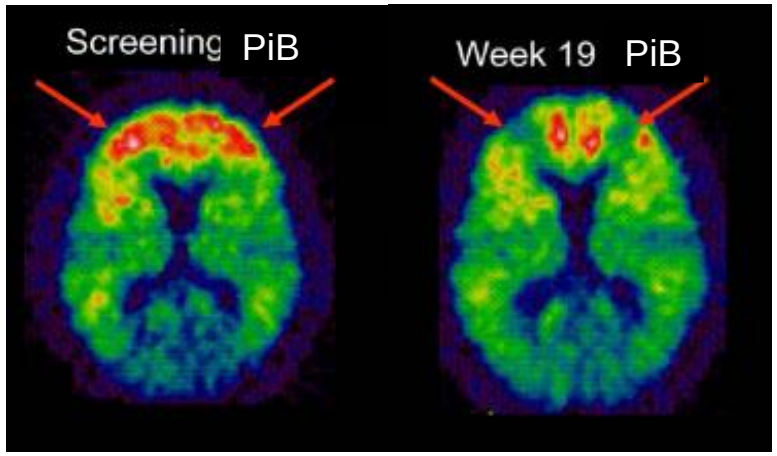
APOE ε4, apolipoprotein E ε4; ARIA, amyloid-related imaging abnormalities including E and H; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; CAA, cerebral amyloid angiopathy; PET, positron emission tomography; PiB, Pittsburgh compound B

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

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 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-E: ARIA-edema/effusion; ARIA-H: ARIA-hemosiderin/hemorrhage; FLAIR, fluid-attenuated inversion recovery; GRE, gradient-recalled echo; MRI, magnetic resonance imaging; PiB-PET, Pittsburgh compound B-positron emission tomography

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] occurrence in trials of monoclonal antibodies that remove amyloid plaque in patients with AD

- *APOE ε4* carrier status is also a risk factor for spontaneously occurring ARIA-like events in microhemorrhage in the general population,[5] microhemorrhage 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;

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 presentation

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

CAA-ri

CAA-ri is a rare and potentially life-threatening autoimmune response to vascular amyloid complication of CAA.[2] It can be a treatment-reversible disease, responsive to immunosuppressive therapies[3]

Aβ, amyloid-β; 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. Grasso, D et al. Radiol Case Rep. 2021;16(9):2514-2521; 3. Antolini, L et al. Neurology 2021;97:e1809–e1822

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 occurs)

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-β; 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

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]

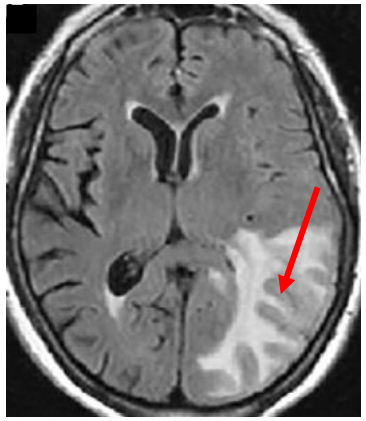


Figure from Barakos et al (2022)[4]

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]

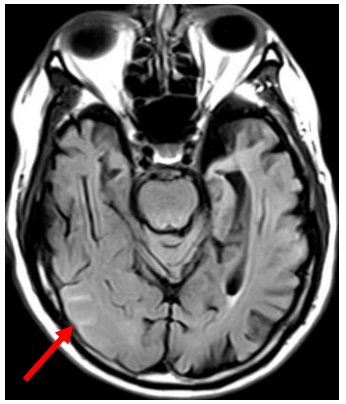


Figure from Barakos et al (2022)[4]

Additional analyses are required to confirm the prevalence of spontaneous ARIA-E[3]. In clinical trials, the rate of spontaneous ARIA-E in the placebo arm over 18 months has been found to range between 0.8% and 3.0%[5–8]

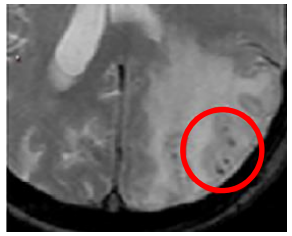
AD, Alzheimer's disease; ARIA, amyloid-related imaging abnormalities; ARIA-E: ARIA-edema/effusion; FLAIR, fluid-attenuated inversion recovery.

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. Carlson C, et al. Alzheimers Dement. 2011;396–401; 4. Barakos J, et al. J Prev Alzheimers Dis. 2022;9(2):211–220; 5. Budd-Haeberlein S, et al. J Prev Alzheimers Dis 2022;9:197–210; 6. van Dyck C, et al. N Eng J Med 2023;388:9–21; 7. Ostrowitzki S, et al. Alzheimers Res Ther. 2017;9(1):95; 8. Vandenberghe R, et al. Alzheimers Res Ther. 2016;8:18.

ARIA-H

Microhemorrhages

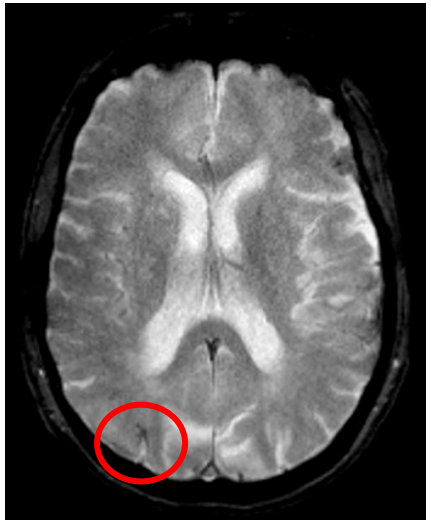
- Small deposits of iron in the brain **parenchyma** in the form of **hemosiderin**[1]
- Typically manifest as new **hypointense lesions on T2*GRE MRI sequences** (typically defined by a cutoff of **<10 mm**)[2]
- Thought to represent residua of a small leakage of blood from a vessel into **adjacent tissue**[1]
- 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, intracerebral hemorrhage (≥10 mm) can also occur**[2]



MRI image data on file

Superficial Siderosis

- **Curvilinear low intensities on T2*GRE MRI sequences** that lie adjacent to the surface of the brain[1]
- 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 old[4]



MRI image data on file

ARIA, amyloid-related imaging abnormalities (includes ARIA-E and H); ARIA-E, ARIA-edema/effusion; 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;34:1958-1965. 3. Poels MM, et al. Stroke. 2010;41:S103-S106
4. 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 and **decrease 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 (includes ARIA-E and H); ARIA-E, ARIA-edema/effusion; ARIA-hemosiderin/hemorrhage

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 usually recognized as incidental ARIA during follow-up evaluation on MRI[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, be 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]

Aβ, amyloid beta; APOE ε4 , apolipoprotein E ε4; ARIA, amyloid-related imaging abnormalities (includes ARIA-E and H); 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 (includes ARIA-E and ARIA-H); ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage

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

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 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 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 (includes ARIAE and H); ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage

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

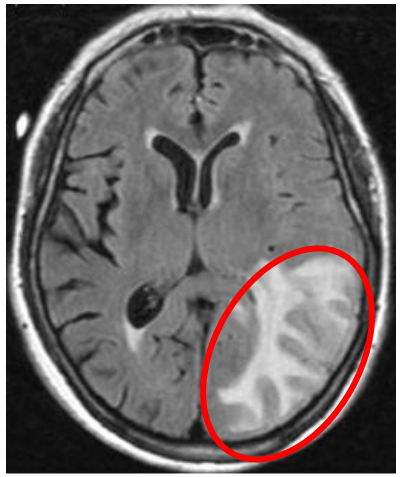


Figure adapted from Barakos et al, (2022)[3]

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 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 including E and H; 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; T2-FLAIR, T2-weighted fluid-attenuated inversion recovery; TE, echo time; SWI, susceptibility-weighted imaging.

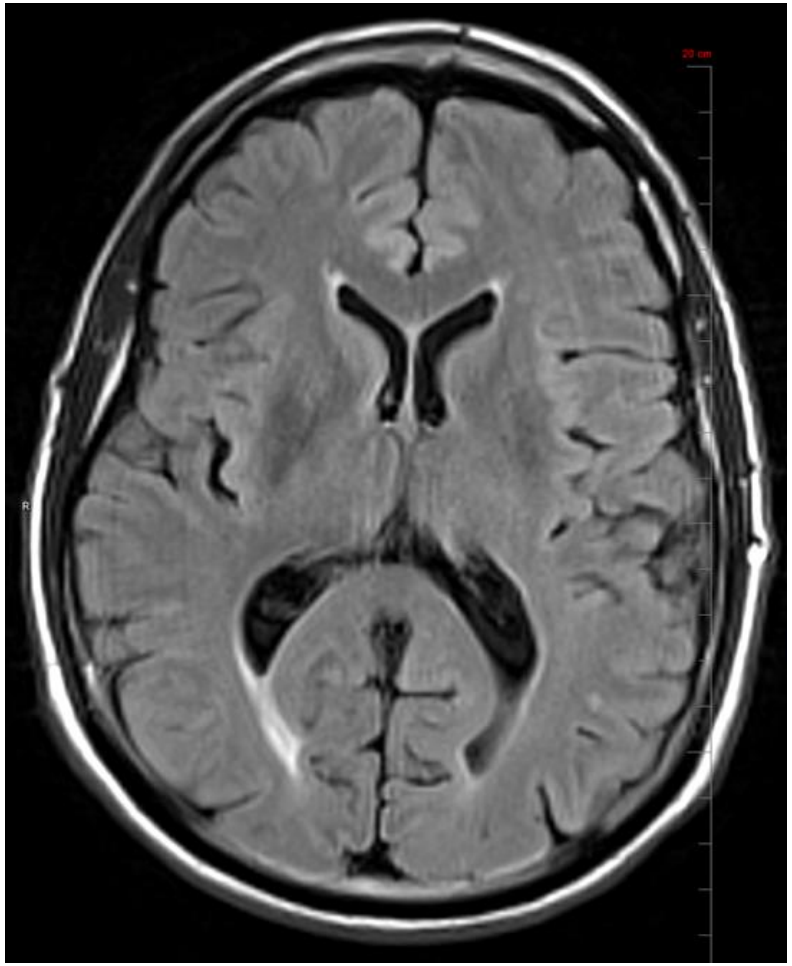
1. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35; 2. Sperling RA, et al. Alzheimers Dement. 2011;7(4):367–385; 3. Barakos J, et al. J Prev Alzheimers Dis. 2022;9(2):211–220

Detection of ARIA-E– parenchymal edema (Mild)

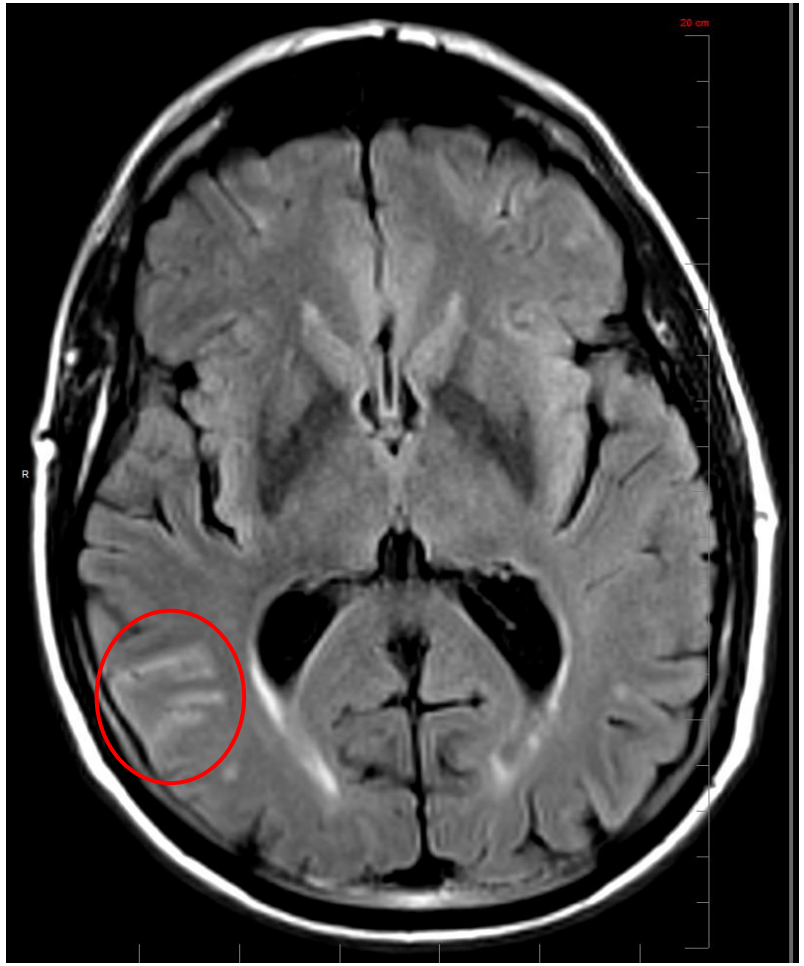
Location < 5 cm

FLAIR

Baseline



Routine monitoring

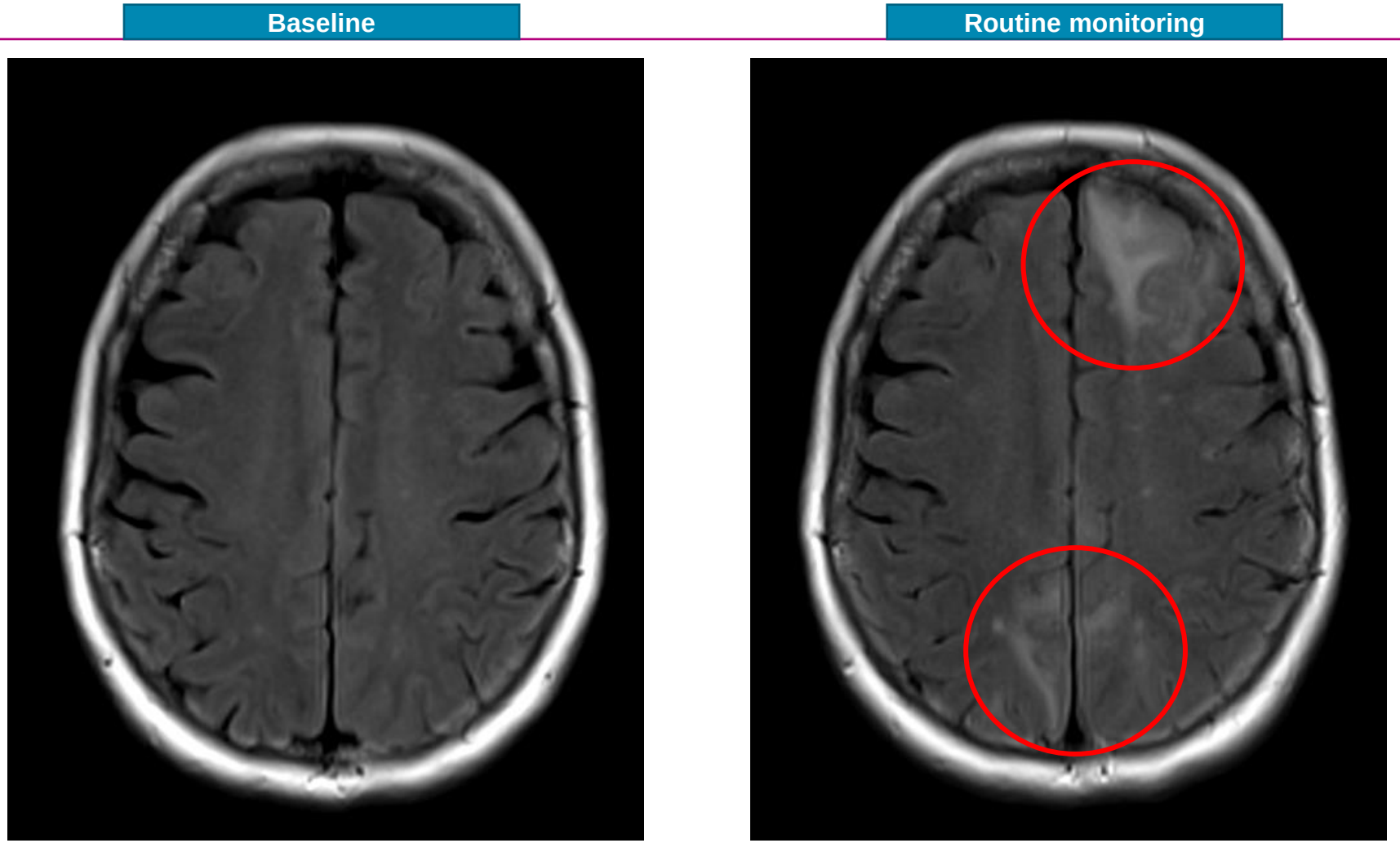


MRI images data on file
ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; FLAIR, fluid-attenuated inversion recovery

Detection of ARIA-E– parenchymal edema (Moderate)

>1 location each <10 cm

FLAIR



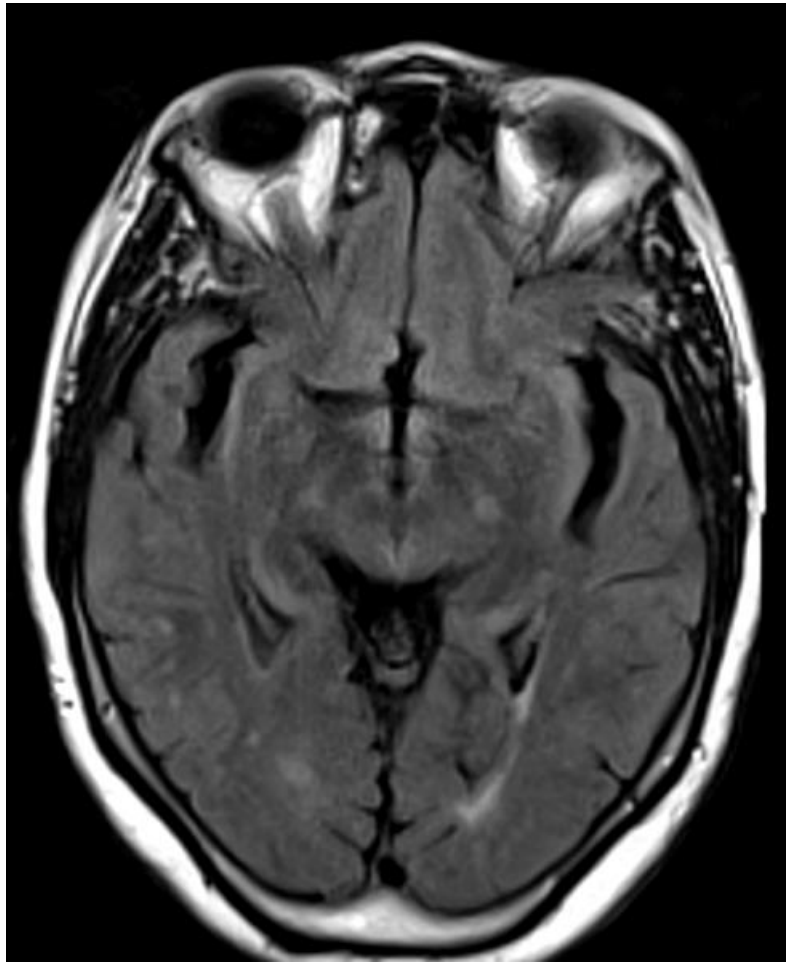
MRI images data on file
ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; FLAIR, fluid-attenuated inversion recovery

Detection of ARIA-E– parenchymal edema (Severe)

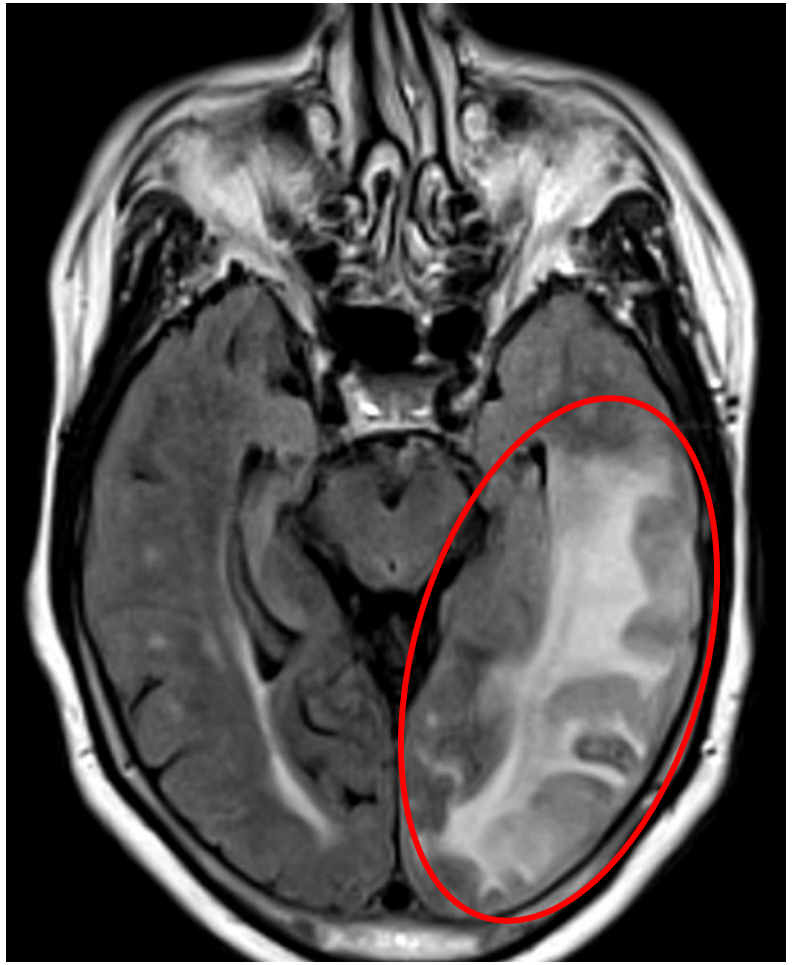
1 or more location each >10 cm

FLAIR

Baseline



Routine monitoring



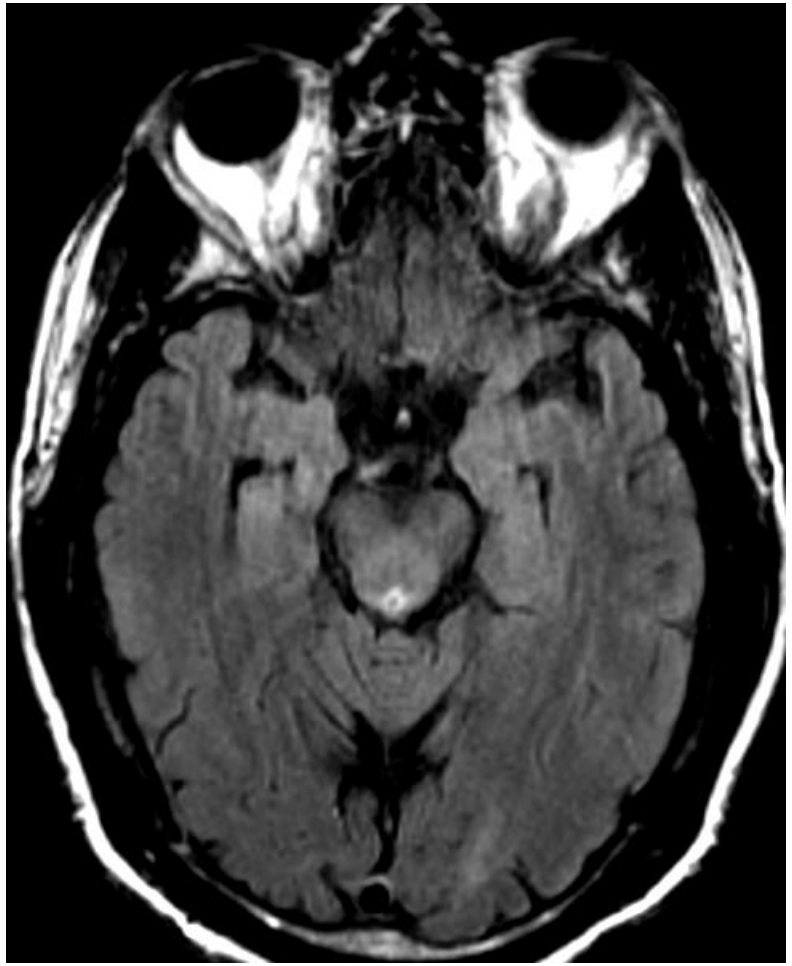
MRI images data on file
ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; FLAIR, fluid-attenuated inversion recovery

Detection of ARIA-E – sulcal effusion (Mild)

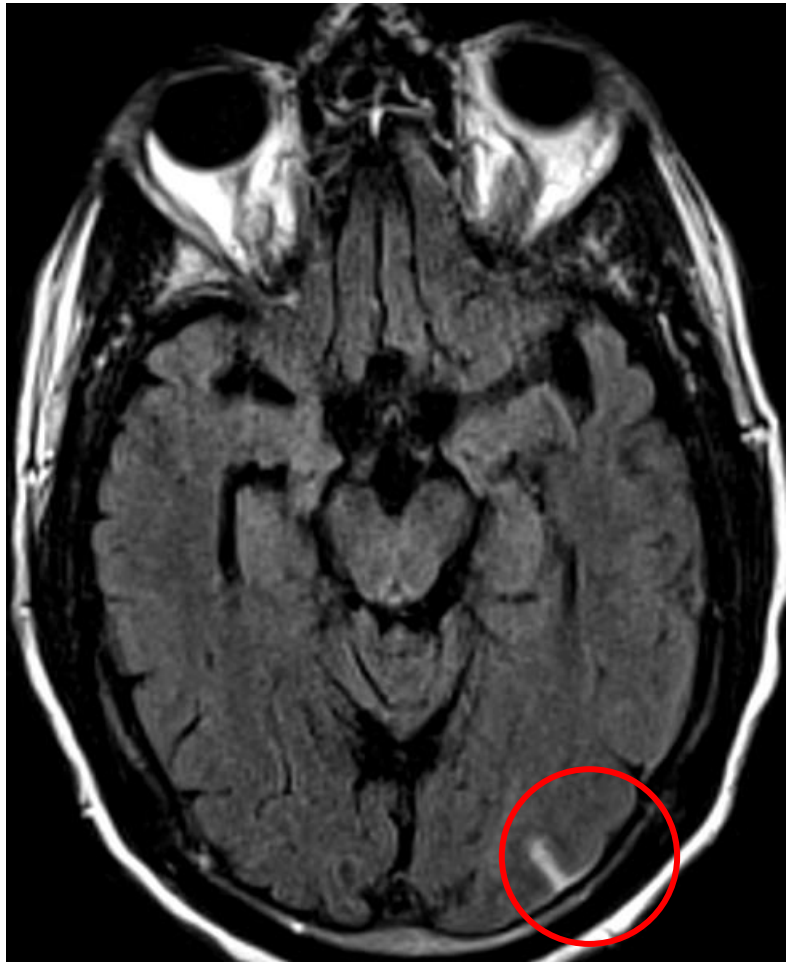
Location < 5 cm

FLAIR

Baseline

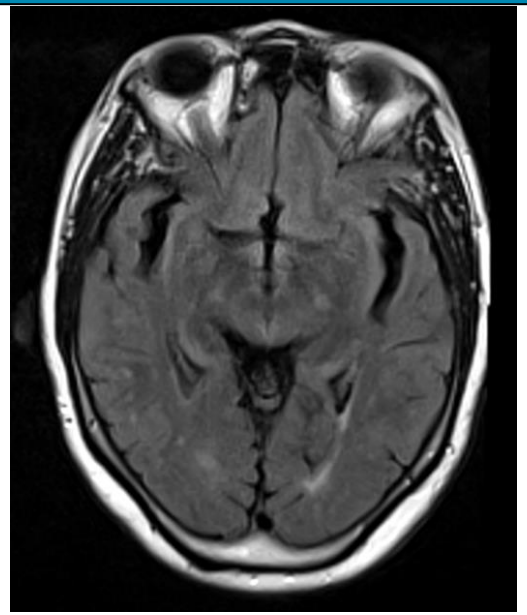
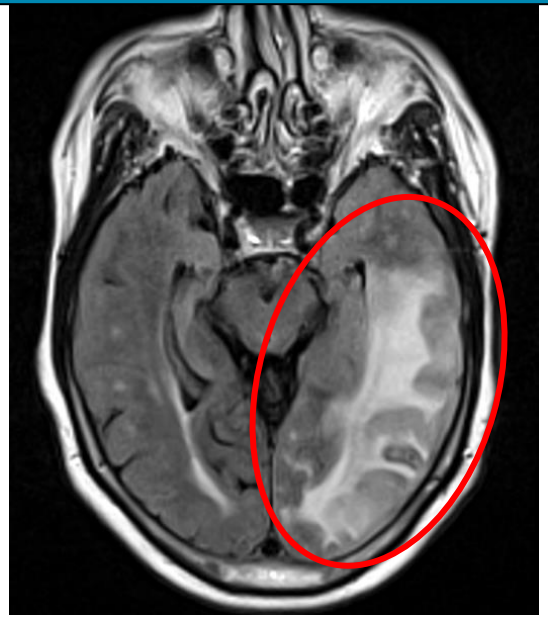


Routine monitoring



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

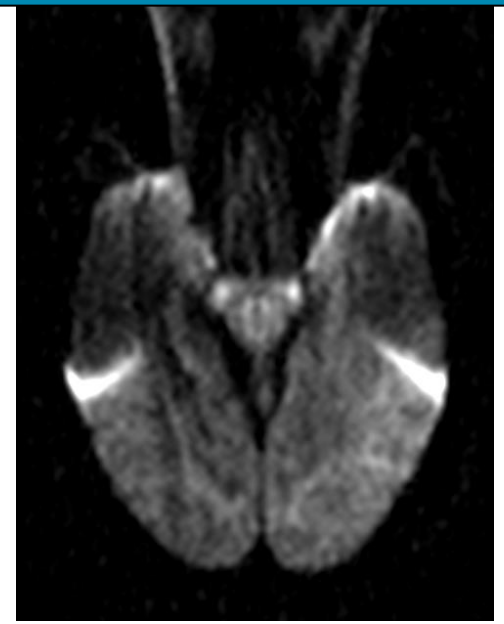
Differentiating ARIA-E from ischemic stroke

Baseline	Week 12
	

Severe ARIA-E

Development of extensive T2-FLAIR hyperintense signal throughout the left frontal and parietal lobes measuring >10 cm (severe ARIA-E)

DWI

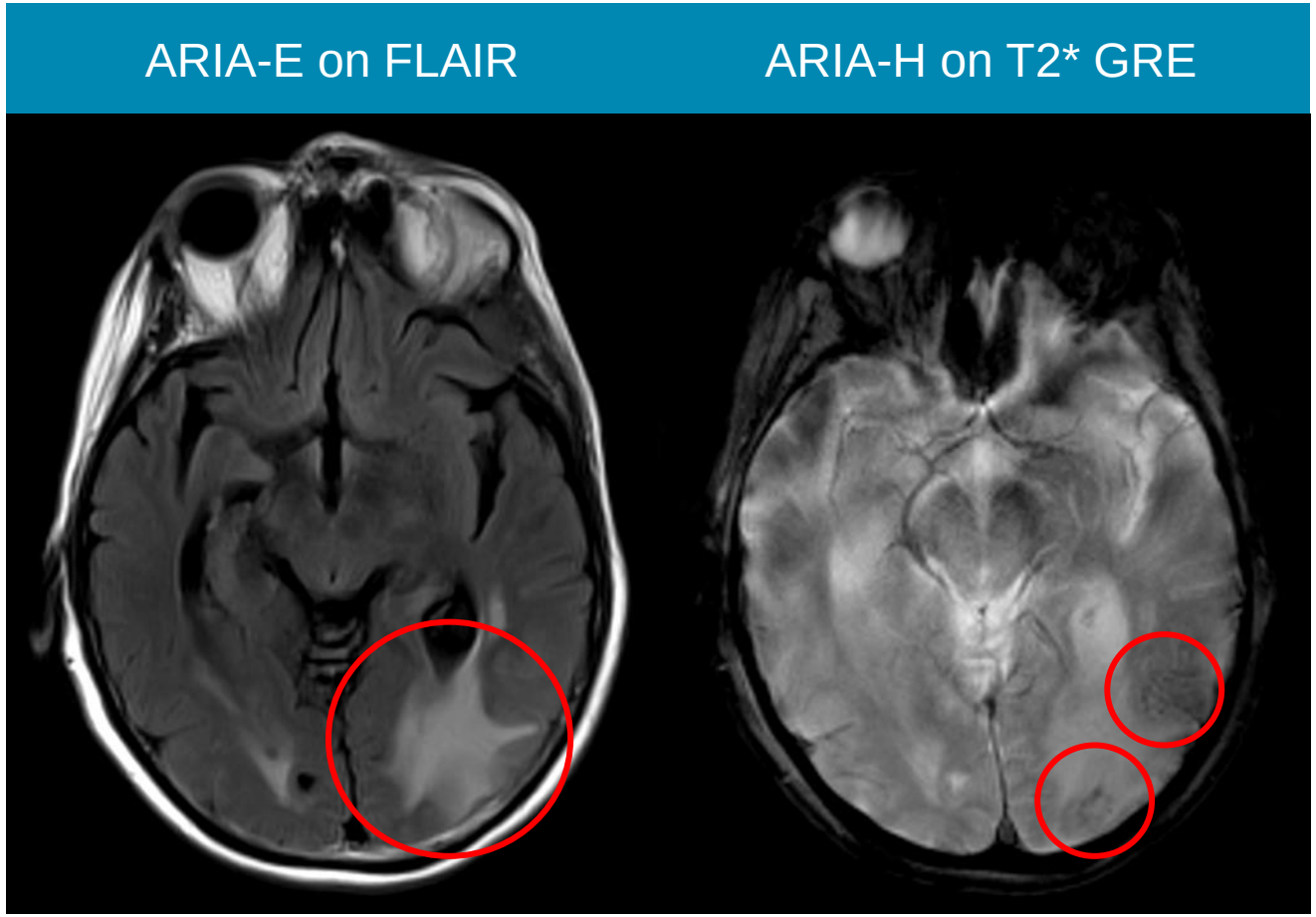


The DWI is negative which differentiates ARIA-E from acute ischemia or other cause of cytotoxic edema

MRI images data on file
ARIA, amyloid-related imaging abnormalities (including E and H); ARIA-E, ARIA-edema/effusion; DWI, diffusion-weighted imaging; T2-FLAIR, T2-weighted fluid attenuated inversion recovery

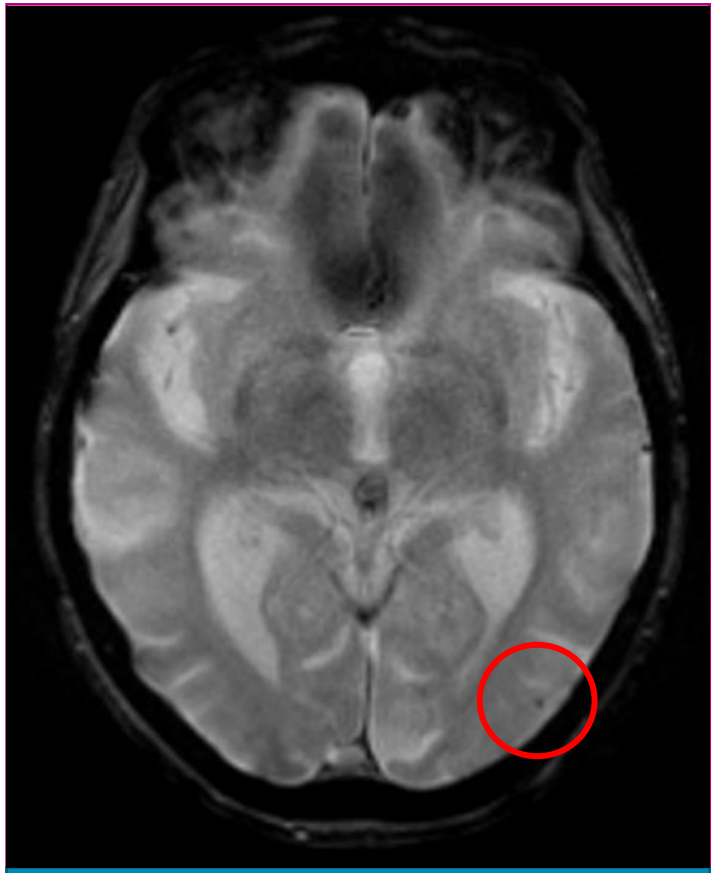
Detection of ARIA-E – microhemorrhages, co-occurring with ARIA-E

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

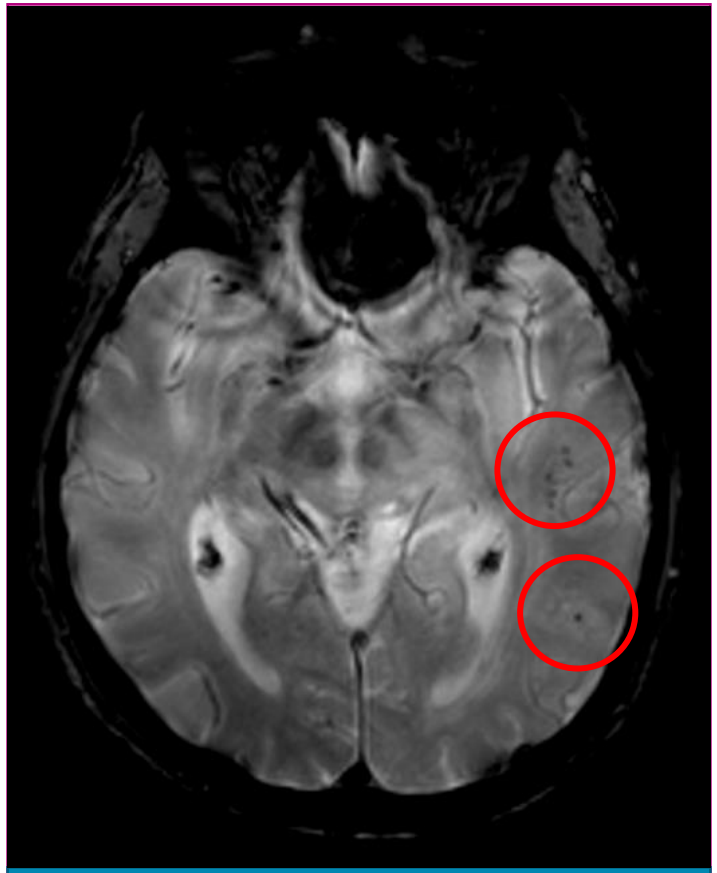


MRI images data on file
ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; FLAIR, fluid-attenuated inversion recovery; GRE, gradient echo sequence
1. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35

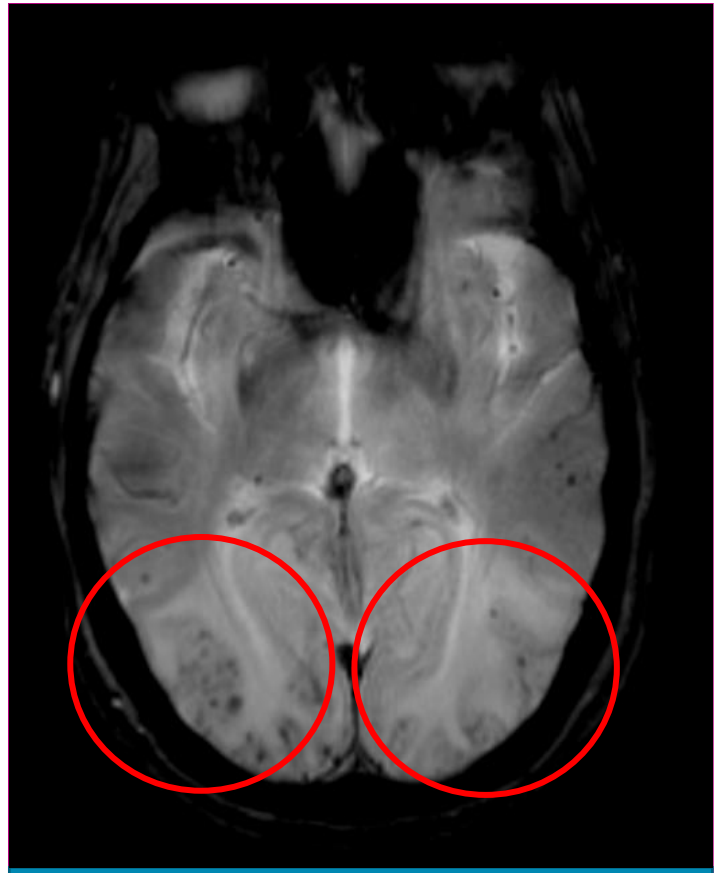
Detection of ARIA-H on T2* GRE – microhemorrhages



Mild: ≤4



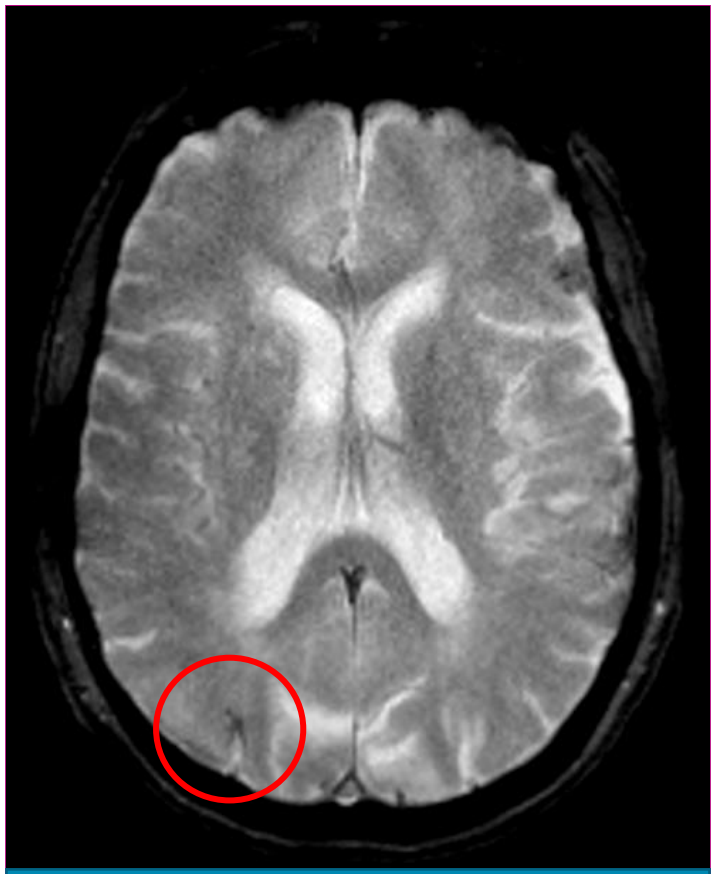
Moderate: 5–9



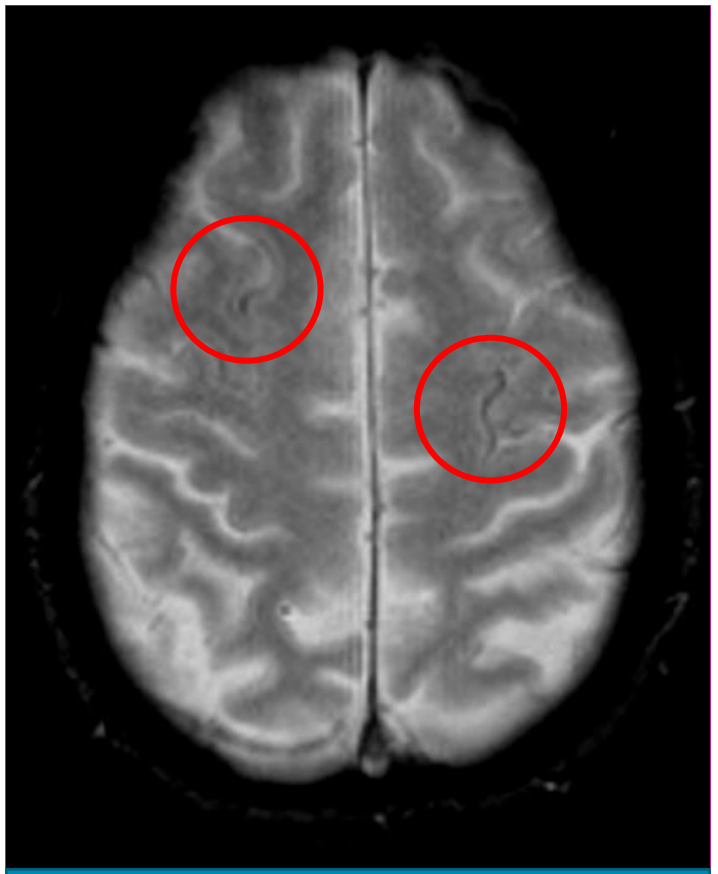
Severe: ≥10

MRI images data on file
ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; GRE, gradient echo sequence

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



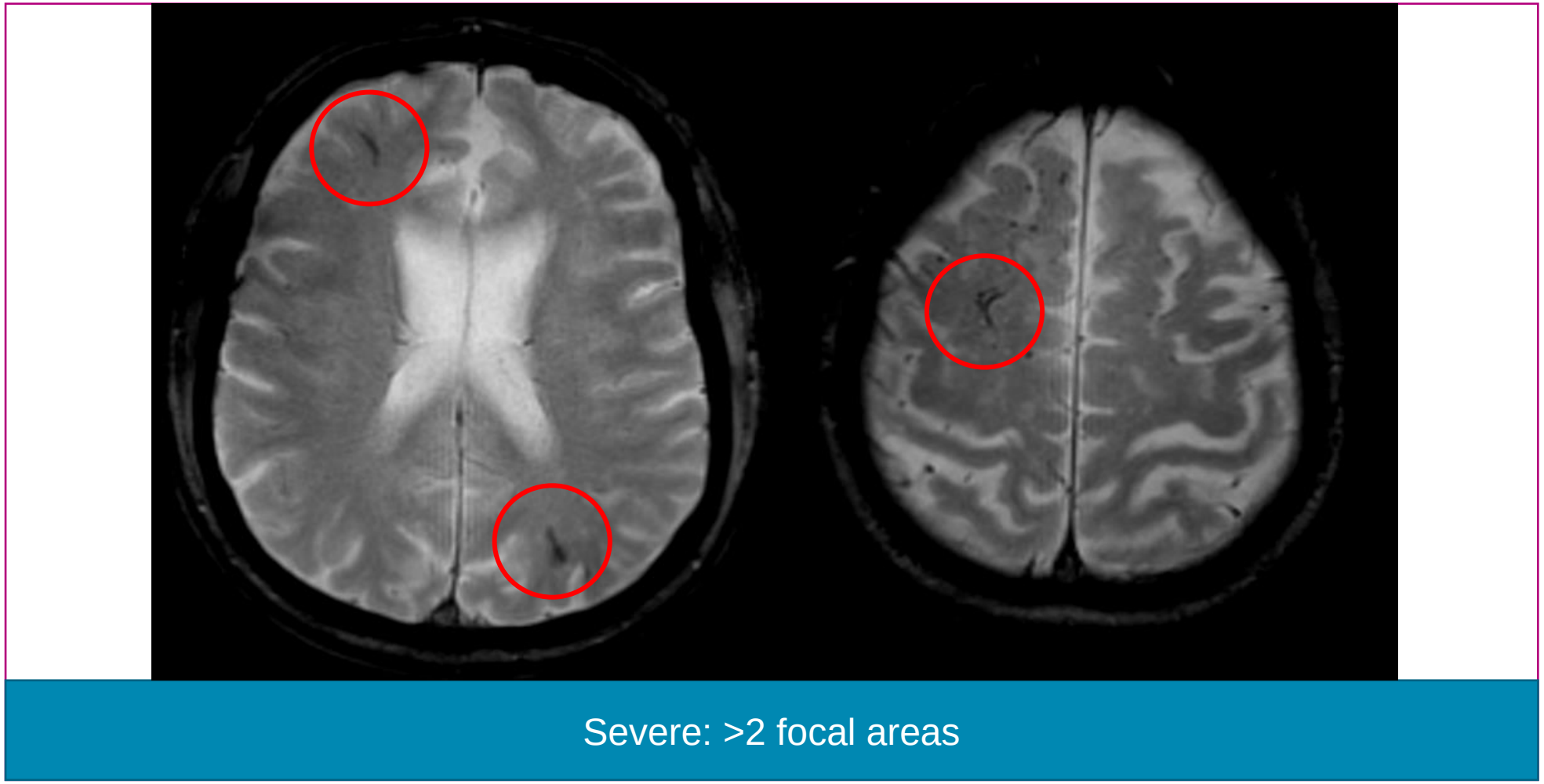
Mild: 1 focal area



Moderate: 2 focal areas

MRI images data on file
ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; GRE, gradient echo sequence

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



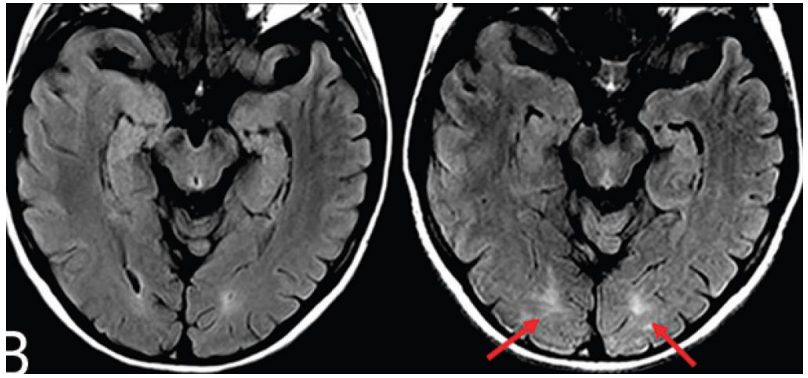
Severe: >2 focal areas

MRI images data on file
ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; GRE, gradient echo sequence

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 versus 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).

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 time points with the two scans performed on different vendor scanners
- Repeat imaging of participant on vendor 1 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[2]

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. 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

Potential interpretation pitfalls of MRI when detecting ARIA-H

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

Enhanced sensitivity with SWI is accomplished by forming both a magnitude and a phase image and multiplying the magnitude image by the phase image[3]

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

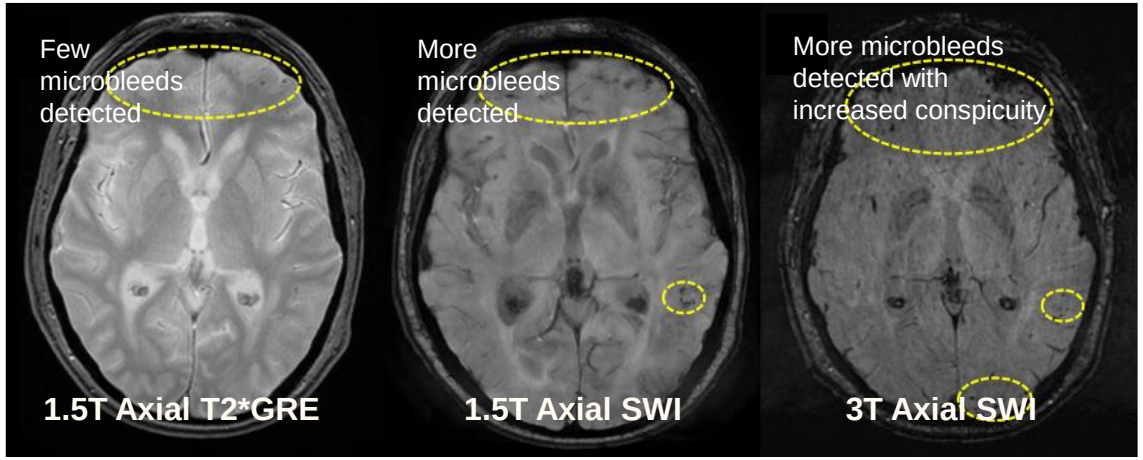


Image of a patient with spontaneous intracerebral hemorrhage. Figure reproduced with permission from Puy et al (2021).

Thick-section acquisitions may make it difficult to distinguish a mH from a vessel flow void[3]

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

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

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

Severe ARIA-E[1]*

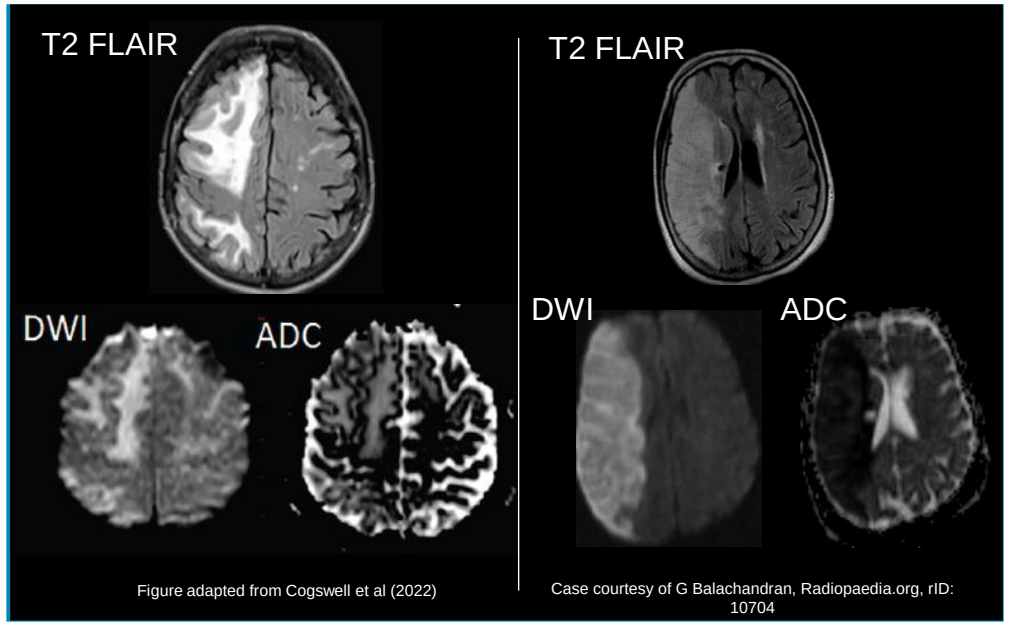


Figure adapted from Cogswell et al (2022)

Right MCA . Ischemic Stroke[2]

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

- 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]
- 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-E, ARIA-edema/effusion; DWI, diffusion-weighted imaging; T2-FLAIR: T2 Fluid attenuated inversion recovery; MCA, middle cerebral artery

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

Differential diagnosis: subarachnoid hemorrhage

T2 axial FLAIR. Effusion

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

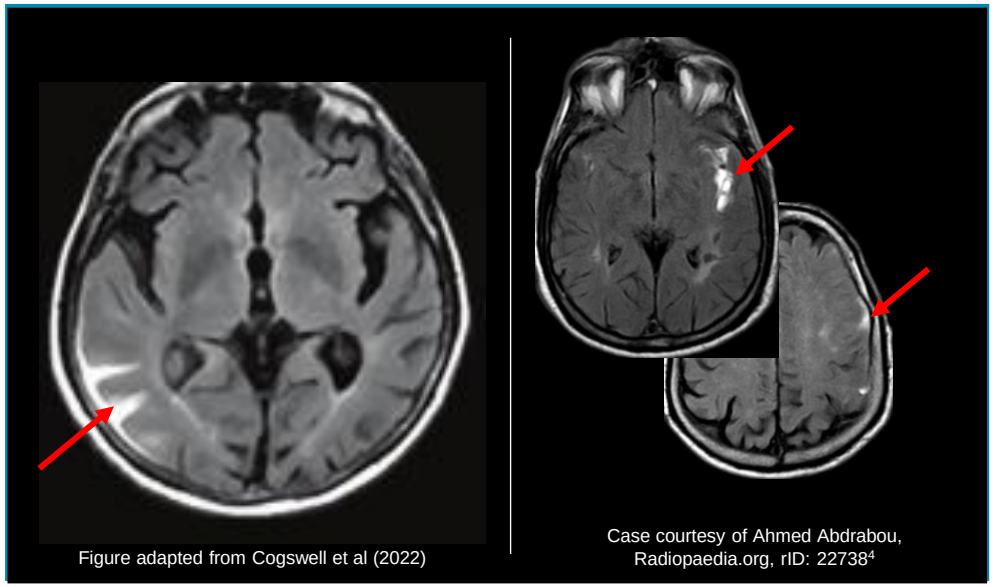


Figure adapted from Cogswell et al (2022)

Case courtesy of Ahmed Abdrabou, Radiopaedia.org, rID: 22738[4]

- 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 and focal neurological signs can also be present[4]

ARIA-E, ARIA-edema/effusion; SAH, subarachnoid hemorrhage; T2-FLAIR, T2-Fluid-attenuated inversion recovery

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 FLAIR Edema

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

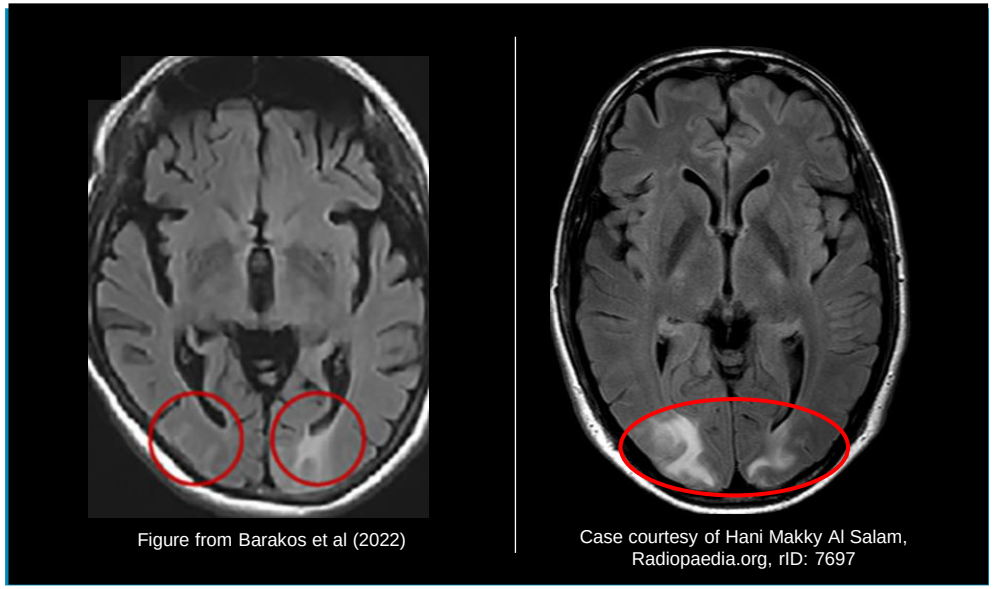


Figure from Barakos et al (2022)

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

- PRES could resemble ARIA-E on imaging[1]
- PRES frequently develops from cytotoxic medication or disorders such as preeclampsia, sepsis, renal disease, or autoimmune disorders[2]
- Signs of PRES[2]:
  - Encephalopathy, epileptic seizures, visual disturbances, and focal neurological deficits
- Less specific signs include:[2]
  - Headache, nausea, vomiting
- In this case, clinical history is **important for differentiation**

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; T2-FLAIR, T2-Fluid-attenuated inversion recovery

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

Management of ARIA

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Management of ARIA

- Refer to prescribing information of monoclonal antibodies that remove amyloid for monitoring and management guidelines of ARIA
- Discuss ARIA and associated symptoms 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[1,2]
- 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[3]
- 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[4]
- In cases of severe or serious ARIA-E or ARIA-H, monitoring neurologic status closely and early empiric administration of high dose intravenous corticosteroids should be considered[1]

ARIA, amyloid-related imaging abnormalities (due to ARIA-E and ARIA-H); ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; CT, computed tomography; MRI, magnetic resonance imaging.

1. Cummings J, et al. J Prev Alzheimers Dis 2022;9:221–230; 2, Cummings J et al. Alzheimers Dement. 2021;7(1):e12179 3. Barakos J, et al. J Prev Alzheimers Dis. 2022;9(2):211–220; 4. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35.

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.