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.
Introducing ARIA
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.

Therapies that remove amyloid beta (Aβ)

Introducing ARIA

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

Introducing ARIA

ARIA-E and ARIA-H

Primary MRI features

**ARIA-E**
Interstitial vasogenic edema or sulcal effusion that manifests as parenchymal or sulcal hyperintensities

<table>
<thead>
<tr>
<th>Edema</th>
<th>Effusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLAIR hyperintense; parenchymal edema in left occipital-parietal lobe&lt;sup&gt;a&lt;/sup&gt;</td>
<td>FLAIR hyperintense; increased MRI signal in sulci within right temporal-occipital lobe&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Microhemorrhage</th>
<th>Superficial siderosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Punctate foci of signal void on T2*GRE in an area of parenchymal edema&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Superficial siderosis on T2*GRE imaging&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Intracerebral hemorrhage
Rare lobar intracerebral hemorrhage occurs spontaneously in AD and with monoclonal antibodies that remove amyloid, related to underlying CAA<sup>2</sup>

Figures reproduced from 1 Barakos et al (2022); 2 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.

**ARIA-E and ARIA-H: characteristics**

ARIA is an umbrella term used to describe two types of amyloid-related imaging abnormalities

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<table>
<thead>
<tr>
<th></th>
<th><strong>ARIA-E</strong>&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th><strong>ARIA-H</strong>&lt;sup&gt;1,2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary diagnostic imaging sequence</strong></td>
<td>FLAIR</td>
<td>T2* GRE</td>
</tr>
<tr>
<td><strong>Nature of leakage products</strong></td>
<td>Proteinaceous fluids</td>
<td>Blood-degradation products</td>
</tr>
<tr>
<td><strong>Location of increased vascular permeability</strong></td>
<td>Leptomeninges: sulcal effusions (i.e., exudates) Parenchyma: vasogenic edema</td>
<td>Leptomeninges: superficial hemosiderin deposits (superficial siderosis) Parenchyma: microhemorrhages (typically defined as &lt;10 mm) Intracerebral hemorrhage (macrohemorrhage; ≥10 mm)</td>
</tr>
<tr>
<td><strong>Evaluation of severity</strong></td>
<td>MRI severity scales&lt;sup&gt;3&lt;/sup&gt; and assessment of symptoms</td>
<td>The number of microhemorrhages and hemosiderin deposits on MRI and assessment of symptoms</td>
</tr>
<tr>
<td><strong>Image</strong></td>
<td>ARIA-E seen on FLAIR images demonstrating increased signal in the left hemisphere, affecting both gray and white matter&lt;sup&gt;4&lt;/sup&gt;</td>
<td>ARIA-H seen on T2* GRE MRI. MRI reveals several microhemorrhages (&lt;10 mm; red circle)&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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**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.
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.

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

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.

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.

References:
Evidence of pathophysiology

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

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)

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

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

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

References:
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.

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
- Therefore, when exposed to anti-Aβ monoclonal antibodies, they would experience a larger antibody-mediated shift in Aβ compared with non-carriers
- The presence of APOE ε4 alleles is one of the most robust known risk factors for ARIA-E and a proposed risk factor for ARIA-H 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, microhemorrhage among patients in memory clinics, and CAA-ri

These findings support the hypothesis that vascular amyloid plays a key role in the induction of ARIA-E and ARIA-H

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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.

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

## Pathophysiology

**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.  

**CAA presentation**

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

**CAA-ri**

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

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Aβ, amyloid-β; AD, Alzheimer’s disease; CAA, cerebral amyloid angiopathy; CAA-ri, CAA-related inflammation.

Commonalities in pathophysiology between CAA-ri and ARIA

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

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Location</th>
<th>Syndrome resemblance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased number of microbleeds and APOE ε4 genotype</td>
<td>CAA develops to a greater extent in cortical and leptomeningeal vessels (the locations where ARIA occurs)</td>
<td>Infiltration of inflammatory cells (microglia, T cells, and Aβ-containing multinucleated cells) in CAA-ri suggests possible spontaneous anti-Aβ immunization</td>
</tr>
</tbody>
</table>

Aβ, amyloid-beta; APOE ε4, apolipoprotein E ε4; ARIA, amyloid-related imaging abnormalities; CAA, cerebral amyloid angiopathy; CAA-ri, CAA-related inflammation.
Deeper focus on ARIA
ARIA-E

Deeper focus on ARIA

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
- Parenchymal signal abnormalities can be quite subtle in a single region, multifocal, or nearly pan-hemispheric

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
- Sulcal FLAIR hyperintensity in the leptomeningeal or sulcal space may be seen in isolation or near gray matter disturbances

Additional analyses are required to confirm the prevalence of spontaneous ARIA-E.
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%.

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

- Small deposits of iron in the brain parenchyma in the form of hemosiderin
  
- Typically manifest as new hypointense lesions on T2*GRE MRI sequences (typically defined by a cutoff of <10 mm)
  
- Thought to represent residua of a small leakage of blood from a vessel into adjacent tissue
  
- The baseline prevalence of microhemorrhages is estimated to be 15.3%
  - 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
  
- Less commonly, intracerebral hemorrhage (≥10 mm) can also occur

Superficial Siderosis

- Curvilinear low intensities on T2*GRE MRI sequences that lie adjacent to the surface of the brain
  
- 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
  
- 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

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ARIA, amyloid-related imaging abnormalities (includes ARIA-E and H); ARIA-E, ARIA-edema/effusion; GRE, gradient-recalled echo; MRI, magnetic resonance imaging.

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 exposure1,2

- 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 disturbance1,3

- 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-threatening4
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
Diagnosis of ARIA
## ARIA risk factors

### Diagnosis of ARIA

**APOE ε4 carrier status**

**Pre-treatment microhemorrhage**

**Treatment with monoclonal antibodies that remove amyloid**

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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

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Diagnosis of ARIA

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_e:19–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:

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIA-E Sulcal and/or cortical/subcortical FLAIR hyperintensity</td>
<td>1 location &lt;5 cm</td>
<td>1 location 5–10 cm OR &gt;1 location each &lt;10 cm</td>
<td>1 or more location &gt; 10 cm</td>
</tr>
<tr>
<td>ARIA-H Superficial siderosis</td>
<td>1 focal area</td>
<td>2 focal areas</td>
<td>&gt; 2 focal areas</td>
</tr>
<tr>
<td>ARIA-H Number of new Microhemorrhages</td>
<td>≤4</td>
<td>5–9</td>
<td>≥10</td>
</tr>
</tbody>
</table>

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

Diagnosis of ARIA
## Recommended MRI protocols for baseline imaging and detection of ARIA

### MRI protocol: standards for detection of ARIA in clinical trials

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3T scanner (recommended)</td>
<td>High-field strength scanners have greater sensitivity but limited availability. 1.5T is endorsed as a minimum standard.</td>
</tr>
<tr>
<td>1.5T scanner (minimal)</td>
<td>Thinner slices increase resolution but should be balanced against the loss in signal-to-noise ratio.</td>
</tr>
<tr>
<td>Slice thickness² ≤5 mm</td>
<td>Thinner slices increase resolution but should be balanced against the loss in signal-to-noise ratio.</td>
</tr>
<tr>
<td>T2* GRE TE² ≥ 20 ms (20 ms at 3T, 30 ms at 1.5T)</td>
<td>Longer TE increases sensitivity to detection.</td>
</tr>
<tr>
<td>2D T2* GRE or SWI²⁻³ (for ARIA-H)</td>
<td>To identify superficial siderosis and microhemorrhages (ARIA-H). T2*GRE and SWI are MRI sequences used to improve the detection and visualization of microhemorrhages.</td>
</tr>
<tr>
<td>T2-FLAIR (for ARIA-E)²</td>
<td>To monitor brain edema or sulcal effusion (ARIA-E).</td>
</tr>
<tr>
<td>Diffusion-weighted imaging (DWI)³</td>
<td>Recommended for differential diagnosis.</td>
</tr>
</tbody>
</table>

### 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).

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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.


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Figure adapted from Barakos et al. (2022)³
Detection of ARIA-E – parenchymal edema (Mild)

Location < 5 cm

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

Diagnosis of ARIA
Detection of ARIA-E—parenchymal edema (Severe)

1 or more 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 – sulcal effusion (Mild)

Location < 5 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
**Differentiating ARIA-E from ischemic stroke**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>![MRI image]</td>
<td>![MRI image with red circle]</td>
</tr>
</tbody>
</table>

**Severe ARIA-E**

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

<table>
<thead>
<tr>
<th>DWI</th>
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<tbody>
<tr>
<td>![DWI scan]</td>
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</tbody>
</table>

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

MRI images 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)\(^1\)

ARIA-E on FLAIR  
ARIA-H on T2* GRE

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

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

Mild: 1 focal area

Moderate: 2 focal areas
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


Vendor 1: Time-point 1
Vendor 2: Time-point 2

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

Figure reproduced with permission from Cogswell et al (2022).
Potential interpretation pitfalls of MRI when detecting ARIA-H

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

The conspicuity of microhemorrhages can be increased based on sequence and magnetic field strength.

SWI is a more sensitive technique for detection of microhemorrhages than T2*GRE images.

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

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

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

- In a suspected ARIA case, the full clinical picture must be taken into account before a diagnosis is confirmed
- MRI is key for the diagnosis and differential diagnosis of ARIA
- 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)
- Training should be provided to ensure reliable diagnosis of ARIA

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

Hyperintense signal on DWI is confirmed to be T2 shine-through 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.


**Differential diagnosis: acute ischemic stroke**

**Parenchymal FLAIR hyperintensity of ARIA-E edema may be mimicked by ischemic stroke**

**Diffusion weighted imaging (DWI) is needed to differentiate between ARIA-E and ischemic stroke**

**Signs and symptoms of ischemic stroke include:** acute onset, hemiparesis, dysphasia or dysarthria, facial paresis, paresthesia, eye movement abnormalities, and visual field defects

**Knowing if a patient is on monoclonal antibodies that remove amyloid helps with determining the diagnosis of ARIA**
Differential diagnosis: subarachnoid hemorrhage

T2 axial FLAIR. Effusion

Moderate ARIA-E\(^1\) Subarachnoid hemorrhage\(^2\)

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

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

Differential diagnosis: posterior reversible encephalopathy syndrome (PRES)

**T2-weighted FLAIR Edema**

<table>
<thead>
<tr>
<th>Moderate ARIA-E³</th>
<th>PRES⁴</th>
</tr>
</thead>
</table>

- **PRES** could resemble ARIA-E on imaging¹
- **PRES** frequently develops from cytotoxic medication or disorders such as preeclampsia, sepsis, renal disease, or autoimmune disorders²
- **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

Management of ARIA
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.


<table>
<thead>
<tr>
<th>Management of ARIA</th>
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<tbody>
<tr>
<td>Refer to prescribing information of monoclonal antibodies that remove amyloid for monitoring and management guidelines of ARIA.</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>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.</td>
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</tbody>
</table>
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.