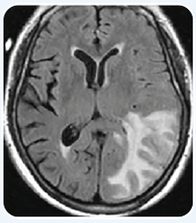
Amyloid Related Imaging Abnormalities

General Overview for the Radiologist

Amyloid Related Imaging Abnormalities (ARIA)

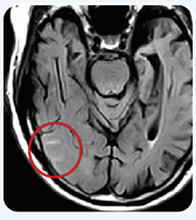
- A **spectrum** of **MRI signal abnormalities** associated with **amyloid clearance** in the **brain**[1-3]
- Can occur spontaneously but more frequently observed during treatment with **amyloid targeting therapies**[1-3]
- There are two types of ARIA: **ARIA-E** and **ARIA-H**[2-4]
  - Both types may be observed on the same scan[5]
  - ARIA type is determined by nature of **leakage product** and **location**[2,5]
- **Monoclonal antibodies** directed against aggregated forms of beta amyloid carry a boxed warning regarding the **increased risk for causing ARIA**, which can be serious and life threatening[1-3]
- **Identification of ARIA** prior to initiation of therapy and ongoing **monitoring via MRI** imaging are crucial during treatment with amyloid targeting therapies[1-3]

Edema[4]



ARIA-Edema example image: Hyperintensity on T2 FLAIR in left parieto-occipital lobe, consistent with parenchymal edema

Effusion[4]



ARIA-Effusion example image: Hyperintensity on T2 FLAIR in the sulci within the right temporo-occipital lobe, consistent with effusion

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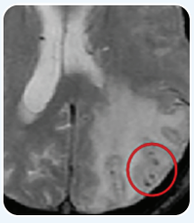
ARIA-E Vasogenic Edema and/or Sulcal Effusion[3-7]

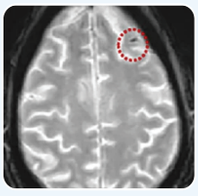
Nature of leakage products	Proteinaceous fluids
Location of increased vascular permeability	Parenchyma: vasogenic edema (parenchymal hyperintensities and gyral swelling)
	Leptomeninges: sulcal effusion/exudate (sulcal hyperintensities)
	Frequently unilateral involving occipital, frontal, and temporal regions
Primary diagnostic imaging sequence	T2 FLAIR
Primary MRI features	T2 FLAIR hyperintense
	DWI negative
	No contrast enhancement
Evaluation of severity	MRI severity scales[7]

Microhemorrhage[4]



ARIA-Microhemorrhage example image: Punctate foci of signal void on T2* GRE in an area of parenchymal edema, consistent with microhemorrhage

Superficial Siderosis[4]



ARIA-Siderosis example image: Signal hypointensity in the left frontal area on T2* GRE, consistent with superficial siderosis on axial

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ARIA-H Hemosiderin Deposits[3-7]

Nature of leakage products	Blood-degradation products
Location of increased vascular permeability	Parenchyma: microhemorrhage (<10 mm) and intracerebral hemorrhage aka macrohemorrhage (≥10 mm)
	Leptomeninges: superficial hemosiderin deposits (superficial siderosis)
	Frequently develops in the context of ARIA-E
Primary diagnostic imaging sequence	T2* GRE and/or SWI
Primary MRI features	GRE and/or T2* weighted hypointense
	SWI hypointense
Evaluation of severity	Number of microhemorrhages and hemosiderin deposits on MRI

Abbreviations: **ARIA-E** = Amyloid Related Imaging Abnormalities-Edema/Effusion; **ARIA-H** = Amyloid Related Imaging Abnormalities-Hemosiderin deposits; **FLAIR** = Fluid-Attenuated Inversion Recovery; **GRE** = Gradient Recalled Echo; **MRI** = Magnetic Resonance Imaging; **SWI** = Susceptibility Weighted Imaging.

1. Salloway S, MD et al. JAMA Neurol. 2022;79:13-21. **2.** Filippi M et al. JAMA Neurol. 2022;79:291-304. **3.** Sperling RA et al. Alzheimer's Dement. 2011;7:367-385. **4.** Figure adapted from Barakos J et al. J Prev Alz Dis. 2022;9:211-220. Copyright © licensed under CC-BY-4.0 (https://creativecommons.org/licenses/by/4.0/). Modified from original by cutting.
5. Cogswell PM et al. Am J Neurol. 2022;43:e19-35. **6.** Barakos J et al. Am J Neurol. 2013;34:1958-1965. **7.** Barkhof F et al. Am J Neurol. 2013;34:1550-1555.

Amyloid Related Imaging Abnormalities

Monitoring and Management of ARIA

Radiographic Severity Monitoring[1]

	Mild	Moderate	Severe
ARIA-E: Sulcal and/or cortical/subcortical FLAIR hyperintensity Measured in single greatest dimension	1 site <5 cm	1 site 5-10 cm, or >1 site each <10 cm	≥1 site(s) >10 cm
ARIA-H: Number of new* microhemorrhages	≤4	5-9	≥10
ARIA-H: Superficial siderosis	1 focal area	2 focal areas	>2 focal areas

*New: cumulative number from baseline

Clinical Symptom Severity Monitoring[2-4]

Common

- Headache
- Nausea
- Confusion / Dizziness

Less common

- Neuropsychiatric symptoms
- Visual disturbance / Blurred vision
- Gait disturbance

Least common

Seizure/status epilepticus, encephalopathy, stupor, coma, stroke-like symptoms / focal neurological deficits

Asymptomatic:
No symptoms noted, no disruption of daily activities

Mild:
Symptoms noted, no disruption of daily activities

Moderate:
Symptoms sufficient to reduce or affect normal daily activities

Severe:
Incapacitating with inability to perform normal daily activities

ARIA Monitoring and Management: General Principles[2-4, 5-7]

- Baseline ARIA evaluation and periodic monitoring with MRI are recommended during treatment with amyloid targeting therapies
- Refer to prescribing information for monoclonal antibodies directed against beta amyloid for ARIA monitoring and management guidelines
- Patients experiencing symptoms suggestive of ARIA should undergo clinical evaluation, including MRI if indicated
- If ARIA is observed on MRI, careful clinical evaluation should be performed. Dose suspension or discontinuation may be considered based on the presence of symptoms and/or radiographic severity
- If required, treatment of ARIA revolves around close monitoring of neurologic status and administration of supportive therapy, which may include corticosteroids
- There is limited experience in patients who continued dosing through ARIA-E
- There is limited data for dosing patients who experienced recurrent episodes of ARIA-E

Abbreviations: **AD** = Alzheimer's Disease; **ARIA-E** = Amyloid Related Imaging Abnormalities-Edema/Effusion; **ARIA-H** = Amyloid Related Imaging Abnormalities-Hemosiderin deposits; **ATT** = Amyloid targeting therapies; **FLAIR** = Fluid-Attenuated Inversion Recovery; **MRI** = Magnetic Resonance Imaging.

1. Cogswell PM et al. Am J Neurol. 2022;43:e19-35. **2.** Cummings J et al. J Prev Alz Dis. 2023;10:362-377. **3.** Cummings J et al. J Prev Alz Dis. 2022;9:221-230. **4.** Cummings J et al. J Prev Alz Dis. 2021;4:398-410. **5.** Salloway S, MD et al. JAMA Neurol. 2022;79:13-21. **6.** Filippi M et al. JAMA Neurol. 2022;79:291-304. **7.** Sperling RA et al. Alzheimer's Dement. 2011;7:367-385.

Amyloid Related Imaging Abnormalities

Detecting ARIA: Recommended MRI Protocol[2]

Scan the QR-code or copy/paste the link to access an ARIA MRI Protocol Overview

Scan the QR code or copy/paste the link to access a standardized reporting template for ARIA MRI imaging, recommended by ASNR

- Imaging protocol standardization is necessary to ensure consistent accuracy for diagnosing ARIA, and specific parameters are needed to achieve cross-platform standardization[1]

3T scanner (recommended), 1.5T scanner (minimal)[1,2]	High field scanners have greater sensitivity but limited availability. The use of 1.5T is endorsed as a minimum standard[2]
Slice thickness2: ≤5 mm	Thinner slices increase resolution but should be balanced against the loss in signal-to-noise ratio[2]
TE[2]: ≥20 ms	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 MRI sequences are used to improve detection and visualization of microhemorrhages[2]
T2 FLAIR (for ARIA-E)[2]	To monitor brain edema or sulcal effusion (ARIA-E)[3]
DWI[3]	Recommended for differential diagnosis[3]
3D T1-GE (optional)[1]	Anatomical[1]

Abbreviations: **ARIA-E** = Amyloid Related Imaging Abnormalities-Edema/Effusion; **ARIA-H** = Amyloid Related Imaging Abnormalities-Hemosiderin deposits; **DWI** = Diffusion Weighted Imaging; **FLAIR** = Fluid-Attenuated Inversion Recovery; **GRE** = Gradient Recalled Echo; **MRI** = Magnetic Resonance Imaging. **SWI** = Susceptibility Weighted Imaging; **TE** = Time to Echo.

1. Pinter NK et al. Alzheimer's Dement. 2022;18(Suppl. 5):e065547. **2.** Cogswell PM et al. Am J Neurol. 2022;43:e19-35. **3.** Sperling RA et al. Alzheimer's Dement. 2011;7:367-385. **4.** Barakos J et al. J Prev Alz Dis. 2022;9:211-220.