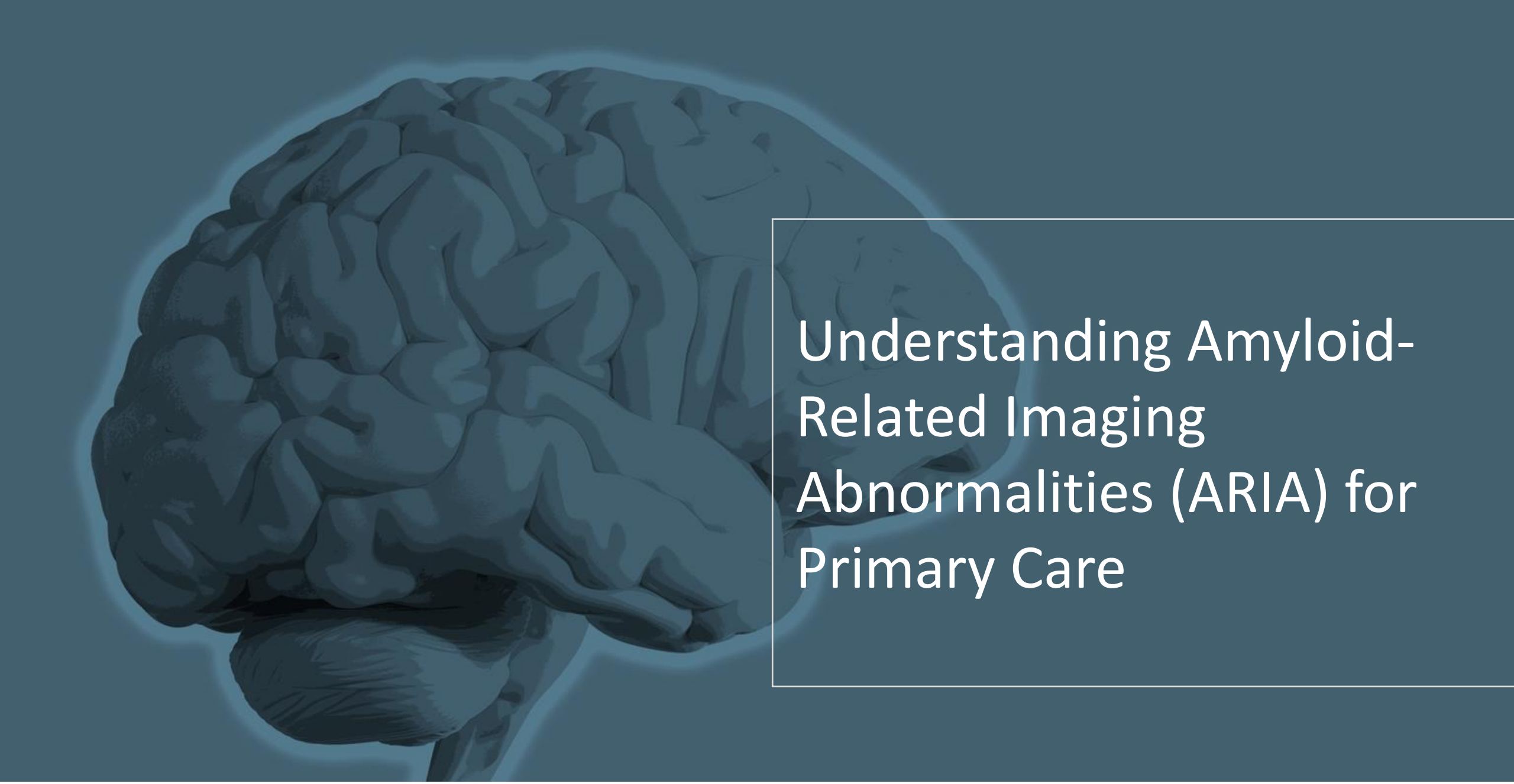
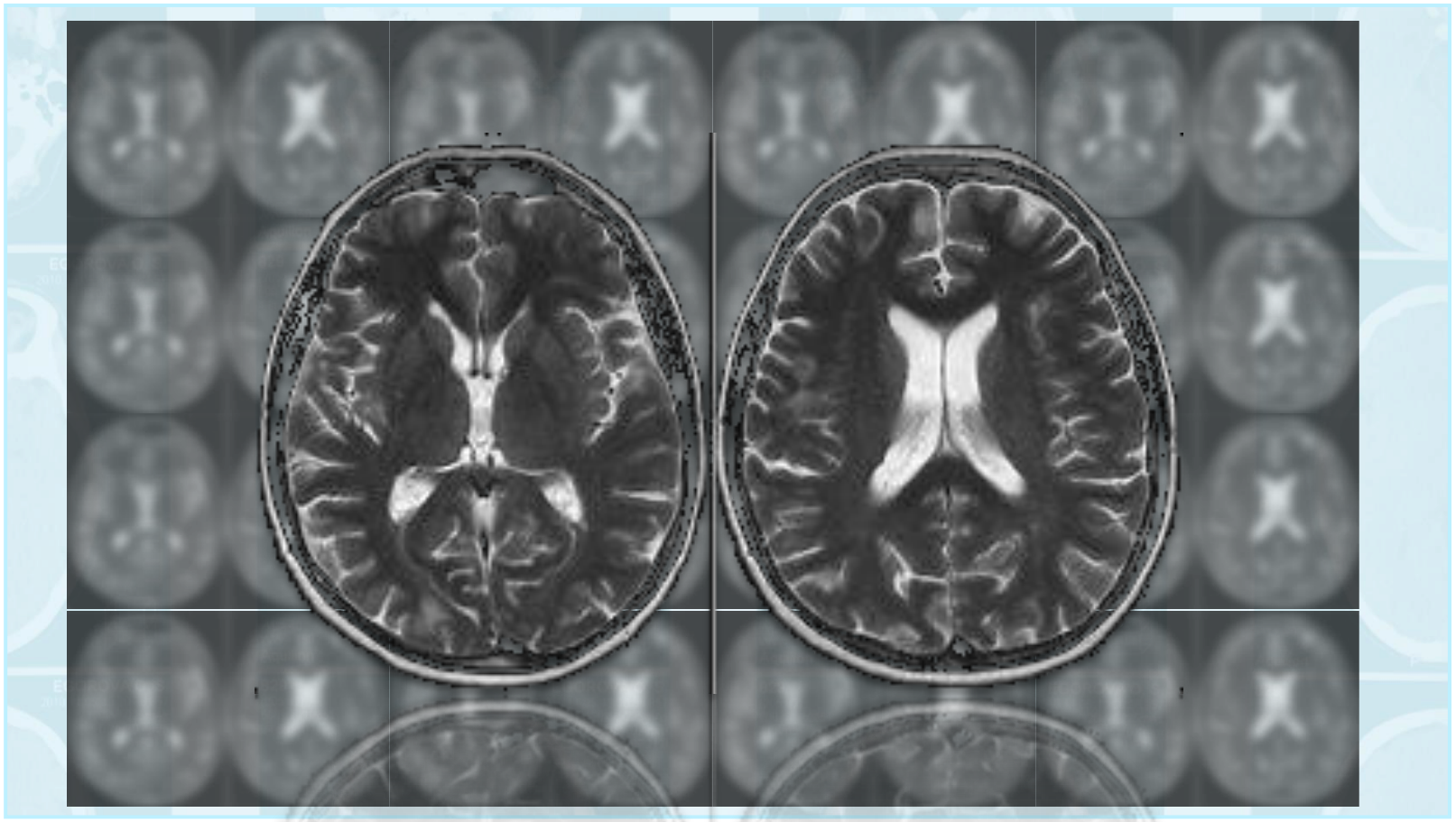


Understanding Amyloid-Related Imaging Abnormalities (ARIA) for Primary Care

Eisai hhc human health care

PIPN-M2938

Outline slide



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

Introducing ARIA

Introduction to Alzheimer's disease

What is Alzheimer's

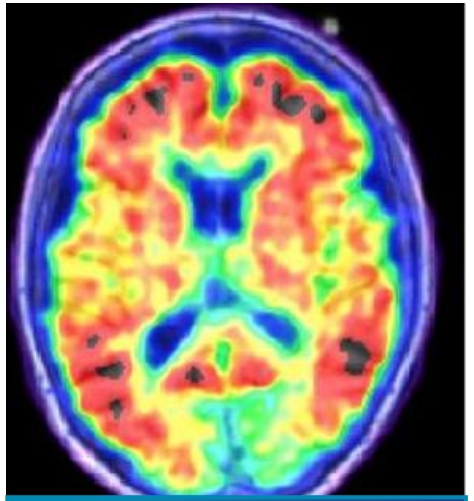
AD is a multifactorial and heterogeneous neurodegenerative disorder, accounting for 60–80% of dementia cases[1,2]

Alzheimer's pathology

The presence of amyloid-beta and tau, synaptic failure, and neuronal dysfunction are common features of AD and are suggested to play a pivotal role in cognitive dysfunction[3–6]

Amyloid deposition visualized on a PET scan[7]

Image from Chapleau M, et al. (2022) [7]



These pathological changes can begin many years before (~15–20 years) before the development of symptoms[4,5]

1. Kazim SF, Iqbal K. Mol Neurodegener 2016;11:50; 2. Alzheimer's Association. Alzheimers Dement. 2022;18(4):700–789; 3. Serrano-Pozo A, et al. Cold Spring Harb Perspect Med 2011;1:a006189; 4. Jack CR, et al. Alzheimers Dement 2018;14:535–562; 5. Bateman RJ, et al. N Engl J Med 2012;367:795–804; 6. Bennet AD, et al. Arch Neurol 2004;61:378–384; 7. Chapleau M, et al. J Nucl Med. 2022 Jun;63(Suppl 1):13S-19S

Symptomatic pharmacologic treatments in Alzheimer's disease

Symptomatic treatment temporarily ameliorates symptoms of AD, but does not affect the underlying disease pathology[1–3]

Acetylcholinesterase inhibitors

Approved for mild, moderate, and/or severe dementia due to AD

NMDA receptor antagonists

Approved for moderate-to-severe dementia due to AD

AD, Alzheimer's disease; NMDA, N-methyl-D-aspartate

1. Cummings J, Fox N. J Prev Alz Dis 2017;4:109–115; 2. Alzheimer's Association: Medications for Memory loss. Available from: http://www.alz.org/alzheimers_disease_standard_prescriptions.asp (Accessed Jan 2023); 3. Jessen F. Dialogues Clin Neurosci 2019;21:27–34

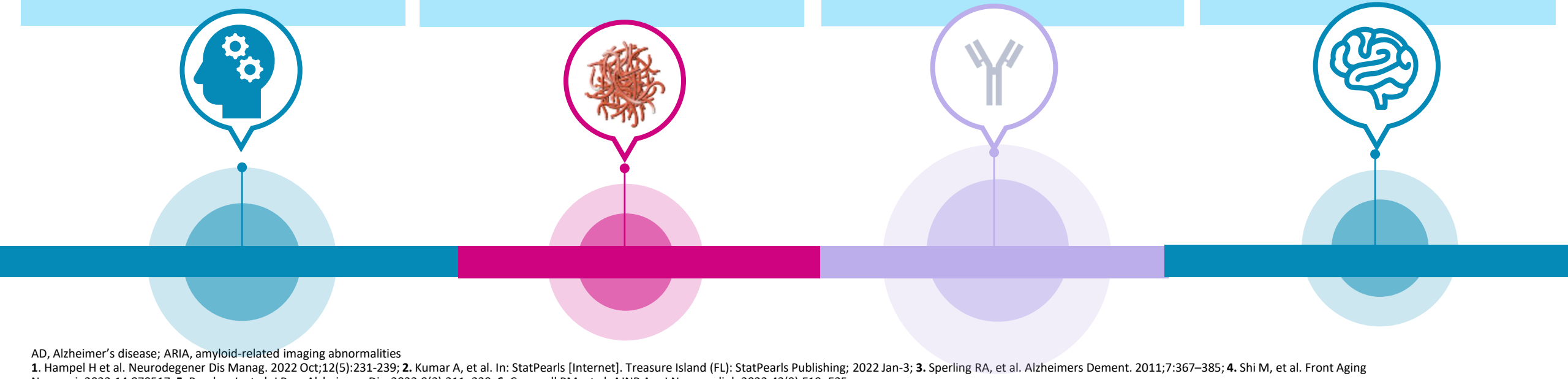
Addressing the underlying pathology of Alzheimer's disease

AD is a neurodegenerative disease that causes problems with memory, language and thinking. You may know these symptoms as dementia[1,2]

Biological changes occur in the brain of people with AD. This includes a build-up of **toxic** protein clusters called **amyloid plaques**, which may lead to **loss of brain function and the symptoms of AD**[1]

"Amyloid Related Imaging Abnormalities" or ARIA is a consequence of the presence of amyloid in cerebral blood vessels walls (cerebral amyloid angiopathy [CAA]). CAA can cause spontaneous ARIA in patients with AD[3]

Monoclonal antibodies that target and **remove toxic amyloid plaque** from the brain to try and slow disease progression[4]
Monoclonal antibodies that remove amyloid plaque increase the risk of ARIA[5,6]



AD, Alzheimer's disease; ARIA, amyloid-related imaging abnormalities

1. Hampel H et al. Neurodegener Dis Manag. 2022 Oct;12(5):231-239; **2.** Kumar A, et al. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-3; **3.** Sperling RA, et al. Alzheimers Dement. 2011;7:367–385; **4.** Shi M, et al. Front Aging Neurosci. 2022;14:870517; **5.** Barakos J, et al. J Prev Alzheimers Dis. 2022;9(2):211–220; **6.** Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35.

What is ARIA?

- 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[2]
- An Alzheimer's Association workgroup defined the term **"amyloid-related imaging abnormalities" or "ARIA"** in AD, based on MRI findings which are subdivided into ARIA-E or ARIA-H[1]
  - ARIA-E: parenchymal vasogenic edema or sulcal effusions detected on FLAIR sequences[3]
  - ARIA-H: microhemorrhages, superficial hemosiderin deposition (superficial siderosis) detected on T2*GRE sequences[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; 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]**

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

1. Sperling RA, et al. Alzheimers Dement. 2011;7:367–385; 2. Sperling RA, et al. Lancet Neurol. 2012;11:241–249; 3. Barakos J, et al. J Prev Alzheimers Dis. 2022;9(2):211–220; 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

Emerging therapies aiming to remove amyloid beta (Aβ)

Monoclonal antibodies that remove amyloid

Strategies to target and remove amyloid are based on our understanding that interfering with the underlying pathophysiologic mechanisms of the disease process could slow disease progression, but need to be initiated early in the course of disease given these changes begin in the early stages of disease[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]

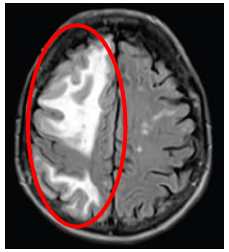
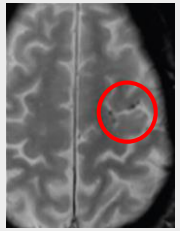
ARIA is a known adverse reaction of monoclonal antibodies that remove amyloid plaque for AD

Aβ, amyloid beta; ARIA: Amyloid-related imaging abnormalities; AD: Alzheimer's Disease

1. Bateman RJ, et al. N Engl J Med 2012;367:795–804; 2. Sperling RA, et al. Alzheimers Dement. 2011;7:367–385

ARIA-E and ARIA-H

ARIA is an umbrella term used to describe two types of 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	**Parenchyma:** vasogenic edema **Leptomeninges:** sulcal effusions (i.e., exudates)	**Parenchyma:** microhemorrhages (typically defined as <10 mm) and intracerebral hemorrhage (≥10 mm) **Leptomeninges:** superficial hemosiderin deposits (superficial siderosis)
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 multiple regions of the right hemisphere, affecting both gray and white matter[4]	 ARIA-H seen on T2* GRE MRI. MRI reveals several microhemorrhages (<10 mm; red circle)[4]

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.

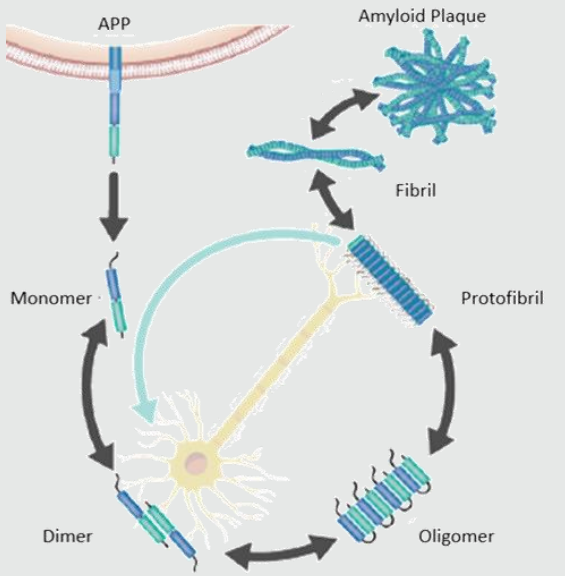
1. Sperling RA, et al. Alzheimers Dement. 2011;7:367–85; 2. Barakos J, et al. AJNR Am J Neuroradiol. 2013;34:1958–965; 3. Barkhof F, et al. AJNR Am J Neuroradiol. 2013;34:1550–1555; 4. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35

Pathophysiology

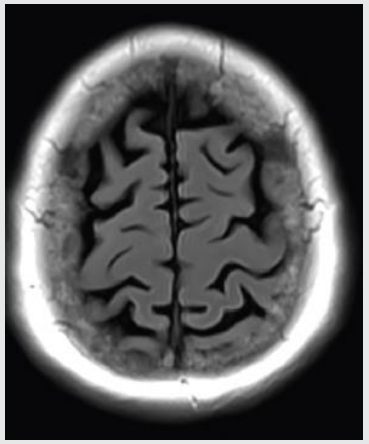
Hypothesized pathophysiology of ARIA

ARIA is a consequence of the presence of amyloid in cerebral blood vessel walls (cerebral amyloid angiopathy [CAA]), which can cause spontaneous ARIA in patients with AD.[1] The increased occurrence of ARIA-E seen with treatments that remove amyloid plaques is thought to be due to the removal of vascular amyloid and disruption of amyloid in blood vessel walls.[1] Other mechanisms are also hypothesized.

Aggregation of toxic **Aβ species** in the brain (amyloid plaques) and blood vessels (CAA) contributes to **Alzheimer's disease** pathogenesis[3]

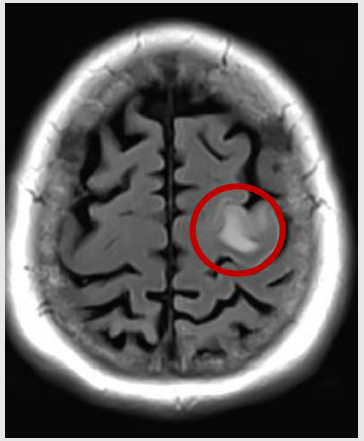


After the introduction of monoclonal antibodies that remove amyloid plaque**, vascular amyloid deposits begin to clear** leading to increased vascular permeability [1]



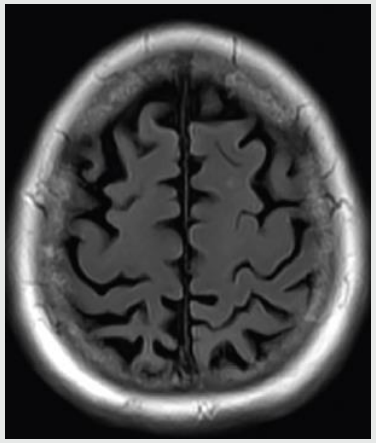
Example of Baseline MRI [3]

This loss of vascular integrity may be thought of as a transient exacerbation of the effects of CAA.[4]
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**[1]



Example of **ARIA-E** post treatment[3]

Limited evidence suggests that with **repeated immunization** and continued Aβ clearance, the integrity of vessels and efficiency of clearance can improve and risk of ARIA decreases[1]



Example of **ARIA-E** post treatment **follow-up**[3]

MRI images from Cogswell et al (2022);[3] figure adapted from Hampel et al. (2021)[4]

Aβ, Amyloid beta; ARIA: Amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage

1. Sperling RA, et al. Alzheimers Dement. 2011;7:367–385; 2. Barakos, J et al. J Prev Alzheimer's Dis 2022; 9(2):211–220; 3. Cogswell, PM et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35; 4. Hampel H, et al. Nature. 2021;26:5481–5503

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 Sep:;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

Clinical manifestations of ARIA

Clinical manifestations of ARIA

In most cases, ARIA is **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; 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

Diagnosis of ARIA

ARIA risk factors

Main risk factors:

***APOE ε*4 carrier status[1–3]**

Pre-treatment microhemorrhage[2,3]

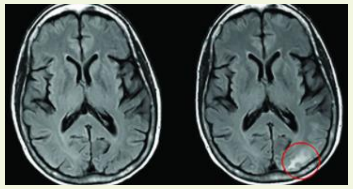
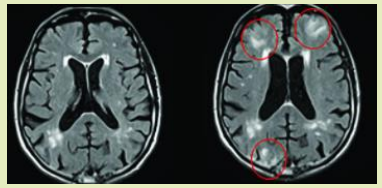
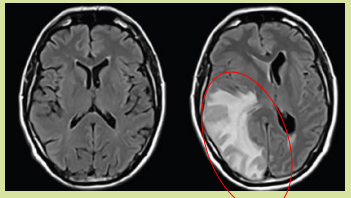
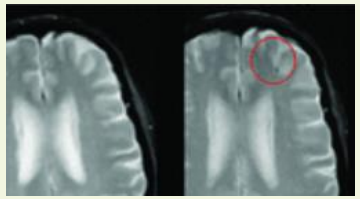
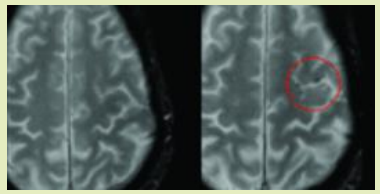
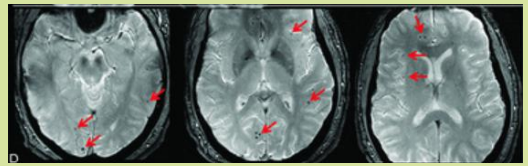
Treatment with monoclonal antibodies that remove amyloid[2,3]

APOE, apolipoprotein E; 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 more location > 10 cm
	 Baseline Posttreatment	 Baseline Posttreatment	 Baseline Posttreatment
ARIA-H Superficial siderosis	1 focal area	2 focal areas	> 2 focal areas
ARIA-H Number of new Microhemorrhages	≤4	5–9	≥10
	 Baseline Posttreatment <5 treatment-emergent microhemorrhages	 Baseline Posttreatment 5 treatment-emergent microhemorrhages	 Posttreatment At least 12 treatment-emergent microhemorrhages (arrows)

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-vasogenic edema; ARIA-H, ARIA-microhemorrhages or hemosiderosis

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

Figure adapted from Cogswell et al (2022)

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]

Ischemic stroke

- MRI of ARIA-E edema may be mimicked by ischemic stroke[1]
- **Signs and symptoms** of ischemic stroke include: acute onset, hemiparesis, dysphasia or dysarthria, facial paresis, paresthesia, eye movement abnormalities, and visual field defects[2]
- Knowing if a patient is on monoclonal antibodies that remove amyloid helps with determining the diagnosis of ARIA[1]

Subarachnoid hemorrhage

- ARIA-E effusion detected on MRI may be mimicked by SAH[1]
- Differentiating ARIA and SAH requires a systematic clinical and diagnostic approach[1]
- Subarachnoid hemorrhage typically presents with a number of signs and symptoms: severe headache accompanied by nausea or vomiting[3]
- Decreased level of consciousness and focal neurological signs can also be present[3]

PRES

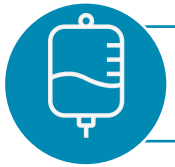
- PRES could resemble ARIA-E on imaging[1]
- PRES frequently develops from cytotoxic medication or disorders such as preeclampsia, sepsis, renal disease, or autoimmune disorders[4]
- Signs of PRES[4]:
  - Encephalopathy, epileptic seizures, visual disturbances, and focal neurological deficits
- Less specific signs include:[4]
  - Headache, nausea, vomiting
- In this case, clinical history is **important for differentiating**

ARIA, Amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; PRES, posterior reversible encephalopathy syndrome; SAH, subarachnoid hemorrhage

1. Barakos J, et al. AJNR Am J Neuroradiol 2013;34:1958–1965; 2. Yew KS, Cheng EM. Am Fam Physician 2015;91:528–536; 3. Tetsuka S, Matsumoto E. BMC Neurol 2016;16:196; 4. Fischer M, Schmutzhard E. J Neurol 2017;264:1608–1616

Management of ARIA

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 is 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.