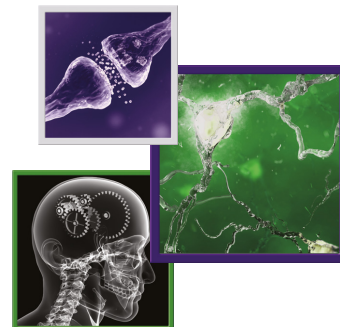


Amyloid-related imaging abnormalities (ARIA) and their radiological, biological and clinical characteristics: a plain language summary



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Summary

What is this summary about?

This is a plain language summary of an article published in the journal *Brain*. People with Alzheimer's disease may receive treatments that target amyloid- β – a protein in the brain that is one of the key characteristics of Alzheimer's disease when it is present in higher levels than normal. This article is about amyloid-related imaging abnormalities (ARIA), which can be **adverse events** for people with Alzheimer's disease receiving antibody treatments targeting amyloid- β (known as anti-amyloid- β antibody treatments). This article also discusses ways to identify and manage ARIA.

ARIA are adverse events that happen due to amyloid- β buildup in the brain or following treatments targeting amyloid- β . ARIA are identified on **MRI scans** as swelling or bleeding in the brain, and people with ARIA do not typically have symptoms. In rare cases, ARIA can cause serious symptoms or lead to disability.

What are the key takeaways?

There are two types of ARIA: ARIA-E (swelling in the brain) and ARIA-H (bleeding in the brain).





Presence of an **APOE $\epsilon 4$ gene variant** and exposure to anti-amyloid- β antibody treatments are major risk factors for ARIA.

With the recent availability in the clinic of antibody treatments targeting amyloid- β , increased awareness is needed to identify, monitor and manage ARIA effectively.

What were the main conclusions reported by the researchers?

Uniform detection, monitoring and management of ARIA are essential in patients receiving antibody treatments targeting amyloid- β . To increase ARIA detection in clinical trials and clinical practice, the authors recommend the implementation of uniform imaging protocols and rigorous reporting standards.

How to say (double click sound icon to play sound)...

- **Amyloid:** am-uh-loid 
- **ARIA:** ahr-ee-uh 
- **Hemosiderin:** hee-mow-si-dr-in 
- **Hemosiderosis:** hee-mow-si-dr-ow-suhs 

Adverse event: A treatment effect that is beyond its desired effect, is related to receiving treatment and can be harmful.

MRI scan: An imaging tool that scans the body with a magnetic field and radio waves to create detailed images of bones, blood vessels and soft tissues in the body.

Gene variant: A permanent change in the DNA sequence of a gene.



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Who is this article for?

Healthcare professionals who diagnose and treat early Alzheimer's disease and who specialize in medical imaging.

Patients who would like to learn more about ARIA.

Who funded this publication?

This publication was funded by Eisai Inc.

What is the purpose of this article?

This plain language summary aims to better assist clinicians in detecting and managing ARIA as well as highlighting their relevance in clinical practice with various therapies available or in development. The results of this review of many studies may differ from those of other studies. Health professionals should make treatment decisions based on all available evidence and not on the results of a single study.

Background

Alzheimer's disease affects the brain and gradually worsens over time. This disease results in a continuing decline in memory, thinking, behavior and social skills.

One of the characteristics of Alzheimer's disease is the buildup of amyloid- β protein in the brain.

These amyloid- β proteins form sticky clumps known as plaques:

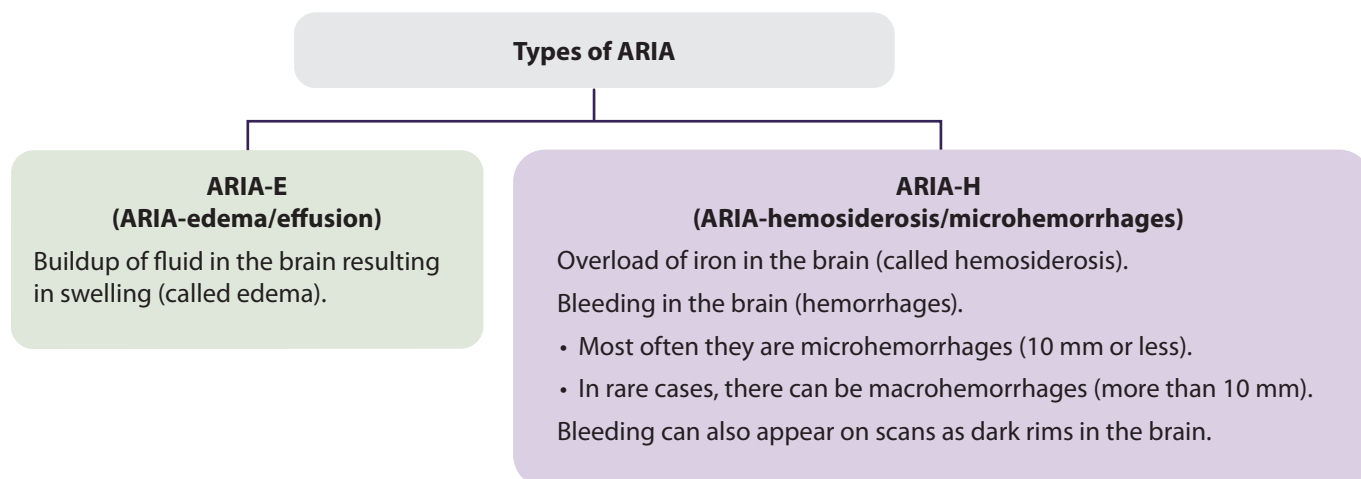
- The plaques may also contain or be surrounded by damaged parts of brain cells and cells that protect the body against injury and infection (known as inflammatory cells).

Antibody treatments that remove amyloid- β from the brain (known as anti-amyloid- β antibody treatments) are now available for people with Alzheimer's disease.

What are amyloid-related imaging abnormalities?

Amyloid-related imaging abnormalities (known as ARIA) are abnormal signal changes seen through MRI scans of the brain.

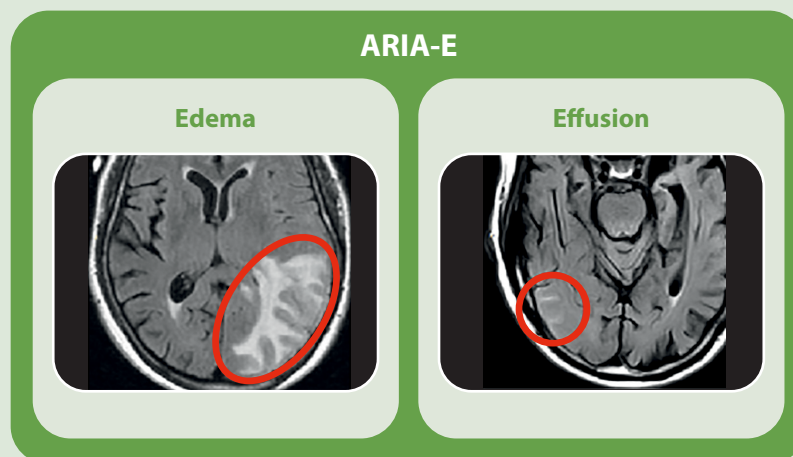
ARIA can happen due to natural amyloid- β buildup in the brain or as possible treatment-related adverse events seen with the use of anti-amyloid- β antibody treatment in people with early Alzheimer's disease.



What are the main MRI features of ARIA-E?

ARIA-E refers to the buildup of fluid in the brain involving the breakdown of the blood-brain barrier, which is the layer of cells that defend the brain from potential harm.

The brain swelling that follows may be seen in regions of brain tissue (called vasogenic edema) and/or its grooves (called sulcal effusion) as white shading on particular brain MRI sequences.

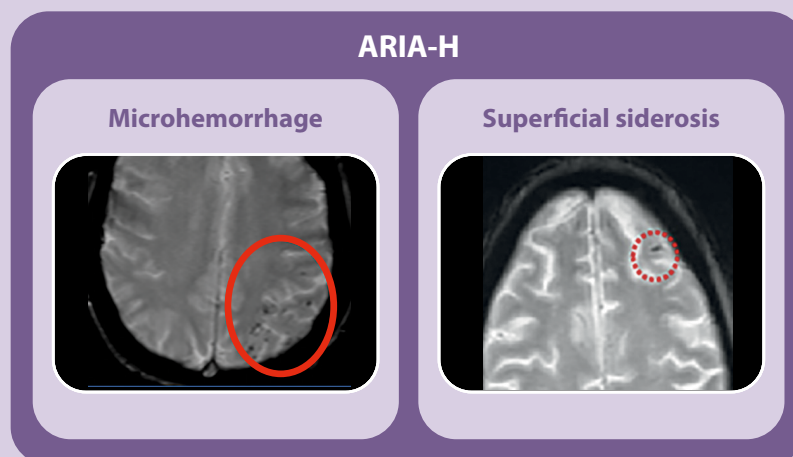


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What are the main MRI features of ARIA-H?

ARIA-H refers to hemorrhages in the brain and is often accompanied by a buildup of partially broken-down proteins that store iron (called hemosiderin).

The bleeds are observed on scans as small dark spots in the brain tissue (called microhemorrhage) or dark linear or wavy lines within the protective layers or spaces on the brain surface known as leptomeningeal or subpial spaces (called superficial siderosis).



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What are the clinical symptoms of ARIA?

The majority of people with ARIA do not show symptoms, and careful monitoring when receiving antibody treatment targeting amyloid- β is critical.

ARIA are treated by decreasing the amount of anti-amyloid- β antibody treatment the patient is receiving or by stopping the treatment.

In a minority of cases, people experiencing severe symptoms may require admission to an intensive care unit or be given urgent treatments such as steroids or anti-seizure medicines.

If people do show symptoms of ARIA, the most common symptoms are usually temporary and include:



Headache



Confusion



Dizziness, nausea or vomiting



Changes in vision



Problems with balance or walking

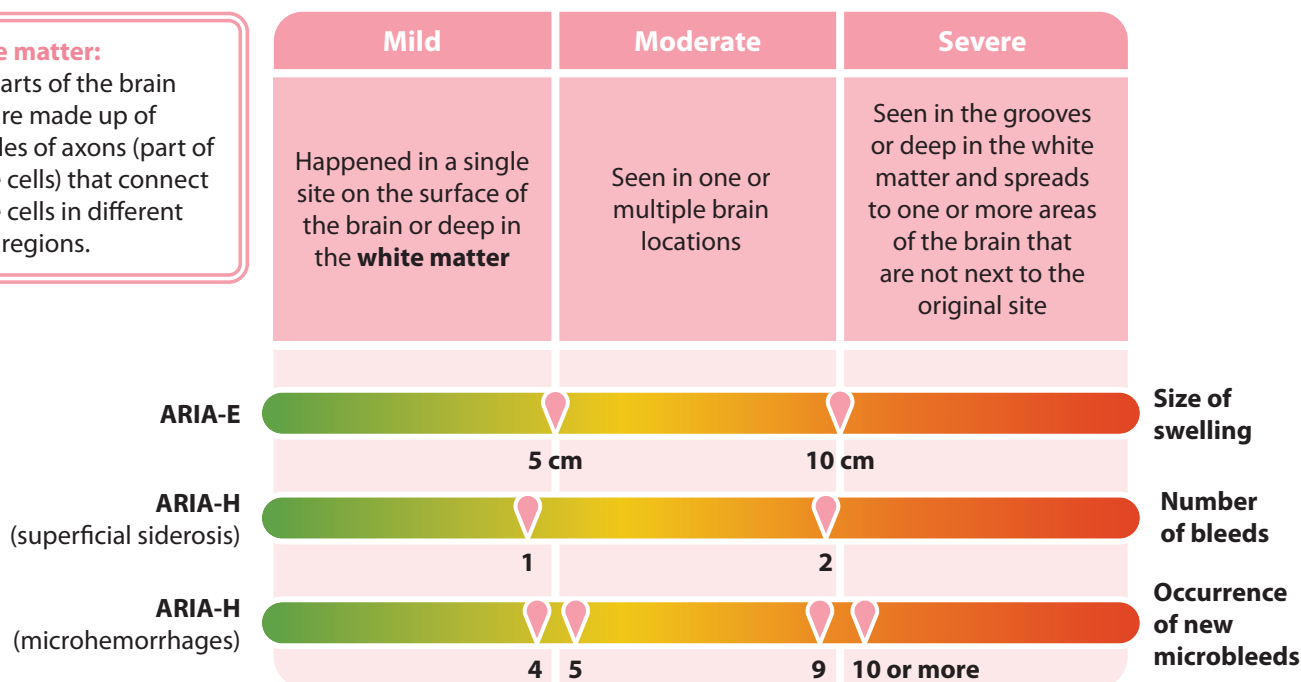
What is the grading scale used to find out how severe ARIA are?

The number of bleeds, as well as the size and location of the bleeding and swelling, seen on an MRI scan shows how severe ARIA-H or ARIA-E are.

ARIA can be categorized into mild, moderate and severe using a grading scale for MRI images.

White matter:

The parts of the brain that are made up of bundles of axons (part of nerve cells) that connect nerve cells in different brain regions.



How common are ARIA?

How often ARIA happens depends on:

- Treatment characteristics: dose, schedule, how the treatment is administered, how long the treatment is given and the type of antibody.
- Patient characteristics: *APOE ε4* status (meaning, does the patient have the *APOE ε4* gene variant?) and whether the patient has had microhemorrhages before.
- Type of ARIA: ARIA-E or ARIA-H.

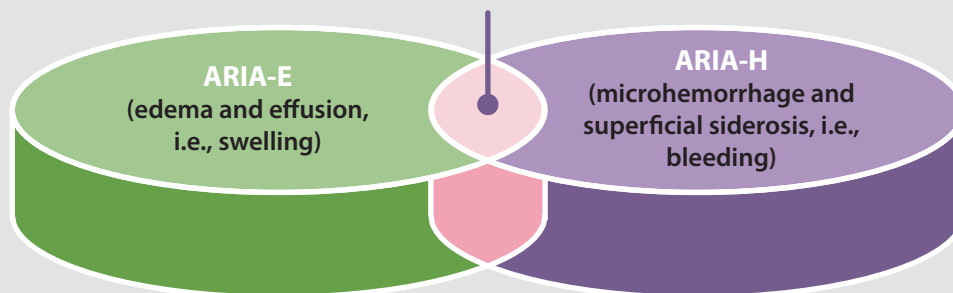
How does receiving anti-amyloid-β treatment impact the frequency of ARIA?



Can ARIA-E and ARIA-H co-exist?

ARIA-H may build up over time in areas where ARIA-E is present.

49% occurrence of both ARIA-E and ARIA-H



Other conditions in the brain related to ARIA: cerebral amyloid angiopathy

What is cerebral amyloid angiopathy?

Alzheimer's disease shares many similar features and is often associated with another condition called cerebral amyloid angiopathy. More information on cerebral amyloid angiopathy is provided in the "Where can readers find more information?" section.

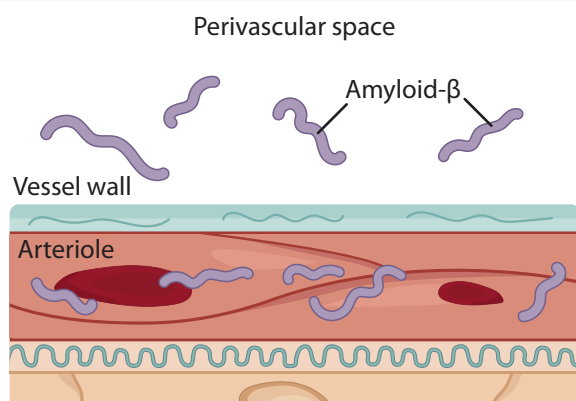
Cerebral amyloid angiopathy is commonly seen in older adults (older than 80 years), particularly in people with Alzheimer's disease.

Cerebral amyloid angiopathy and Alzheimer's disease are different in how they cause brain injury:

- Alzheimer's disease advances the loss of brain tissue and the connections between brain cells.
- Cerebral amyloid angiopathy injuries come from damage to blood vessels.

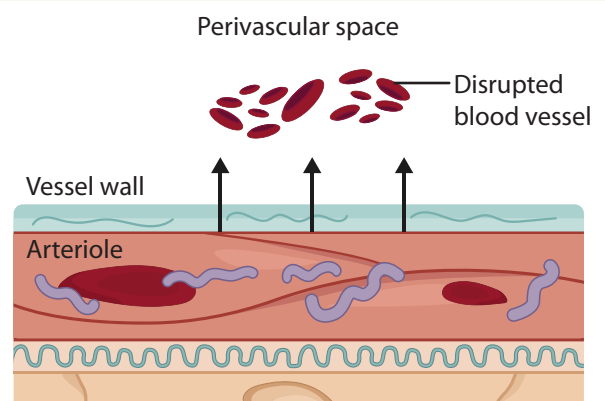
The chances of developing ARIA are higher in people with Alzheimer's disease receiving anti-amyloid- β antibody treatment who have had cerebral amyloid angiopathy before.

In cerebral amyloid angiopathy, amyloid- β 40 builds up in the walls of small- to medium-sized blood vessels leading to stiffening and fragility of blood vessels.



Cerebral amyloid angiopathy severity may worsen due to increased buildup of amyloid- β causing disruption in blood vessels and preventing its removal from the brain.

These events may lead to brain bleeding (microhemorrhages).



Cerebral amyloid angiopathy-related inflammation

- Cerebral amyloid angiopathy-related inflammation is a rare inflammation of the brain resulting from amyloid- β buildup in brain blood vessels.

Shares similar MRI abnormalities with ARIA-E and ARIA-H.



Often occurs without a clear cause and can lead to ARIA.



What are the disease processes that may lead to ARIA?

ARIA can occur when a high-level of anti-amyloid- β **autoantibodies** promote the natural removal of amyloid- β plaques in the brain.

During this removal, amyloid- β plaques can leak into brain tissue and the space around blood vessels.

The chance of developing ARIA can increase with cerebral amyloid angiopathy, especially in people with inflammation from cerebral amyloid angiopathy, also known as cerebral amyloid angiopathy-related inflammation.

People with damaged blood vessels are also at an increased risk of developing ARIA.

In Alzheimer's disease, amyloid- β plaques in brain tissue are associated with gradual loss of brain blood vessel ability to control blood flow and reduced removal of amyloid- β in **perivascular spaces** (which can be measured by checking for reduced levels in the **cerebrospinal fluid**).

Amyloid- β buildup in the blood vessels can also disrupt **smooth muscle cells** in blood vessels and cause cerebral amyloid angiopathy.

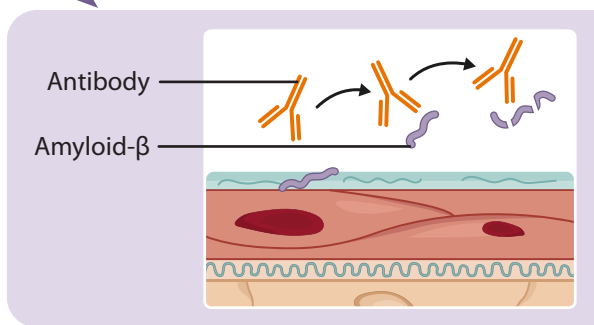
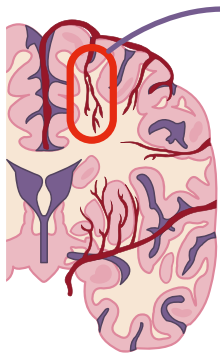
Autoantibodies: An antibody made by the immune system that targets normal proteins in the body.

Perivascular spaces: Brain passageways where substances can move.

Cerebrospinal fluid: Liquid that surrounds and protects the brain and spinal cord.

Smooth muscle cells: Cells that make up a type of muscle that is contracted and controlled involuntarily.

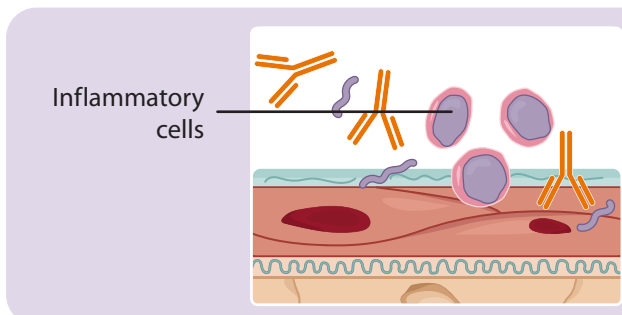
ARIA due to anti-amyloid- β treatment



Anti-amyloid- β treatments can break down amyloid- β plaques.

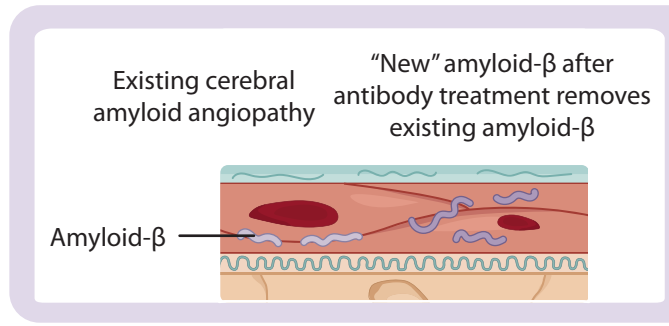
Amyloid- β leaks into the brain tissue and space surrounding the blood vessels.

Too much amyloid- β can lead to a temporary buildup and slow down the removal of amyloid- β in the walls of blood vessels, such as arteries.



Inflammation may be seen in the blood vessel walls (similar to cerebral amyloid angiopathy-related inflammation).

Increased inflammation can cause decreased blood vessel ability to control blood flow and breakdown of amyloid- β in the blood vessel walls.

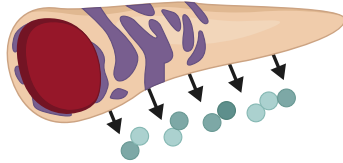


The combination of disease processes along with existing cerebral amyloid angiopathy and related inflammation further damages the blood vessels.

ARIA-E

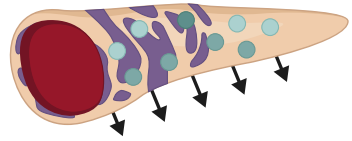
Maybe caused by the leakage of fluids with proteins due to poor regulation and damage to the blood-brain barrier.

Edema



Buildup of fluid in the brain resulting in swelling seen in regions of brain tissue

Effusion



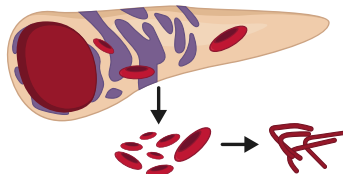
Fluid leakage into the membrane surrounding the brain resulting in swelling

ARIA-H

May be caused when anti-amyloid- β antibodies displace amyloid- β from the plaques in the brain tissue to the walls of blood vessels, which increases the severity of potentially pre-existing cerebral amyloid angiopathy.

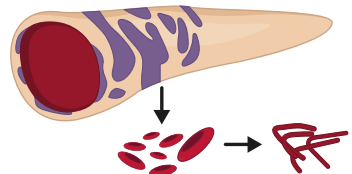
This results in inflammation and ultimately leakage of blood products through damaged blood vessel walls.

Microhemorrhages



Bleeding that appears on MRI scans as small dark spots in the brain

Superficial siderosis



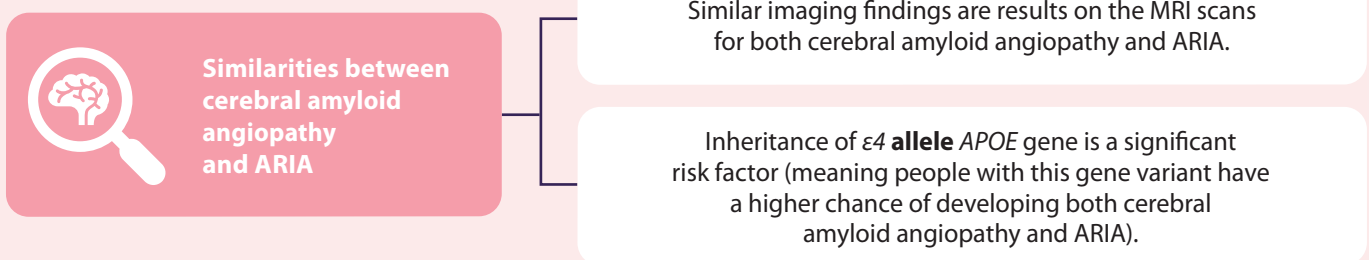
Bleeding that appears on MRI scans as dark rims in the brain

What are the similarities and differences between cerebral amyloid angiopathy and ARIA?

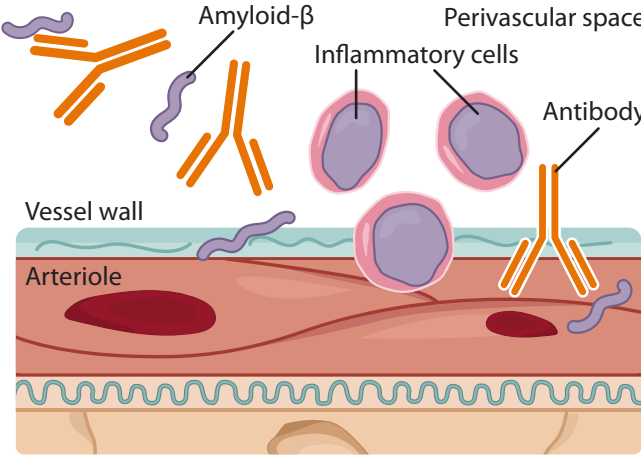
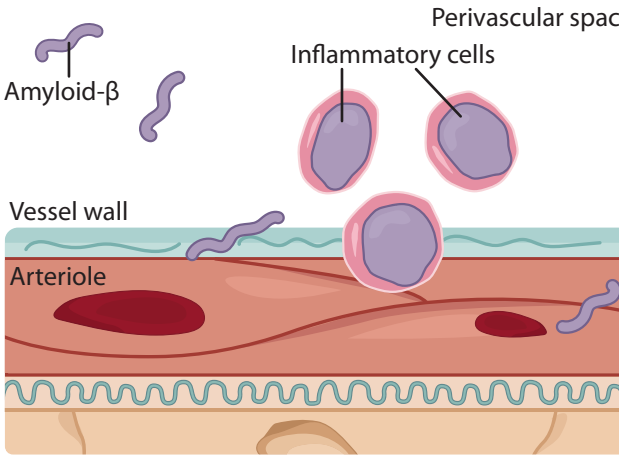
Cerebral amyloid angiopathy and ARIA share similar MRI abnormalities and clinical features. The most important evidence of shared clinical features between cerebral amyloid angiopathy and ARIA is spontaneous ARIA-E, which can result from cerebral amyloid angiopathy-related inflammation.

Allele: One of two or more alternative forms of a gene.

ARIA may be worsened by anti-amyloid- β antibody treatment in people with cerebral amyloid angiopathy.







ARIA due to antibody exposure are similar to cerebral amyloid angiopathy-related inflammation, but there are a few notable differences




ARIA	Cerebral amyloid angiopathy-related inflammation
<p>May occur spontaneously or following anti-amyloid-β antibody treatment.</p> <p>May heal without treatment, by interrupting or stopping the treatment or treating with steroids.</p>	<p>May occur spontaneously in individuals with cerebral amyloid angiopathy.</p> <p>May be treated with steroid treatment.</p>
 <p>The diagram illustrates ARIA. It shows a cross-section of a blood vessel (arteriole) with a vessel wall. In the perivascular space, amyloid-β (purple) is present. Orange Y-shaped antibodies bind to the amyloid-β. This process recruits inflammatory cells (purple) into the perivascular space. Labels include: Amyloid-β, Inflammatory cells, Perivascular space, Antibody, Vessel wall, and Arteriole.</p>	 <p>The diagram illustrates cerebral amyloid angiopathy-related inflammation. It shows a cross-section of a blood vessel (arteriole) with a vessel wall. In the perivascular space, amyloid-β (purple) is present. Inflammatory cells (purple) are recruited into the perivascular space. Labels include: Amyloid-β, Inflammatory cells, Perivascular space, Vessel wall, and Arteriole.</p>

What are the risk factors for developing ARIA?

Main risk factors

-  Exposure to anti-amyloid- β antibody treatment.
-  Presence of *APOE* ϵ 4 gene.
-  Presence of bleeds in the brain before treatment.
-  Drug treatment characteristics (dose, schedule, type of antibody and length of treatment).

Additional risk factors

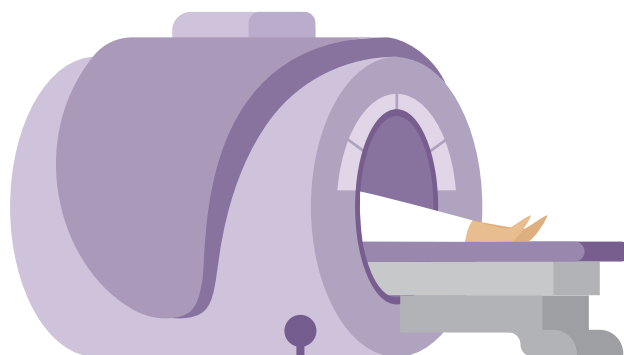
-  Amount of amyloid- β clumps in the brain tissue or blood vessels.
-  Level of pre-existing cerebral amyloid angiopathy.
-  Treatments that block clotting.

The risks of developing ARIA are reduced when people start on a low dose of anti-amyloid- β treatment and are introduced to higher treatment doses over time to achieve a final ideal treatment dose

What are the recommended MRI protocols for detection of ARIA?

A brain MRI is recommended for people when starting anti-amyloid- β antibody treatment, or within 3–4 months of beginning treatment, in order to be appropriately assessed for eligibility and risks of treatment.

Patients must have regular MRI scans for monitoring during the treatment to help detect any potential ARIA that may develop.



Use higher magnetic strength MRI scanners for improved sensitivity for detecting ARIA.



Acquire thinner slices of the brain during MRI scanning to improve clarity or resolution of brain images.



Use a longer echo time (time between delivery of radio frequency pulse and receipt of the echo signal in MRI scans) to increase sensitivity, especially to detect bleeding in ARIA-H.



Use more sensitive MRI measures such as susceptibility weighted imaging, especially to detect bleeding in ARIA-H.



Use specialized MRI sequences (the settings used to visualize specific features) such as T2-FLAIR especially to detect swelling in ARIA-E.



Use specialized MRI sequences, such as diffusion weighted imaging.

How should ARIA be treated?

The clinical guidance on managing ARIA is based on the appropriate use of anti-amyloid- β treatment in people with early Alzheimer's disease.

Appropriate use recommendations are developed by clinicians, are treatment-specific and vary by treatment.



If people experience mild ARIA without any symptoms during treatment, they can continue to receive anti-amyloid- β antibody treatment and should have regular follow-up MRI scans to monitor their ARIA.



In people who develop moderate to severe ARIA but do not experience any symptoms, the treatment should be stopped and regular follow-up MRI scans performed to monitor their ARIA. In rare cases of severe or serious ARIA symptoms, steroids should be given to reduce symptoms and their re-appearance, as with treatment of any cerebral amyloid angiopathy-related inflammation that may have developed.



Use of anti-amyloid- β antibody while treatments that block clotting are being taken is known to increase the risk of ARIA (especially ARIA-H) and should be avoided.



As new therapies become available, the development of standard guidelines and recommendations on the management of ARIA will facilitate patient safety.

How can we better manage ARIA in the future?



Medical history should be reviewed to identify any medical conditions that may increase the risk of ARIA or make ARIA worse.

Close medical checks for potential ARIA symptoms should be ongoing, particularly in the first 12 months of treatment (as per the Appropriate Use Recommendations of anti-amyloid treatments).



ARIA protocols

Future study protocols should consider including a radiologist who is unaware of whether people are receiving the treatment or a placebo to avoid knowledge of treatment impacting MRI scan interpretation.

Medical checks and symptom monitoring

MRI



Scheduled MRIs for safety surveillance of ARIA should be performed multiple times, particularly within the first 3–4 months of starting treatment.

Follow-up MRI scans should be performed if ARIA develop.

APOE genotyping



APOE genotyping will help:

- Identify people who carry an APOE $\epsilon 4$ gene variant, especially those with two copies of the gene, as they are at much higher risk for developing ARIA.
- With risk assessment, safety monitoring and management of ARIA.

What are the take-home messages?

- ARIA can occur naturally or as an adverse event with the use of anti-amyloid- β antibody treatment in people with early Alzheimer's disease.
- There are two classes of ARIA: ARIA-E (swelling of the brain) and ARIA-H (bleeding in the brain) identified through MRI scans.
- The most common symptoms of ARIA include headache, confusion, vomiting, changes in vision or problems walking.
- The presence of an *APOE ϵ 4* gene variant and exposure to anti-amyloid- β antibody treatment are major risk factors for developing ARIA.
- Uniform genetic testing, medical history and regular MRI scans are crucial to better manage ARIA.
- An update or agreement on the existing definition of terminologies for people with co-existing conditions affecting blood vessels will aid in ARIA detection and classification.

Where can readers find more information?

The original article titled "Amyloid-related imaging abnormalities (ARIA): radiological, biological and clinical characteristics," published in the journal *Brain*, can be freely accessed through their website: <https://academic.oup.com/brain/article/146/11/4414/7191051>.

Harald Hampel, Aya Elhage, Min Cho, Liana G Apostolova, James A R Nicoll, Alireza Atri, Amyloid-related imaging abnormalities (ARIA): radiological, biological and clinical characteristics, *Brain*, Volume 146, Issue 11, November 2023, Pages 4414–4424, <https://doi.org/10.1093/brain/awad188>.

Boston criteria 2.0 for cerebral amyloid angiopathy can be found here: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9389452/>.

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