SMALL BLEEDS, BIG CONSEQUENCES:

Recognizing and Diagnosing Inflammatory Forms of Cerebral Amyloid Angiopathy

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Acknowledgements

VANDERBILT UNIVERSITY MEDICAL CENTER

Dr. Michelle Roytman, Dr. Andrew Schweitzer, Dr. Santosh Murthy, and everyone at Weill Cornell Radiology and Neurology who cultivated my interest in CAA and its inflammatory subtypes.

OUTLINE

- **What it is**
  Pathophysiology, subtypes
- **Why it matters**
  Underdiagnosis, treatment
- **Who to suspect**
  Patient presentation
- **What to look for**
  Radiological findings
- **How to diagnose**
  Official criteria, examples

What it is

- Cerebral Amyloid Angiopathy (CAA)
  - A cerebrovascular disorder characterized by the accumulation of amyloid within the leptomeninges and small/medium-sized cerebral blood vessels
  - No known treatment
  - Contributes to cognitive decline and bleed risk
- CAA + Inflammation = Inflammatory CAA (ICAA)
  - CAA + perivascular inflammation = CAA-RI
    - Stands for: CAA-related inflammation
  - CAA + mural inflammation = ABRA
    - Stands for: amyloid beta-related angiitis

TERMINOLOGY

Which is the umbrella term? ICAA or CAA-RI?

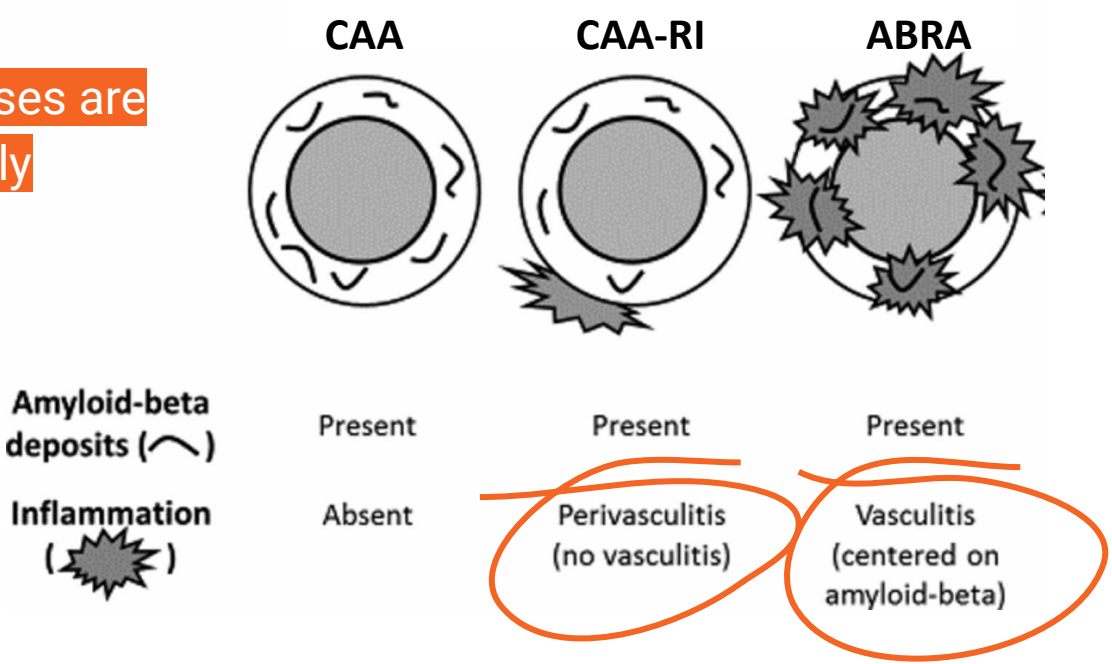
For purposes of this talk, ICAA will encompass CAA-RI and ABRA, but this isn't always the case.

Some papers will use CAA-RI as the umbrella term for ICAA and ABRA. Goes to show how in flux the CAA world is.

(Wu et al., 2021)
(Kuhn and Sharman, 2023)

What it is

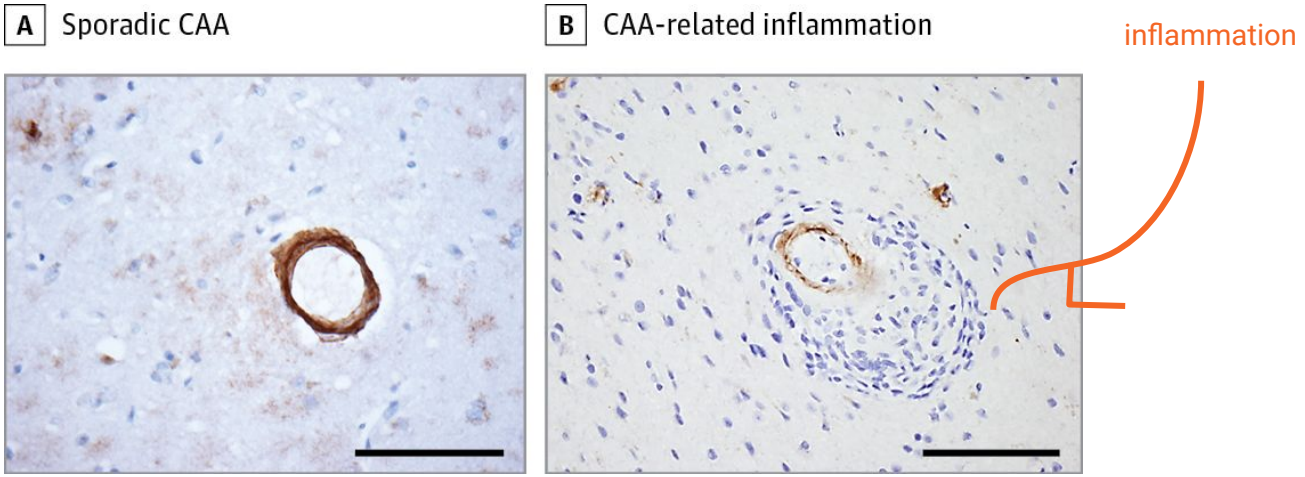
These diseases are pathologically distinct.



(Moussady et al, 2015)

What it is

They require pathology to confirm diagnosis.



But they also differ clinically and radiographically.

(Auriel et al., 2015)

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Why it matters

ICAA happens relatively early and has long-term sequelae.

- 67 years at presentation (compared to 76 for CAA)
- Inflammatory CAA results in:
  - Vascular dysfunction
  - Increased bleeding risk
  - Early cognitive decline
- Given its earlier presentation, inflammatory CAA disease-affected years can be higher. And, these episodes of inflammatory CAA can recur, adding further vascular insult.

(De Souza and Tasker, 2023)
(Bozovic et al., 2023)
(Chwalisz BK, 2021)

Why it matters

Unlike CAA, ICAA is treatable.

- Immunosuppressive agents and/or high dose steroids are the main treatments
- Can lead to both clinical and radiological improvement
- May reduce the rate of recurrence
- Still a developing area - no official guidelines on treatment yet

(Regenhardt et al., 2020)
(Corovic et al., 2018)
(Castro et al., 2015)
(Sakaguchi et al, 2011)

Why it matters

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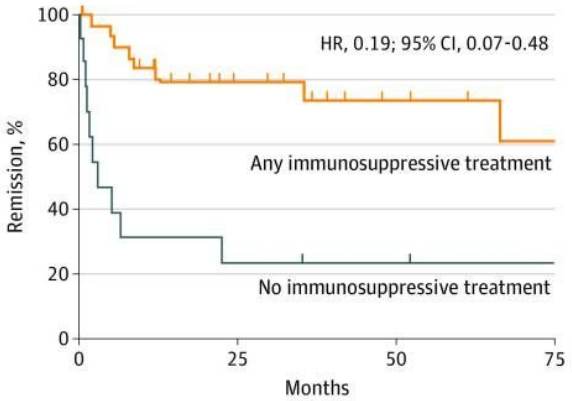

No. at risk				
Any immunosuppressive treatment	34	27	26	25
No immunosuppressive treatment	14	4	4	4

Patients who receive immunosuppressive treatment are more likely to achieve remission.

(Regenhardt et al., 2020)

Why It Matters

ICAA might be underdiagnosed.

- A combination of being rare diagnosis and having widely varied presentations makes ICAA hard to characterize and diagnose.
- A recent abstract on a multi-center single healthcare retrospective study found that in 10 years, only half of the patients with inflammatory CAA were diagnosed initially, while the rest were diagnosed up to 9 months later.

(Bozovic et al., 2023)
(Kharal et al., 2023)

Why It Matters

long-term sequelae
treatable
underdiagnosed
\+ *distinct imaging features*

Radiologists play a key role in early diagnosis and treatment.

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Who to suspect

- Patients are usually younger than those with just CAA
- Tend not to present with intracranial hemorrhage
- Encephalopathy and headaches are common
- Can be focal or multifocal neurological deficits
    - Including vision changes, aphasia, ataxia, hemiparesis
- Can present like strokes
- Typically acute/subacute but can be up to years

(De Souza and Tasker, 2023)

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What to Look For on Imaging

1 **CAA**
Cortical/subcortical hemorrhagic lesions, ± superficial siderosis

2 **Inflammation**
Asymmetric cortical/subcortical FLAIR hyperintensities, ± enhancement

(Auriel et al., 2021)

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How to Diagnose

Table 1. Criteria for the Diagnosis of CAA-ri

Diagnosis	Criteria
Probable CAA-ri	1. Age ≥40 y 2. Presence of ≥1 of the following clinical features: headache, decrease in consciousness, behavioral change, or focal neurological signs and seizures; the presentation is not directly attributable to an acute ICH 3. MRI shows unifocal or multifocal WMH lesions (corticosubcortical or deep) that are asymmetric and extend to the immediately subcortical white matter; the asymmetry is not due to past ICH 4. Presence of ≥1 of the following corticosubcortical hemorrhagic lesions: cerebral macrobleed, cerebral microbleed, or cortical superficial siderosis[8] 5. Absence of neoplastic, infectious, or other cause
Possible CAA-ri	1. Age ≥40 y 2. Presence of ≥1 of the following clinical features: headache, decrease in consciousness, behavioral change, or focal neurological signs and seizures; the presentation is not directly attributable to an acute ICH 3. MRI shows WMH lesions that extend to the immediately subcortical white matter 4. Presence of ≥1 of the following corticosubcortical hemorrhagic lesions: cerebral macrobleed, cerebral microbleed, or cortical superficial siderosis[8] 5. Absence of neoplastic, infectious, or other cause

Abbreviations: CAA-ri, cerebral amyloid angiopathy–related inflammation; ICH, intracerebral hemorrhage; MRI, magnetic resonance imaging; WMH, white matter hyperintensity.

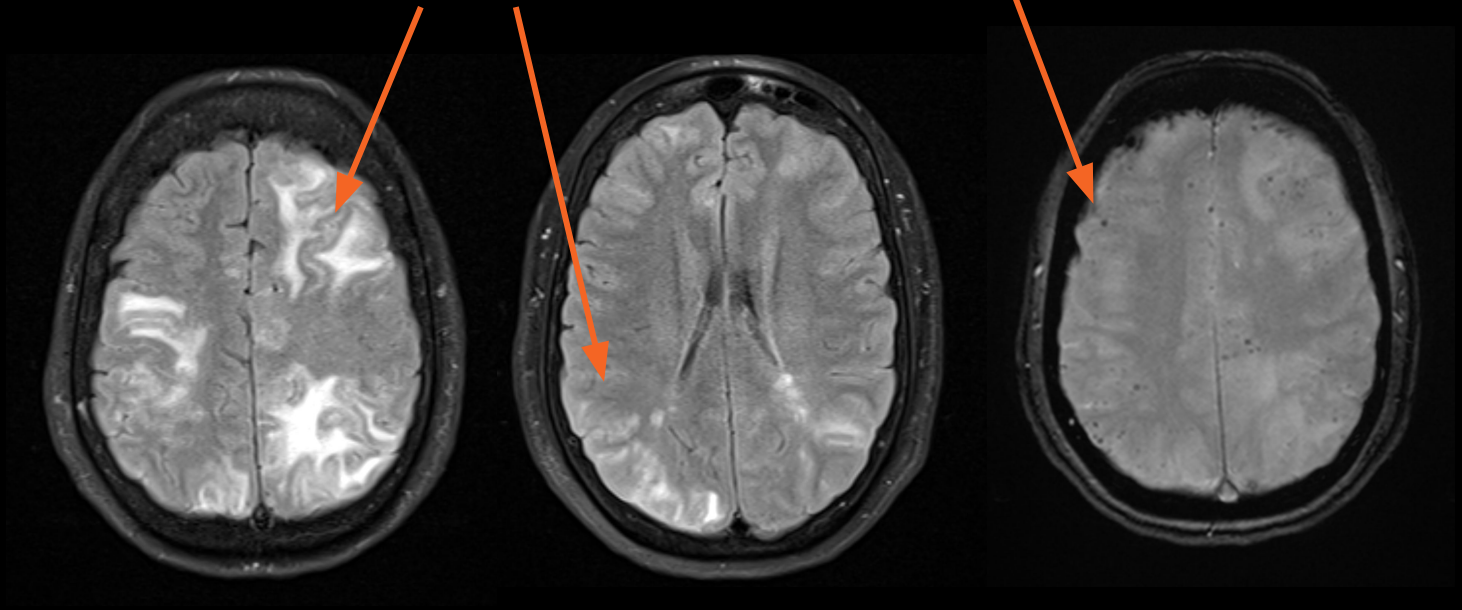
(Auriel et al., 2021)

A Straightforward Example

Example #1: 60F, new stereotyped “spells”

Subcortical white matter hyperintensities

Cortical/juxtacortical microhemorrhages



FLAIR

GRE

NEXT STEP

Check the criteria.

Example #1: “probable CAA-ri” diagnosis

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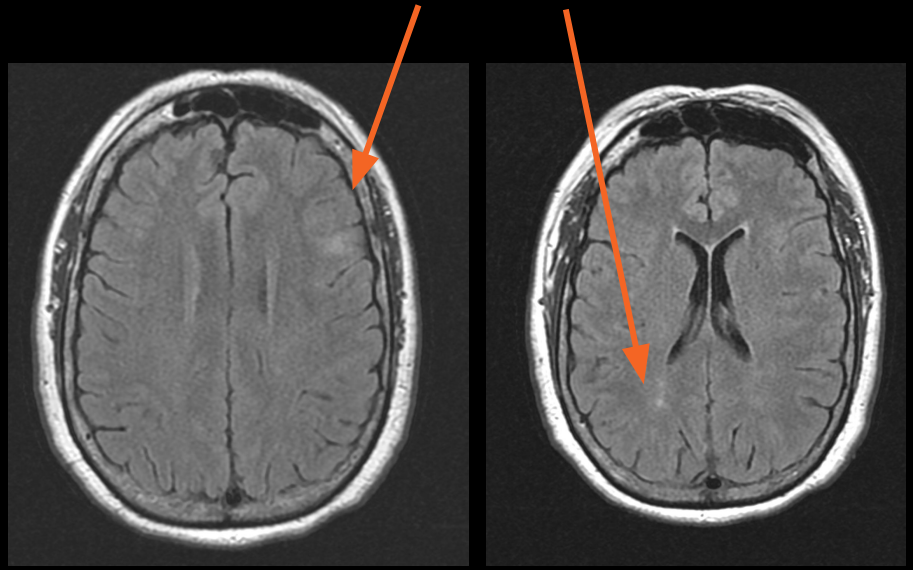
NEXT STEP

Start steroids.

Example #1: improves with steroids

Decreased white matter hyperintensities



FLAIR

CONCLUSION

Patient improved both radiographically and clinically. Per physician note, treatment resulted in “a very dramatic change in a short period of time.”

Patient recommended follow-up MRIs and to avoid blood thinners.

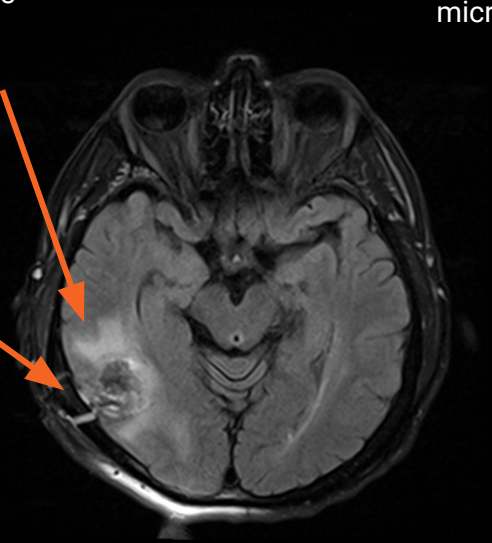
A Less Straightforward Example

Example #2: 61M, seizures

Patient with new onset seizures who was biopsied at an outside hospital for concern for malignancy presents for workup.

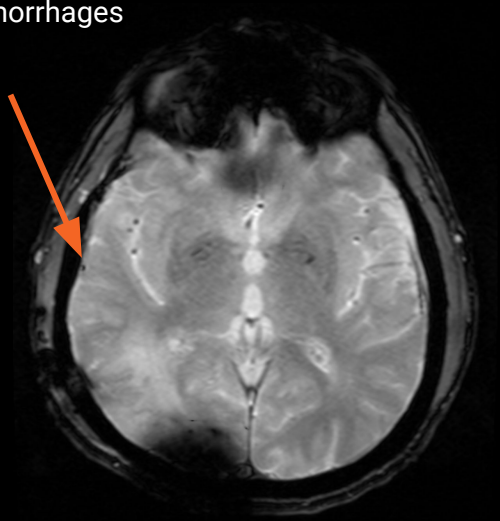
Subcortical white matter hyperintensities

Leptomeningeal signal



FLAIR

Cortical/juxtacortical microhemorrhages



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NEXT STEP

Check criteria.

Follow-up biopsy results.

Example #2: “probable CAA-ri” diagnosis

Table 1. Criteria for the Diagnosis of CAA-ri

Diagnosis	Criteria
Probable CAA-ri	1. Age ≥40 y 2. Presence of ≥1 of the following clinical features: headache, decrease in consciousness, behavioral change, or focal neurological signs and seizures; the presentation is not directly attributable to an acute ICH 3. MRI shows unifocal or multifocal WMH lesions (corticosubcortical or deep) that are asymmetric and extend to the immediately subcortical white matter; the asymmetry is not due to past ICH 4. Presence of ≥1 of the following corticosubcortical hemorrhagic lesions: cerebral macrobleed, cerebral microbleed, or cortical superficial siderosis[8] 5. Absence of neoplastic, infectious, or other cause
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NEXT STEP

Check biopsy.

(In this case, they did not treat before biopsy results came back.)

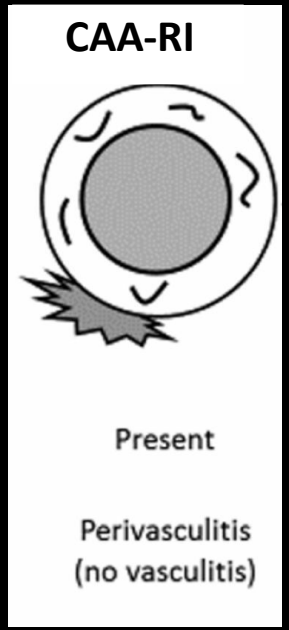
Example #2: biopsy proves the diagnosis

Neuropathology Final Report

Diagnosis — Amyloid Angiopathy

Comments —

Sections predominantly show fragments of gray matter and leptomeninges with admixed acute hemorrhage. Blood vessels show thickened, hyalinized walls. A chronic inflammatory infiltrate surrounds many of these abnormal vessels. Congo red stains are positive for amyloid within the vessel walls. Per report, an immunohistochemical stain for beta amyloid performed at Johns Hopkins is also positive in vessel walls. There is no evidence of neoplasm.



(Moussady et al, 2015)

NEXT STEP

Start aricept.

Example #3: improves with combo therapy

3/2014 - First seizure.

4/2014 - Biopsy.
5/2014 - Second seizure.

9/2014 - Started Aricept, no improvement.
9/2014 - Stopped Aricept. Completed course of Cellcept and steroids.

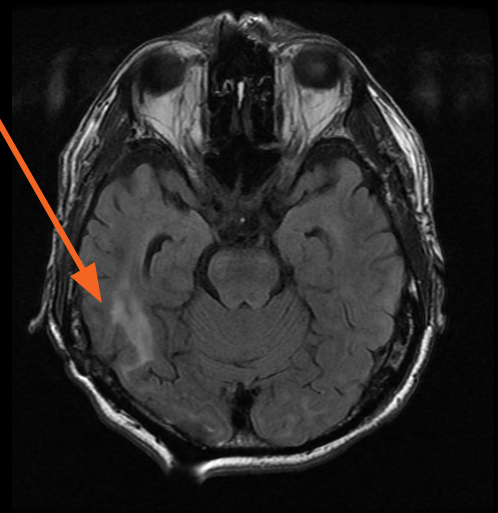
12/2014 - MRI worsening off steroids.

1/2015 - Started Cellcept and steroids again.

Sometime in 2015 - Last seizure.

TODAY - On lifelong AEDs. Decreased inflammation on MRI.

Decreased white matter hyperintensities



T2 FLAIR

Summary of Inflammatory CAA

- **What it is**
  A pathological diagnosis of CAA + vascular/perivascular inflammation
- **Why it matters**
  Radiologists play a key role in identifying this treatable disease that, left untreated, has significant long term sequelae.
- **Who to suspect**
  A patient in their 60's with headache, seizure, encephalopathy, or new neuro-deficits.
- **What to look for**
  Microhemorrhages and white matter changes suggesting inflammation.
- **How to diagnose**
  Utilize the modified Boston criteria and collaborate with other disciplines to initiate prompt treatment.

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