CEREBRAL AMYLOID ANGIOPATHY

SALONI SHIRKE, MS-4
CARIBBEAN MEDICAL UNIVERSITY SOM
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INTRODUCTION

- Cerebral Amyloid Angiopathy (CAA) is characterized by **β-amyloid (Aβ)** deposition in the leptomeningeal or cortical arterioles or capillaries
- Occipital regions are favoured for unknown reasons
- Sporadic or hereditary forms
- Strong association with Alzheimer's disease (but is its own entity)

Table 1. Sporadic and familial (hereditary) CAA forms

Amyloid peptide	Precursor protein	Chromo-some	Disease	Notes	Hemorrhagic stroke
Aβ	APP	-	Sporadic CAA		+
Aβ	APP	-	CAA related to sporadic AD	No increase in lobar ICH risk	-
Aβ	APP	21	CAA related to familial AD	Associated to presenilin-1 and presenilin-2 mutations	-
Aβ	APP	21	CAA in Down syndrome	Lobar ICH is rarely observed	-
Aβ	APP	21	Hereditary Cerebral Hemorrhage with Amyloidosis: Dutch type	Described in 2 large families from the Netherlands Age at onset: 50 years Lobar hemorrhages, focal neurological deficits, dementia, and leukoencephalopathy	+
Aβ	APP	21	Hereditary Cerebral Hemorrhage with Amyloidosis: Italian type	Described in 3 Italian families Age at onset: 50 years Lobar hemorrhages and dementia	+
Aβ	APP	21	Hereditary Cerebral Hemorrhage with Amyloidosis: Flemish type	Described in a dutch family (discovered in Belgium, therefore called "Flemish") and a British family Age at onset: 45 years Progressive AD-like dementia, in some patients associated with a lobar hemorrhage	+/-
Aβ	APP	21	Hereditary Cerebral Hemorrhage with Amyloidosis: Iowa type	Described in a Iowa family and a Spanish family Age at onset: 50-66 years Memory impairment, expressive language dysfunction, personality changes, myoclonic jerks, short-stepped gait, no clinically manifest ICH (family from Iowa) or lobar hemorrhages (family from Spain)	+/-
Aβ	APP	21	Hereditary Cerebral Hemorrhage with Amyloidosis: Piedmont type	Described in one family from Piedmont (Italy) Age at onset: 50-70 years Recurrent lobar hemorrhages, cognitive decline	+

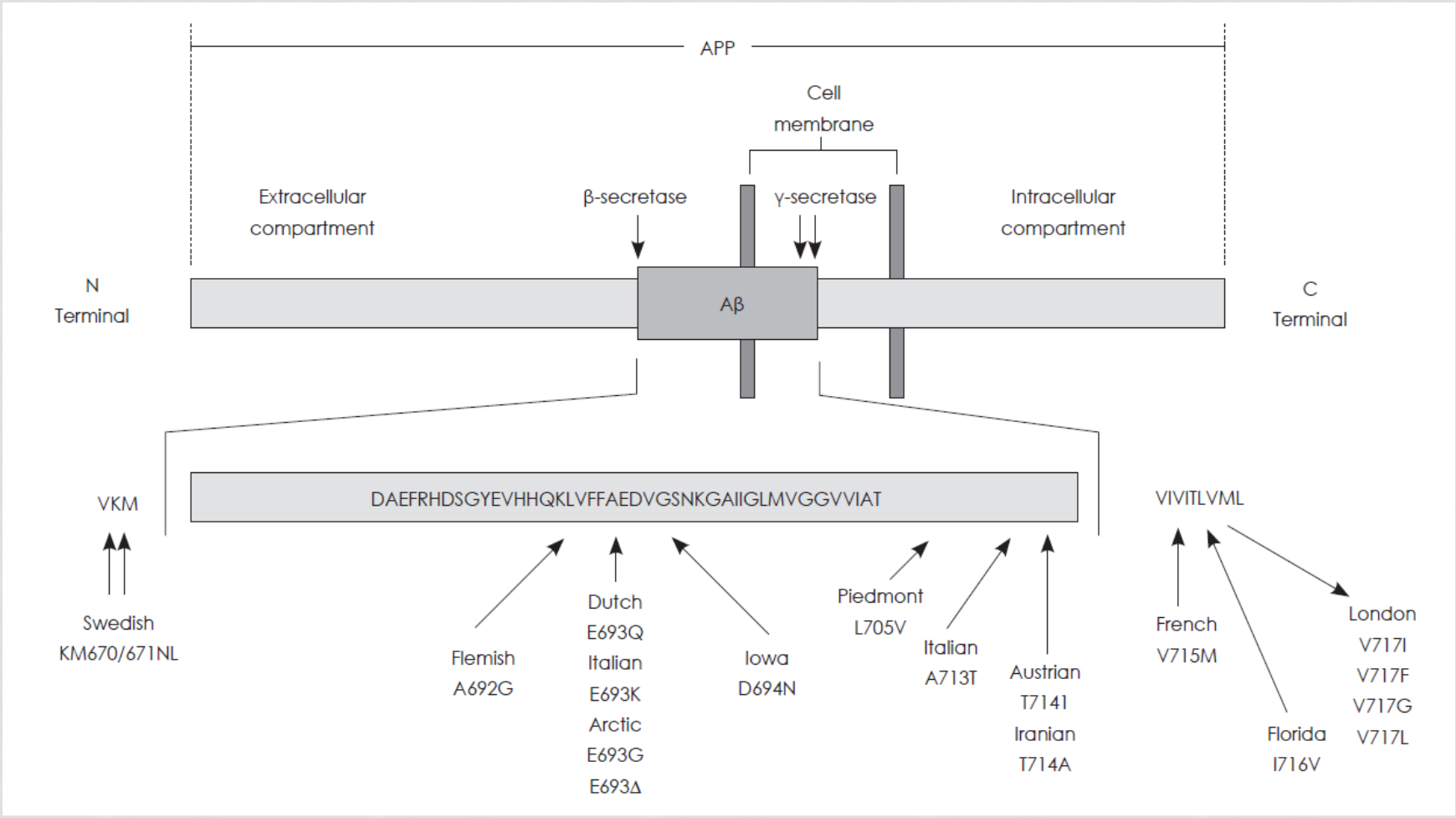
Aβ	APP	21	Hereditary Cerebral Hemorrhage with Amyloidosis: Arctic (Icelandic) type	Described in one family from northern Sweden Age at onset: ~60 years Progressive cognitive decline (no strokes)	-
ACys	Cystatin C	20	Hereditary Cerebral Hemorrhage with Amyloidosis: Icelandic type	Described in 9 sub-families in Iceland (one sporadic case in the US) Causes systemic amyloidosis Age at onset: 20-30 years Recurrent lobar hemorrhages	+
ATTR	Transthyretin	18	Meningovascular amyloidosis	Polyneuropathy is the main clinical symptom Rarer findings: ataxia, spasticity and dementia Systemic amyloidosis	In some families (rare)
AGel	Gelsolin	9	Familial Amyloidosis-Finnish Type	Progressive corneal lattice dystrophy, cranial and peripheral neuropathy, cutaneous amyloidosis Systemic amyloidosis	-
PrPSc	Prion Protein	20	Gerstmann-Sträussler-Scheinker syndrome	Described in one family Progressive cognitive decline	-
ABri	ABri precursor protein	13	Familial British Dementia	Described in 4 families Age at onset: 45-50 years Progressive dementia, cerebellar ataxia, spastic tetraparesis	-
ADan	ADan precursor protein	13	Familial Danish Dementia	Described in 1 family from Denmark Age at onset: 30 years Cataracts, deafness, progressive ataxia, dementia (previously known as "heredopatia ophtalmo-oto-encephalica")	-

AD: Alzheimer's disease, CAA: cerebral amyloid angiopathy, ICH: intracerebral hemorrhage.

Comparing Familial & Sporadic CAA

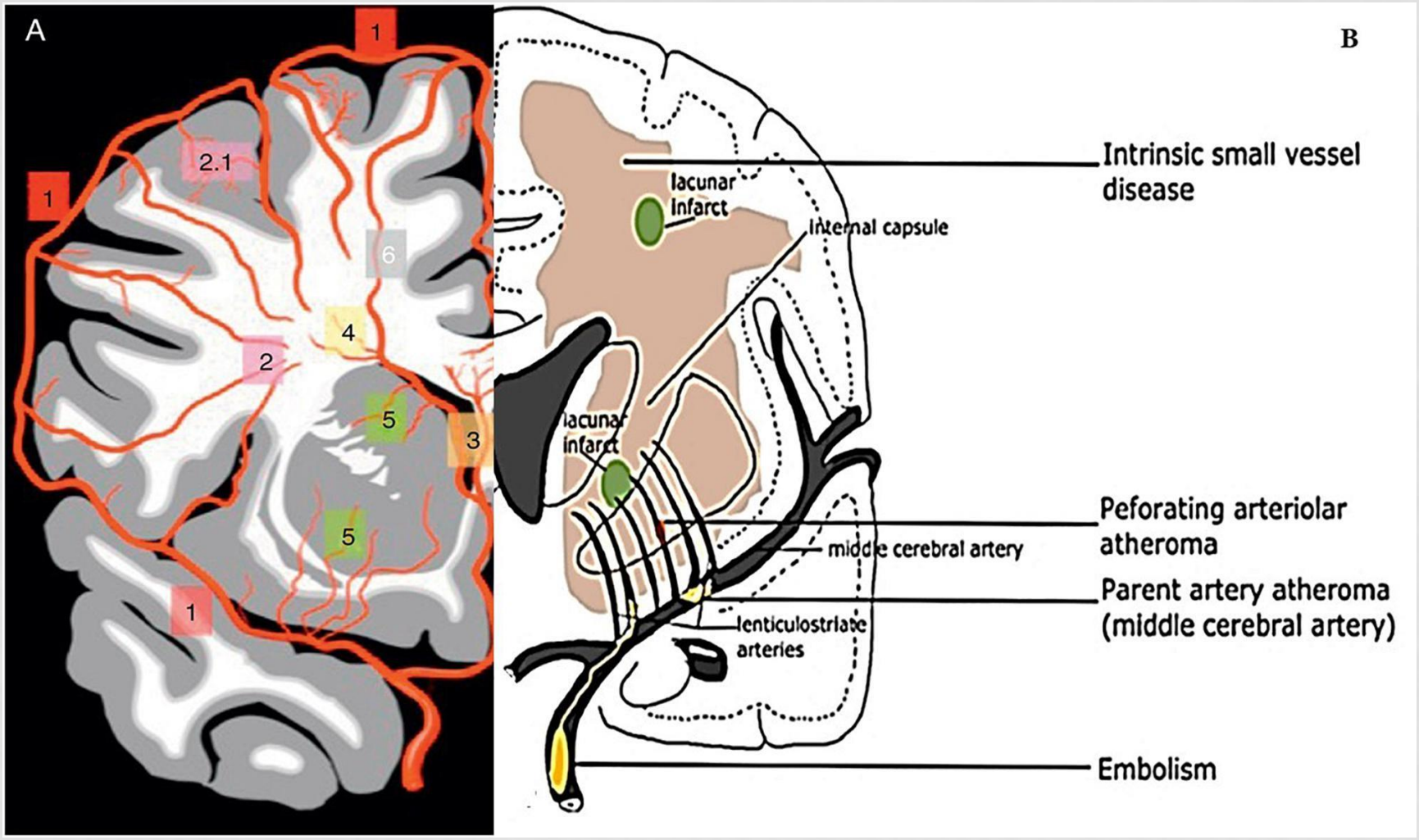
Characteristics	Familial	Sporadic
Incidence	Rare	More common
Age of onset	Younger	Older (>55)
Predominant clinical manifestation	Cognitive Impairment	Lobar ICH
Genetic Mutations or Risk Factors	Genes coding APP (Autosomal dominant)	APOE ε4/ε2
Prognosis	Poor	Worsen with age

Mutations in Amyloid Precursor Protein (APP) Gene



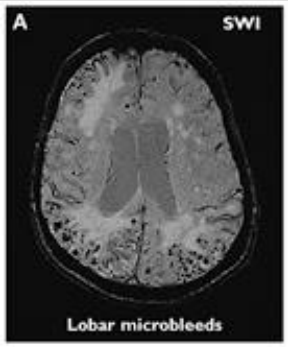
Sporadic Small Vessel Disease

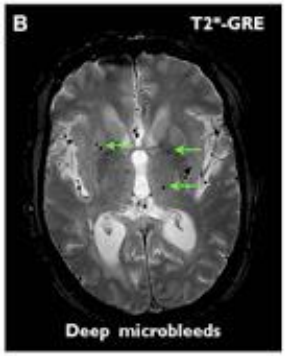
- Cerebral Amyloid Angiopathy
- Sporadic Nonamyloid Microangiopathy
  (Hypertensive Arteriopathy)

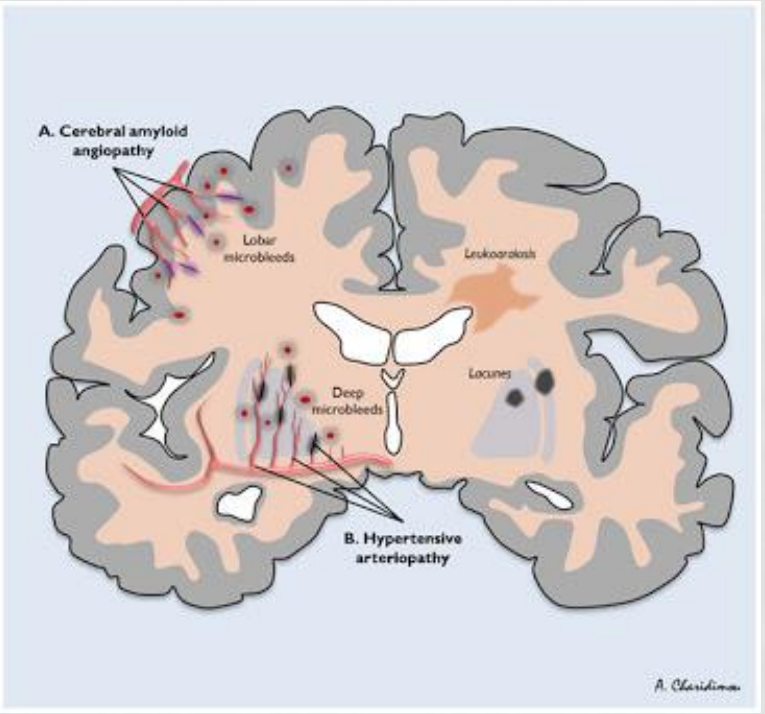


Larger cortical vessels have short and long penetrating arterioles to supply the cortex & subcortical white matter. Deep perforators of the cortical arteries supply the base of the brain. These arteriolar systems do not interconnect and end around the lateral ventricles.

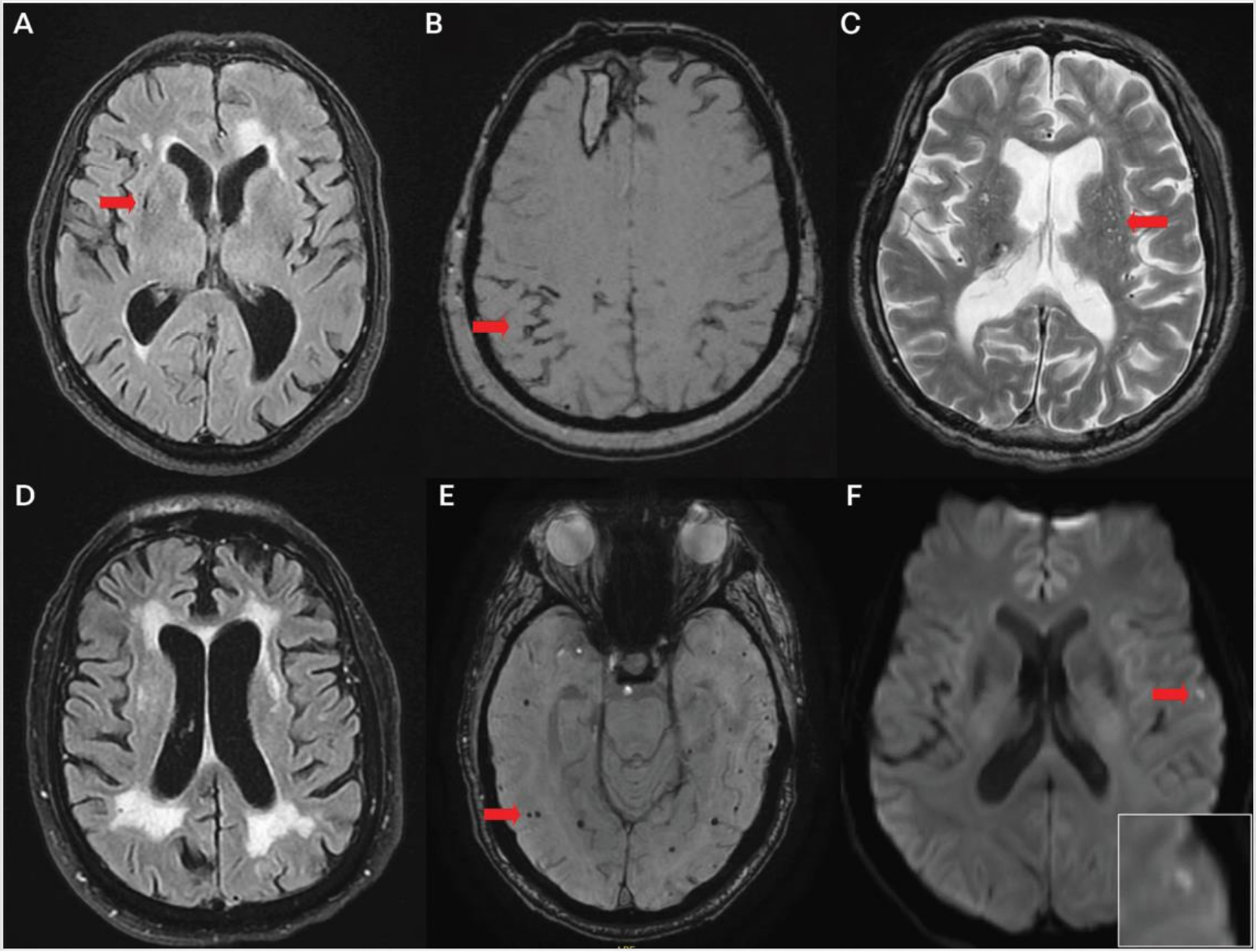
Neuroimaging Features of Cerebral Small Vessel Disease







1) Lacunar infarcts
2) White matter hyperintensities
3) Enlarged perivascular spaces
4) Cerebral microbleeds
5) Cortical superficial siderosis
6) Cortical microinfarcts


A
B
C
D
E
F

HISTORY

Gustav Oppenheim (1909)

- Described vascular Aβ deposition in CNS
- 6/14 brain autopsies of patients with senile dementia had necrotic foci adjacent to hyalinized capillaries

Scholz WZ (1938)

- Published first article on cerebrovascular abnormalities

Stefanos Pantelakis (1954)

- Observed that CAA is limited to vascular media and lacks parenchymal involvement
- Described the 6 hallmark features of CAA

Okazaki (1979)

- Published an article, clarifying the relationship betweeen CAA and lobar ICH
- Studied 23 autopsies of CAA at the Mayo Clinic and found ICH to be common

6 Hallmark Features of CAA

[Stefanos Pantelakis 1954]

1) Preferential involvement of the small arteries and capillaries of the meninges, cerebral cortex, and cerebellar cortex

2) Topographical distribution favouring the posterior brain regions

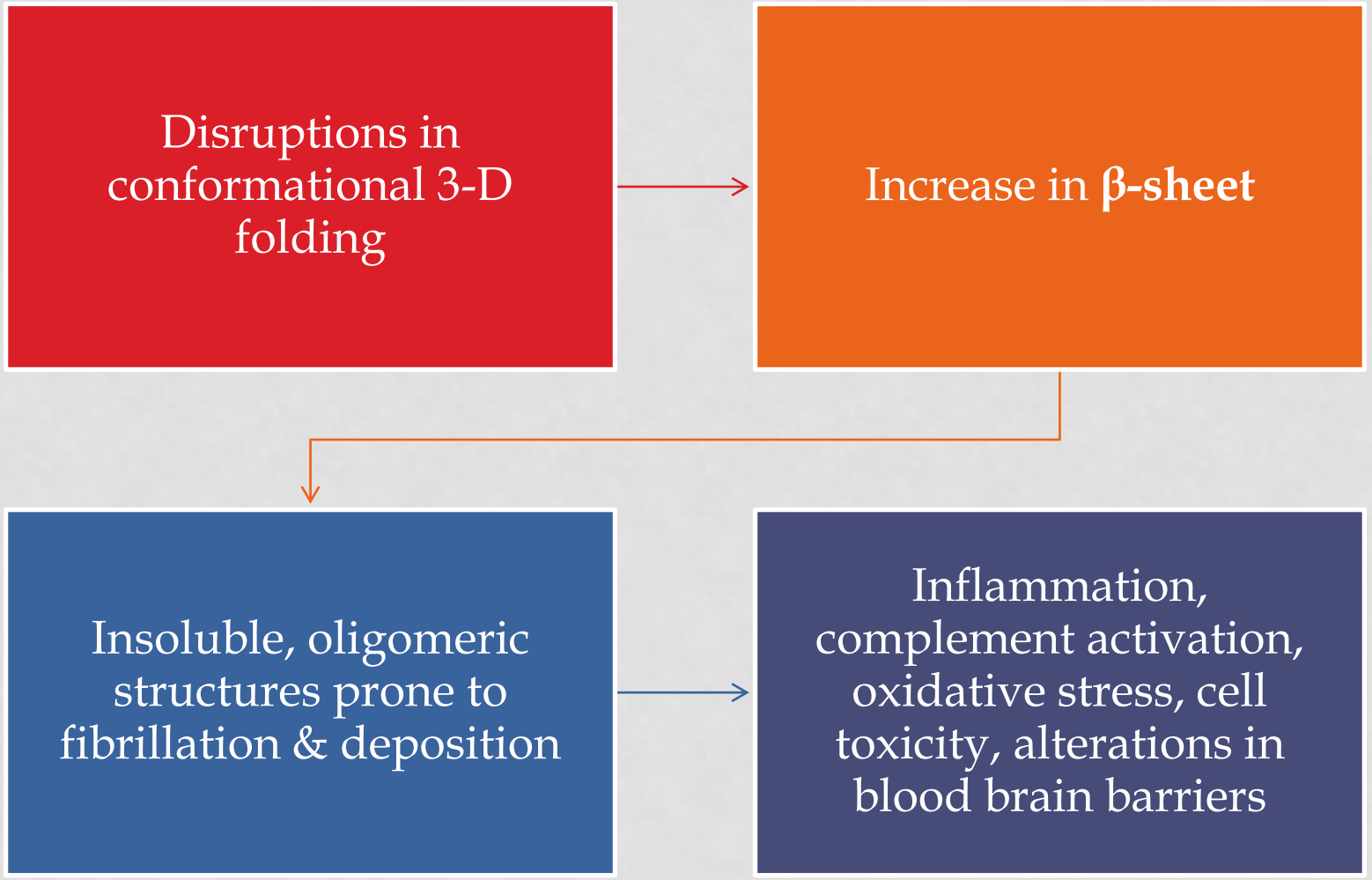
3) Lack of staining of vessels in the white matter

4)Association with increased age and dementia

5) Lack of association with hypertension and arteriosclerosis

6) Lack of association with amyloidosis of the other organs

Pathophysiology of CAA



Amyloid Ratios

Aβ-40

- Shorter
- More soluble
- Predominates in arterial walls
- CAA characterized by ↑ Aβ40:Aβ42

Aβ-42

- Longer
- Less soluble
- Predominates in neuritic plaques
- AD characterized by ↓ Aβ40:Aβ42

Pathophysiology of CAA

Abnormalities in **perivascular drainage** of Aβ from interstitial fluid is also strongly implicated in CAA & AD.

Two strongly proposed pathways include:

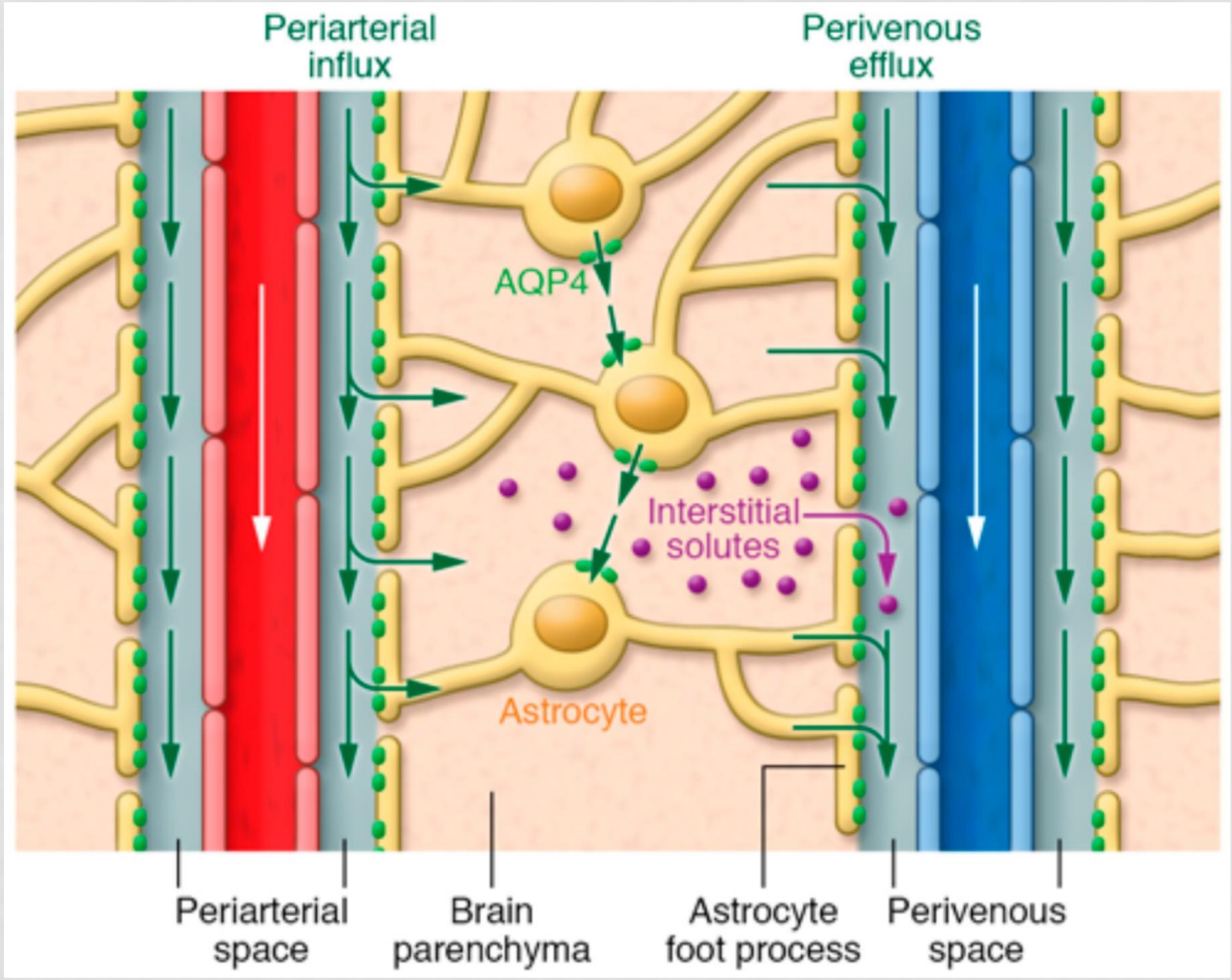
1. Glymphatic system:

- Aquaporin-4 (AQP4) channel is an important protein in the pathway
- Mice with AQP4 knockout showed a reduction in tracer clearance
- Post-mortem autopsies in patients with CAA or AD show absent/decreased AQP4 channels in astrocyte foot processes

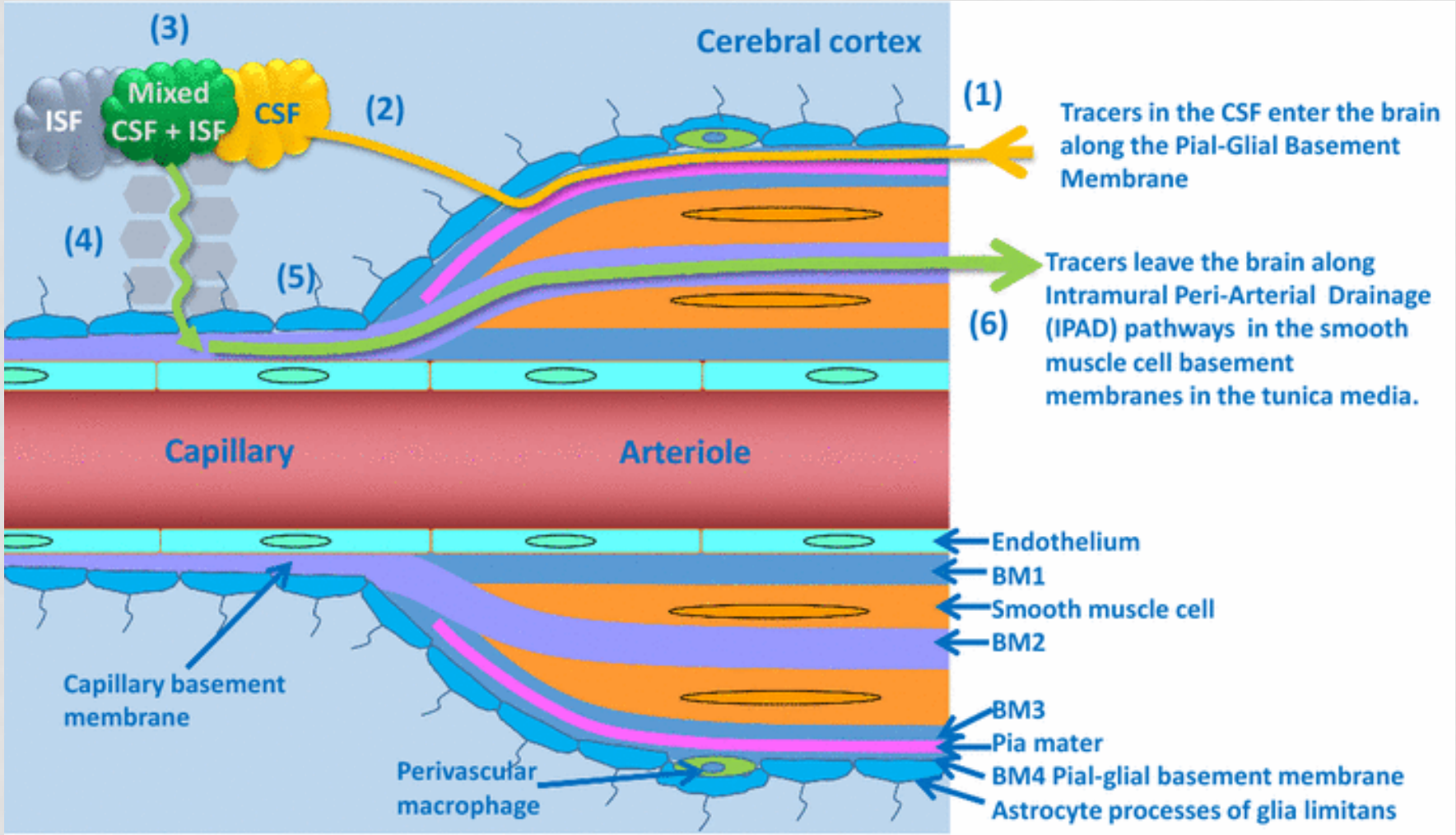
2. Intramural Peri-Arterial Drainage (IPAD):

- Drainage between smooth muscle basement membrane in tunica media of arterioles
- Matches the predominant distribution of Aβ deposition in CAA

Glymphatic Pathway



IPAD Pathway

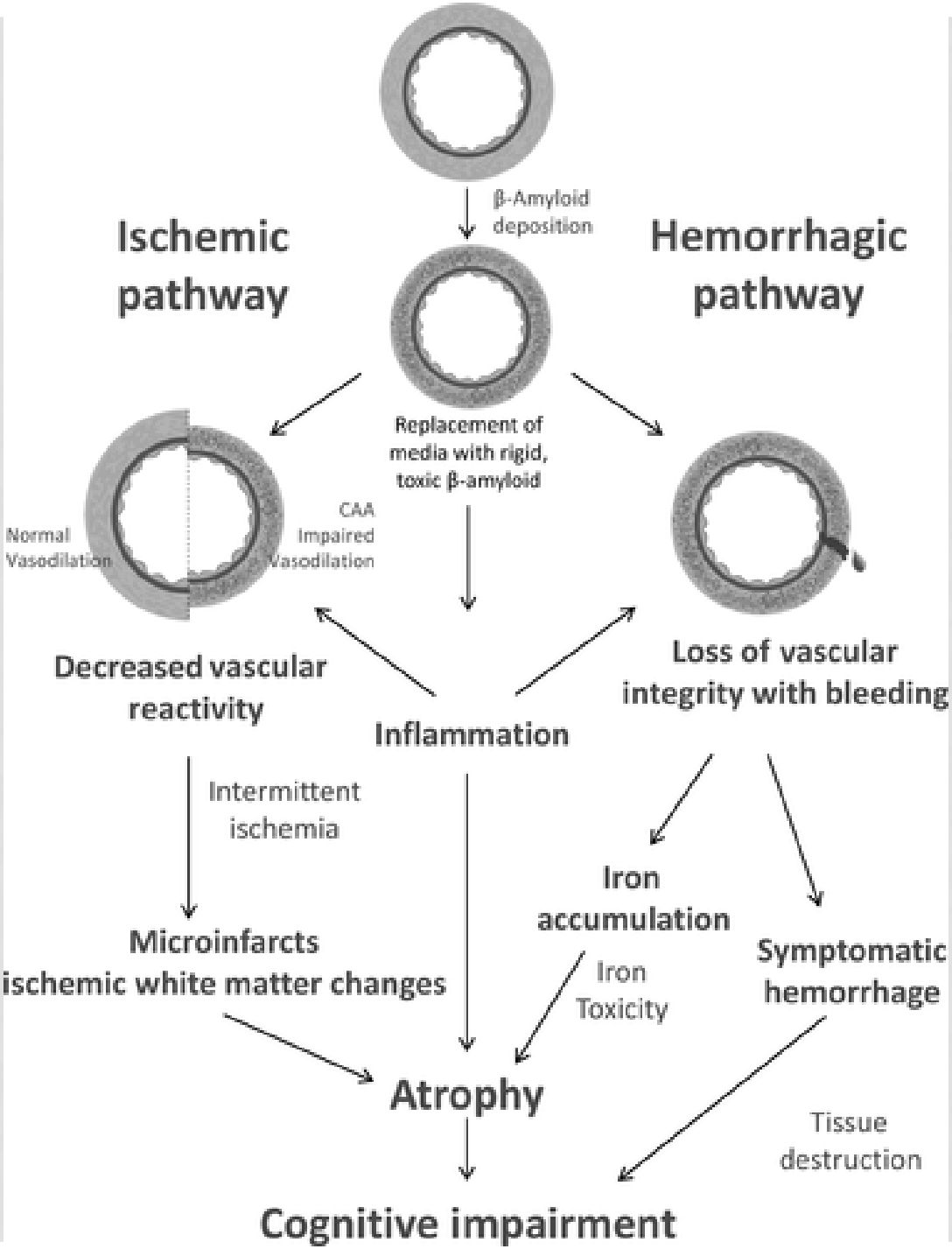


Pathways for influx of CSF into the brain and drainage of CSF/ISF out of the brain along periarterial basement membranes

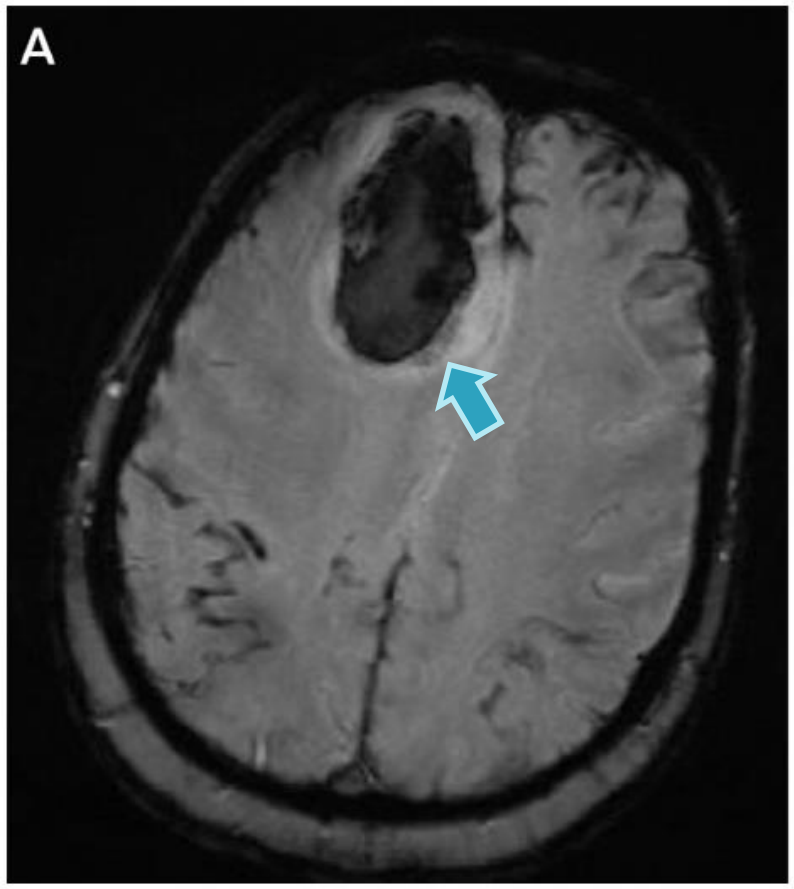
Clinical Manifestations

- Hemorrhagic Patterns
  - **Acute intraprenchymal hemorrhage**
  - Convexal subarachnoid hemorrhage
  - Cerebral microbleeds
  - Cortical superficial siderosis
- CAA-related inflammation (CAA-RI)
- Cognitive Impairment

Cognitive Impairment in Cerebral Amyloid Angiopathy

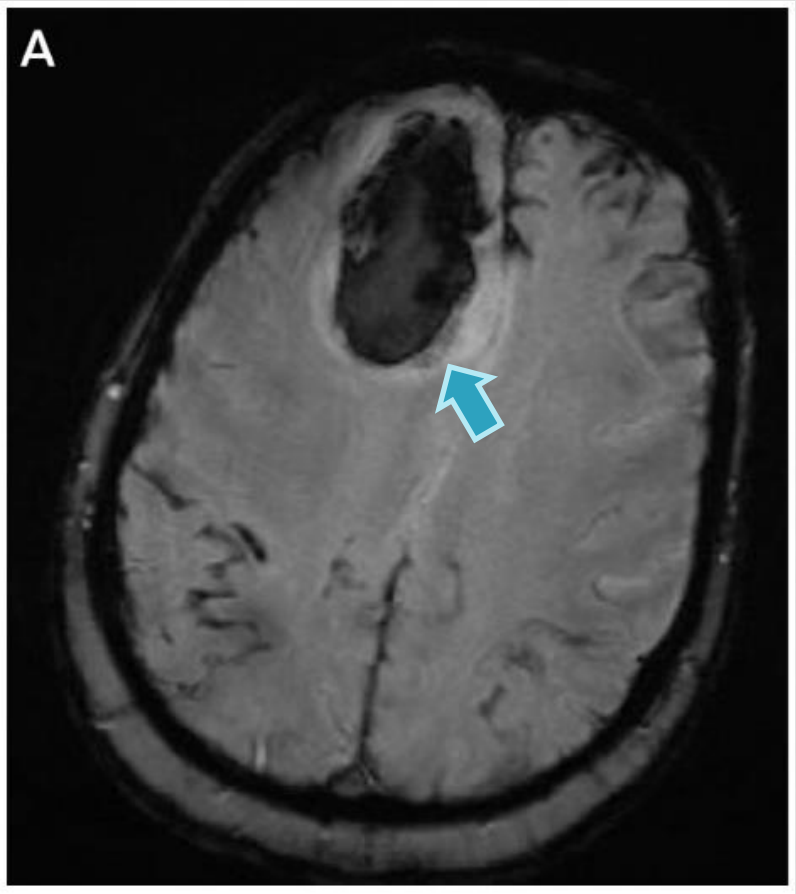


Acute ICH
(most common)



- **Location**: Lobar hemorrhage (cortex and subcortical white matter)
- **Presentation**: Headaches, transient focal neurological deficits(TFNS), seizures, altered consciousness
  - Symptoms severity depends on the size & location of hematoma
- **Diagnosis**: CT, MRI-GRE

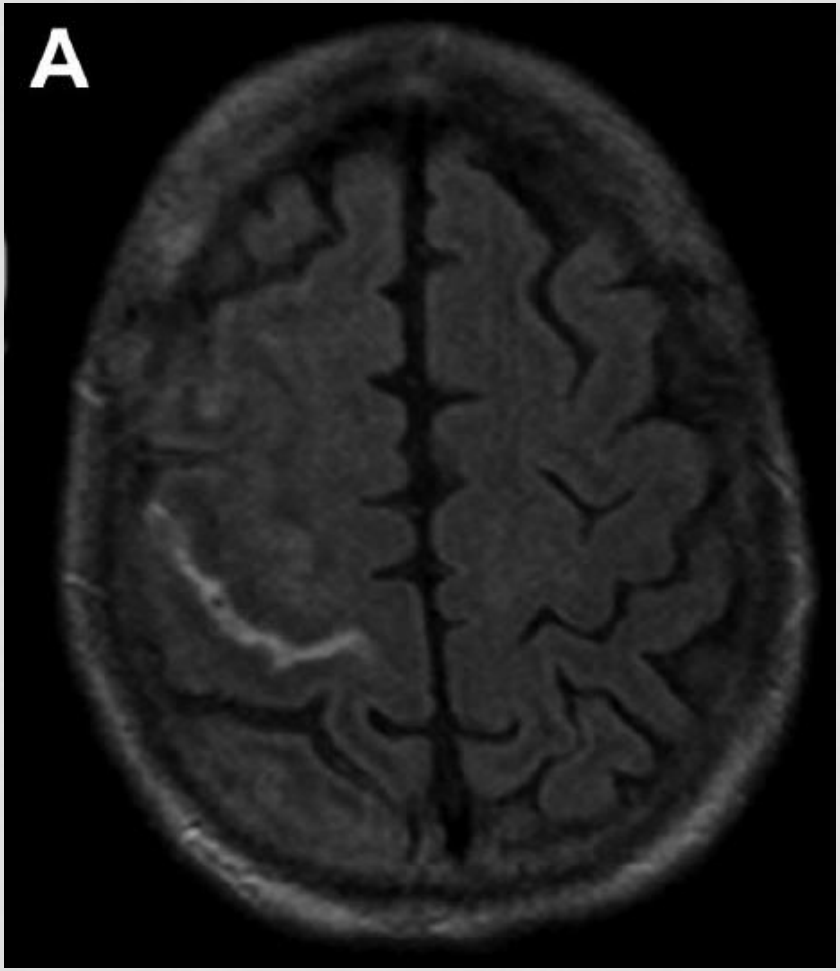
Acute ICH

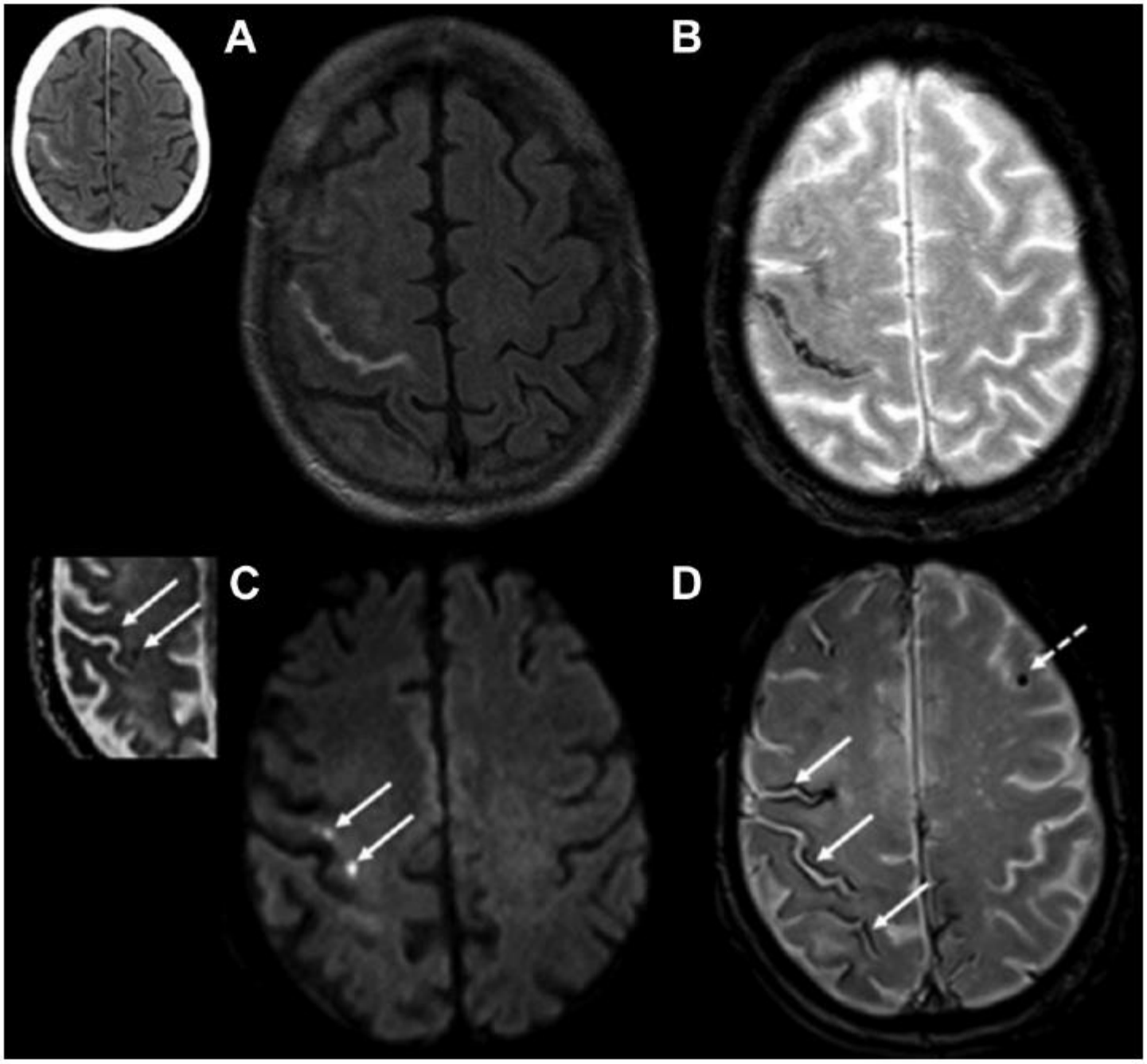


- **Treatment**: surgical vs. supportive
  - Aggressive blood pressure control (**PROGRESS** trial)
- **Prognosis**: highest cause of morbidity & mortality in CAA patients
  - Associated with a high risk or recurrence
  - WMH and cerebral microbleeds independently increase risk

Convexal Subarachnoid Hemorrhage

- **Presentation:** TFNS, progressive headache, or seizures, nausea/emesis, vertigo, confusion, mental
  - Amyloid Spells (TFNS): motor/sensory deficits, dysphagia, aphasia
- **Pathophysiology**: Due to amyloid accumulation in leptomeningeal vessels

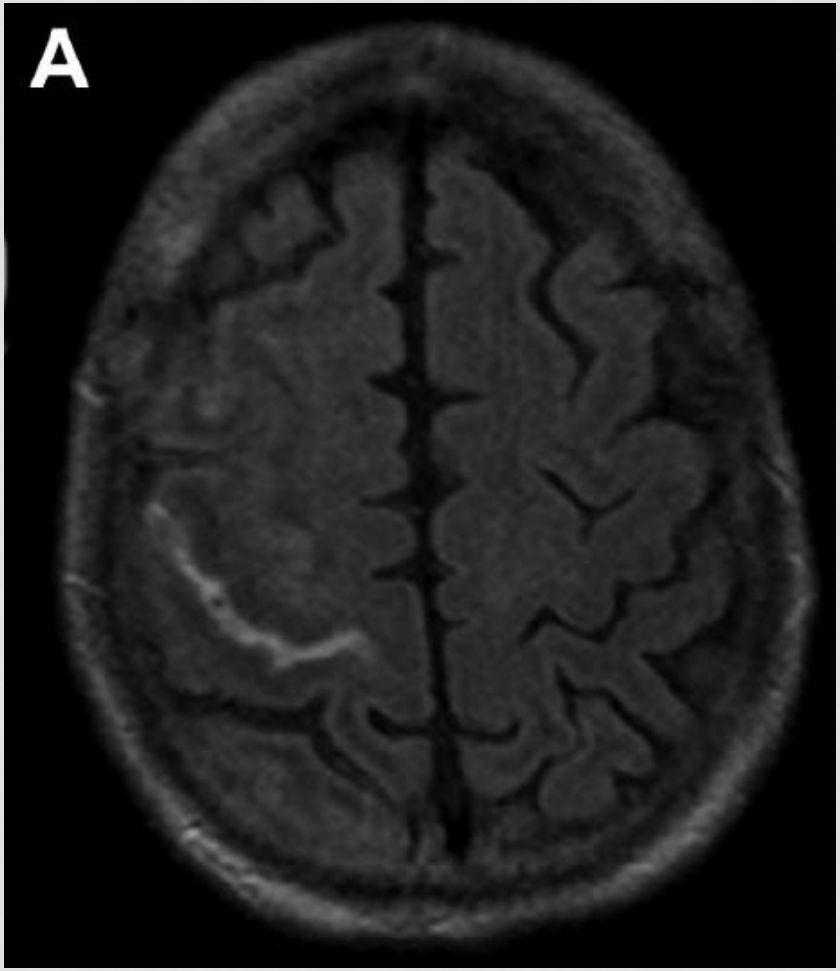




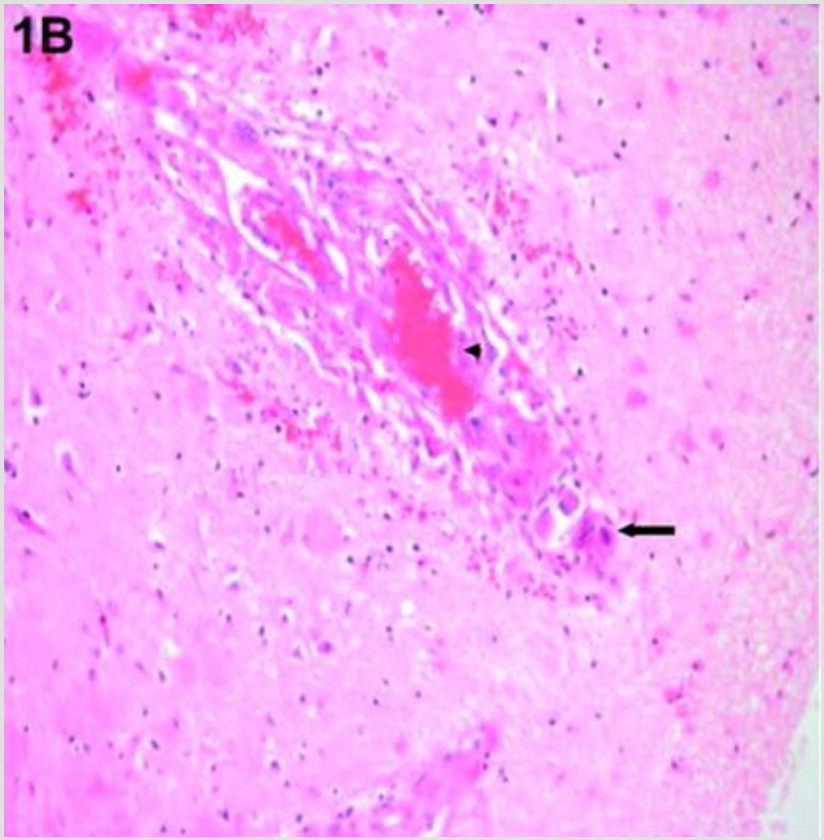
A, Intrasulcal high signal intensity on FLAIR MRI, linear hyperdensity on unenhanced CT (inset), and signal loss on gradient echo T2* MRI (**B**) indicate acute subarachnoid blood in the right central sulcus. On readmission 31 months later due to sudden left arm paresis, DWI MRI (**C**; ADC map: inset) demonstrated small acute ischemic infarcts in the right precentral gyrus (arrows). On T2*-weighted MRI (**D**), widespread meningeal hemosiderosis (arrows) beyond the region of the initial cSAH and a contralateral cortico-subcortical microbleed (dotted arrow) had developed (Note: **B** does not represent the exact corresponding slice). cSAH indicates convexal subarachnoid hemorrhage; FLAIR, fluid-attenuated inversion recovery; DWI, diffusion-weighted imaging.

Convexal Subarachnoid Hemorrhage

- **Diagnosis:** CT, MRI-GRE
- **Treatment**: supportive
- **Prognosis**: Poor. Unfavourable outcomes in patients with:
  - Age >60
  - Cerebral microbleeds
  - Early/Late confluent white matter hyperintensities



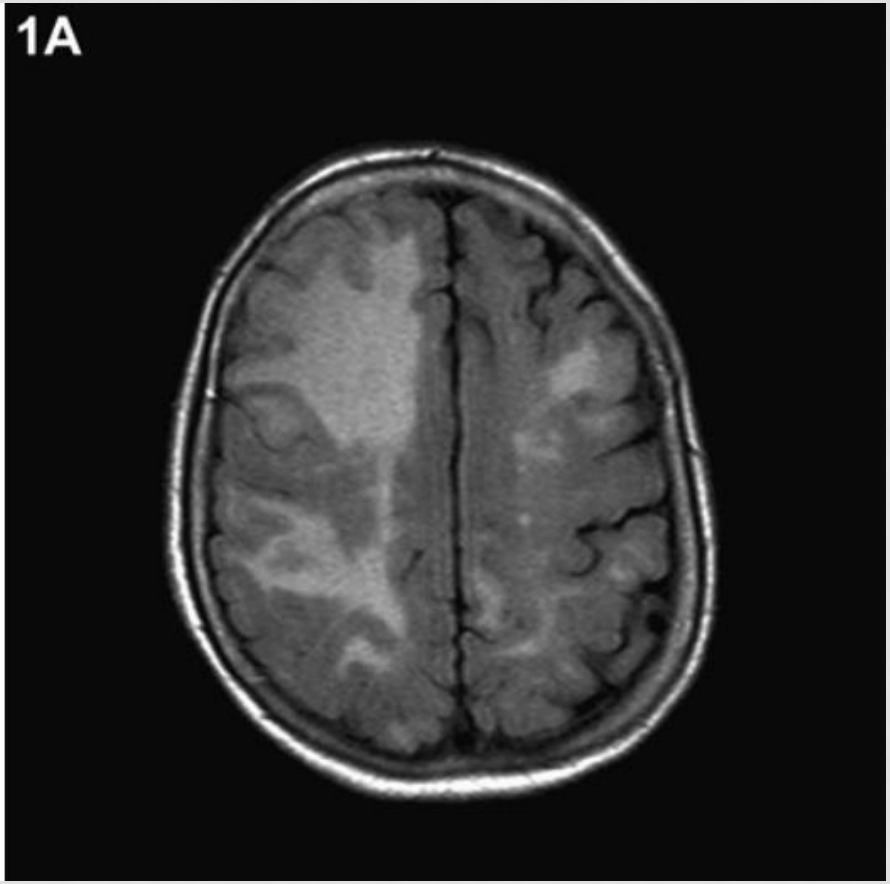
CAA-Related Inflammation (CAA-RI)



High power view of the histology demonstrating transmural inflammation of a cortical blood vessel with red blood cells in the lumen (arrowhead) and a multinucleated giant cell (long arrow).

- **Pathophysiology**: Anti-Aβ autoantibodies causing vasculitis or perivasculitis
  - Both can co-exist
  - Perivascular type has better prognosis
- **Presentation**: acute/subacute onset of headache, cognitive decline, seizures, encephalopathy, focal deficits

CAA-Related Inflammation (CAA-RI)



Diagnosis

- MRI Findings: Large, confluent, asymmetrical areas of WMH & microbleeds
- Labs: elevated ESR, CRP
- CSF Analysis: pleocytosis, elevated protein & opening pressure
- EEG: generalized or focal slowing

Proposed Diagnostic Criteria for CAA-RI [Chung 2011]

Probable CAA-I

All of the following:

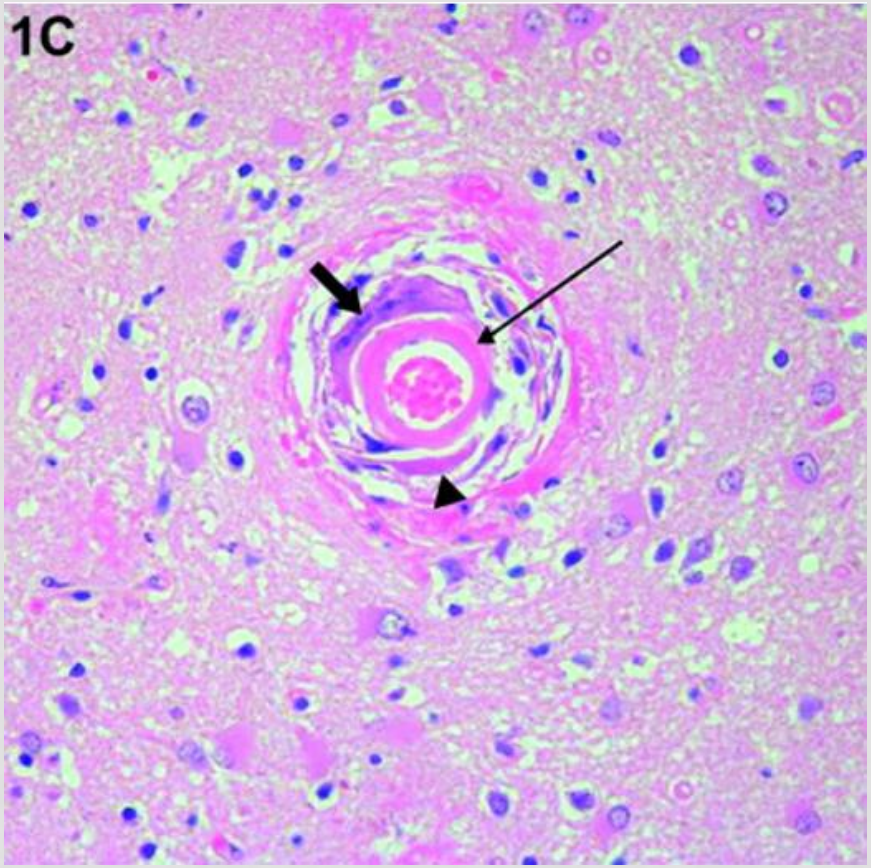
- Acute or subacute onset of symptoms.
- 40 years of age or older.
- At least one of the following clinical features: headache, mental status or behavioural change, focal neurological signs and seizures.
- MRI shows patchy or confluent T2 or fluid attenuation inversion recovery hyperintensity which is:
  - usually asymmetric
  - with or without mass effect
  - with or without leptomeningeal or parenchymal enhancement.
- Evidence of pre-existing CAA on susceptibility weighted MRI sequences:
  - multiple cortical and subcortical hemorrhages or microhemorrhages and/or
  - recent or past lobar hemorrhage
- absence of neoplastic, infectious or other cause

Definite CAA-I

All of the above plus histopathological confirmation with:

- perivascular, transmural and/or intramural inflammation
- amyloid deposition within vessels of affected area in the cortex and leptomeninges.

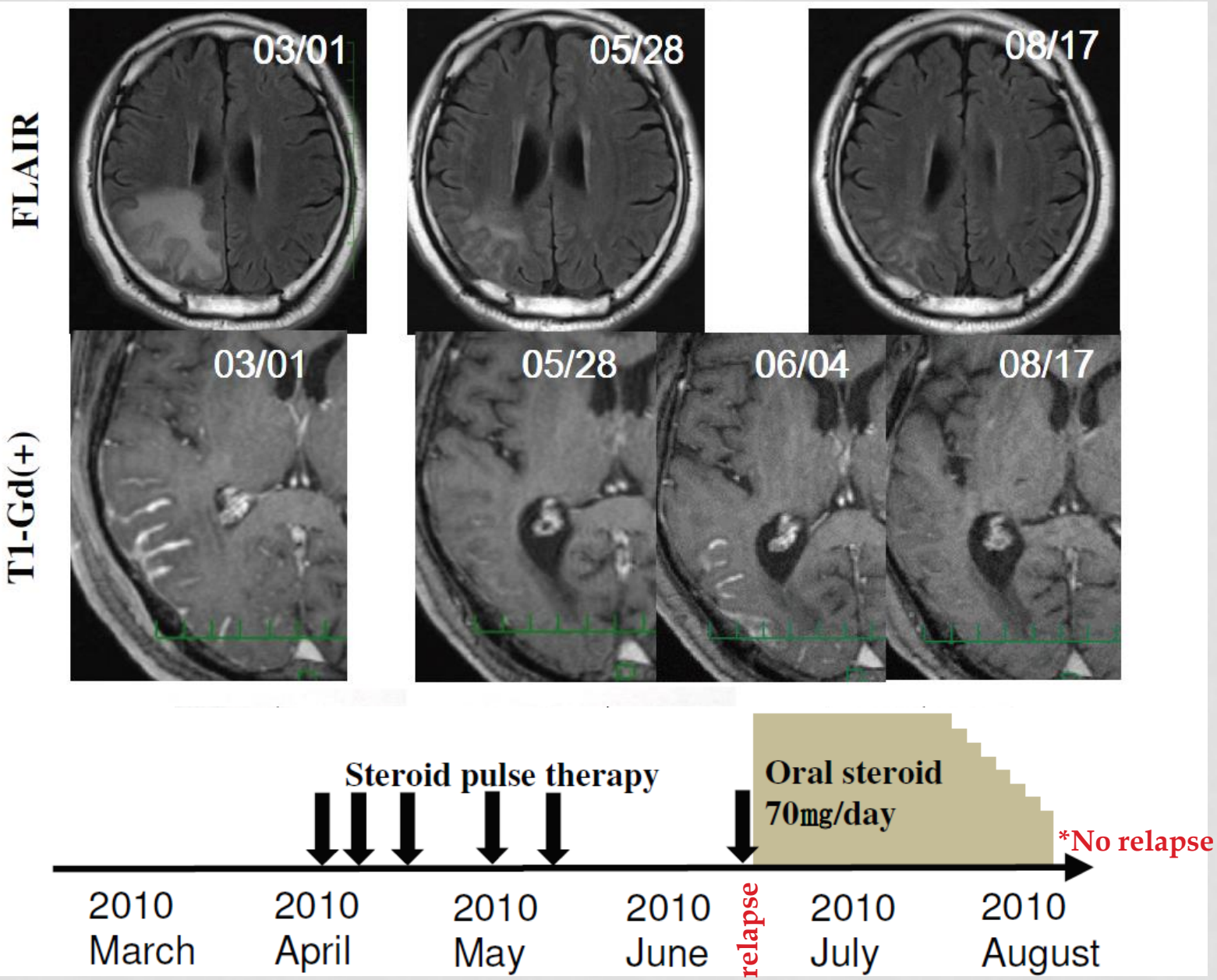
CAA-RELATED INFLAMMATION (CAA-RI)



Perivascular inflammation, amyloid deposition in artery (thin arrow), epithelioid cell (arrowhead) and multinucleated giant cell (thick arrow)

- **Treatment:** Pulse-dose corticosteroids
  - Consider immunotherapy with cyclophosphamide, methotrexate, mycophenolate mofetil
- **Prognosis**: responds well to treatment within first few weeks. Relapse is common with reduction or cessation of immunotherapy

Clinical course of treatment with steroid in CAA-RI [Case Report by Sakaguchi et.al]



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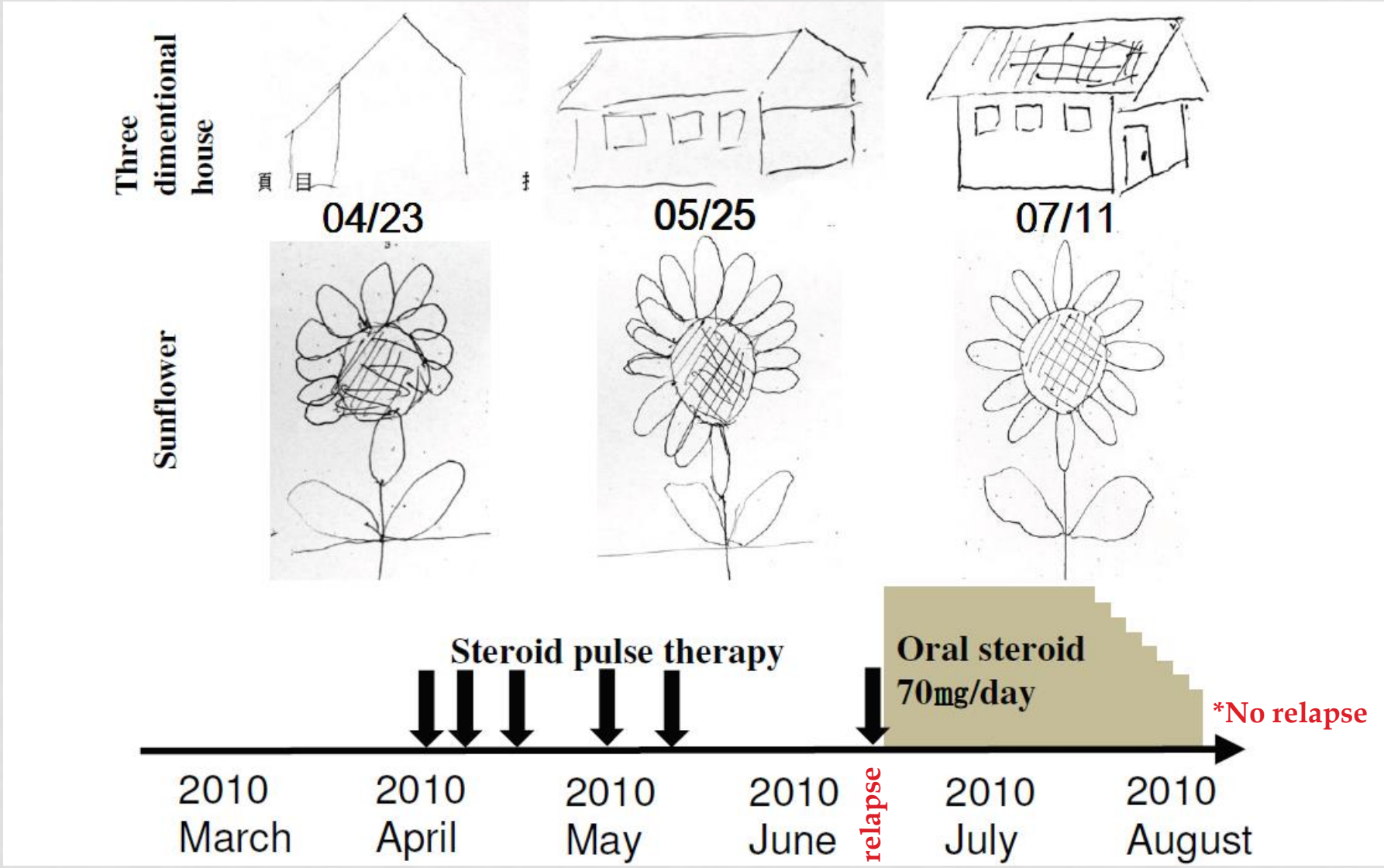


OTHER FEATURES OF CAA

Microbleeds

- 2-5 mm punctuate hemosiderin deposits
- Result from blood extravasation through microvasculature
- Evident on MRI (GRE or SWI sequences)

Superficial Siderosis

- Chronic foci of hemorrhage in the cortical sulci
  - Thought to be a chronic manifestation of a convexal subarachnoid hemorrhage
- Uncommon in patients with ICH of other causes
- Disseminated SS increases the risk of recurrent ICH

Diagnosing CAA:
Boston Criteria

Pathology Available

- Definite CAA
  - Full postmortem
    - Lobar intraparenchymal hemorrhage
    - Severe CAA with vasculopathy
- Probable CAA
  - Pathologic tissue
    - CAA in specimen (biopsy or evacuated hematoma)
  - Neuroimaging Data
    - Lobar intraparenchymal hemorrhage, cerebral MBs, or superficial siderosis

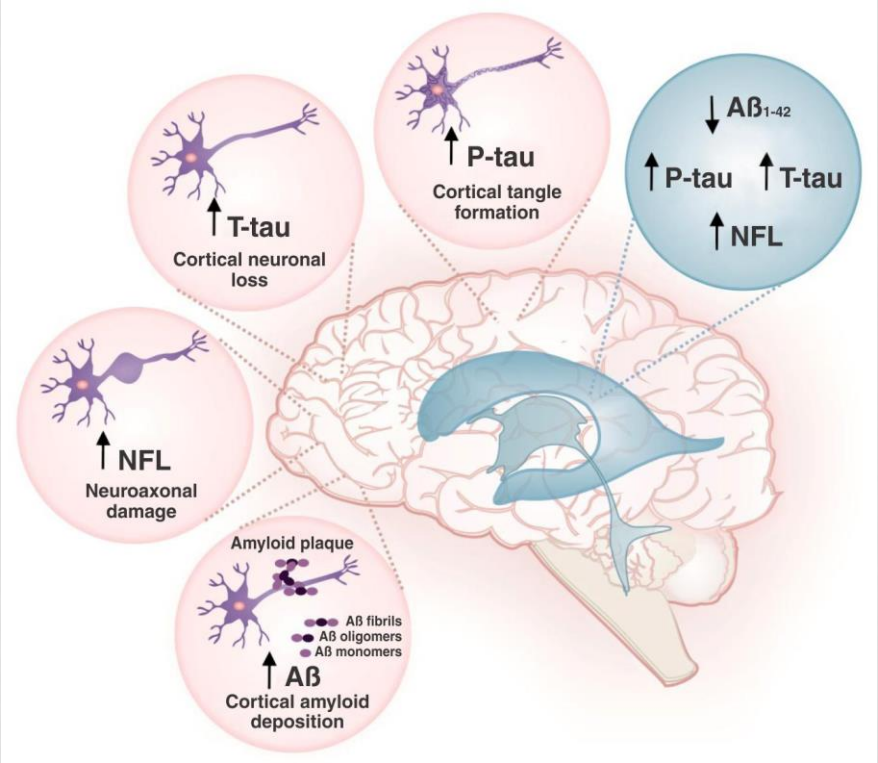
No Pathology Available

- Probable CAA
  - Age >55 years
  - Neuroimaging data
    - Multiple lobar intraprenchymal hemorrhages and cerebral MBs
    - Single lobar intraparenchymal hemorrhage and superficial siderosis
- Possible CAA
  - Age >55 years
  - Neuroimaging data
    - Single lobar intraparenchymal hemorrhage and superficial siderosis

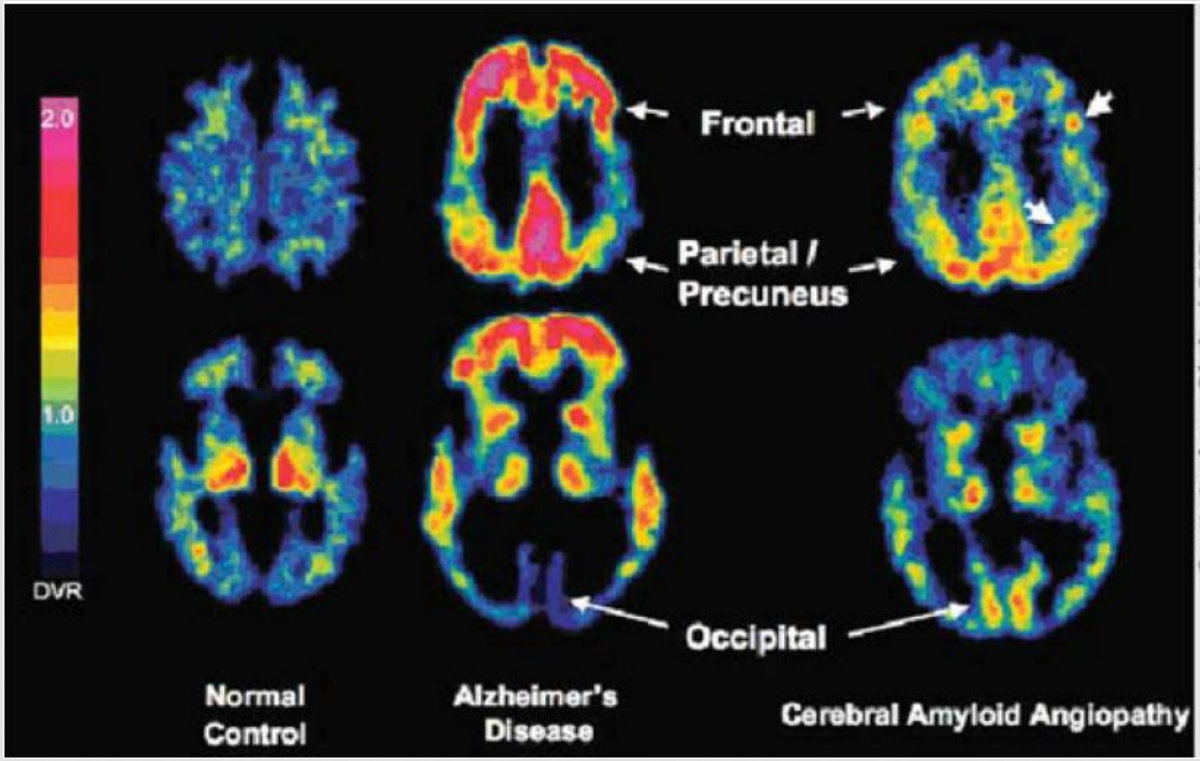
Diagnosing CAA:
CSF Biomarkers for Early Detection

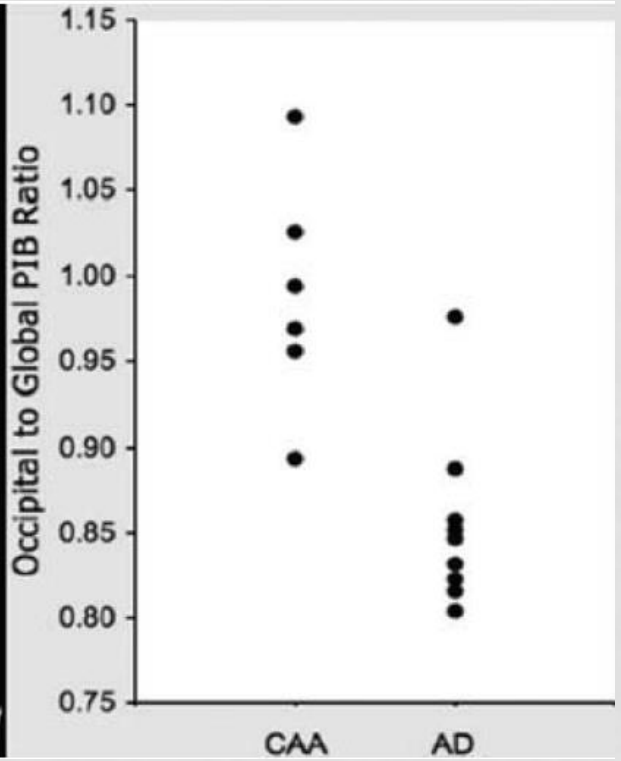
- **Rationale**: patients with Alzheimer's Disease (AD) have decreased Aβ42 and increased Tau protein in the CSF

- Decreased CSF concentrations of Aβ42 and Aβ40 have been found in CAA patients
  - Aβ40 helps differentiate between CAA and AD



Diagnosing CAA:
PiB-PET Imaging for Early Detection





THERAPEUTICS & CONTRAINDICATIONS IN CAA

Ponezumab

- Monoclonal antibody against Aβ; initially trialled in AD
- Well tolerated among patients

Antihypertensives:

- **PROGRESS Trial** – for patients with a probable diagnosis of CAA, active treatment versus placebo reduced the risk of further bleeds by 77%.
- Rigorous BP control with target of:
  - <140 mmHg (systolic) and <90 mmHg (diastolic)

Statins:

- May increase the risk of ICH recurrence
- **SPARCL trial**
  - Statins had a positive effect in patients with a history of stroke /TIA
  - Incidence of ICH was increased in patients taking statins versus placebo

TREATMENT OF CAA

Thrombolysis:

- Insufficient evidence to justify withholding antithrombotics in patients with ischemic strokes (risk versus benefits analysis)

Anticoagulants:

- Presence of microbleeds may increase vitamin-K-antagonists associated ICH
- NOACs carry a lower risk of ICH compared to vitamin-K-antagonists
- In patients with Atrial Fibrillation, consider other therapeutic options (i.e. left atrial appendage closure)

Antiplatelets:

- Aspirin (ASA) is associated with lobar hemorrhages and microbleeds
- Clopidogrel + ASA increase the risk of fatal bleeds

Severity Grading
(used routinely in neuropathology)

Olichney et al.

- **0 -** no Aβ positive blood vessel
- **1 -** scattered Aβ positivity in leptomeningeal or intracortical blood vessels
- **2 -** strong circumferential Aβ positivity in leptomeningeal or intracortical blood vessels
- **3 -** widespread, strong, circumferential Aβ positivity in leptomeningeal or intracortical blood vessels
- **4 -** same as (3) with additional dysphoric features

Vonsattel et al.

- **Mild:** amyloid is restricted to the tunica media without significant destruction of smooth muscle cells
- **Moderate:** tunica media is replaced by amyloid and is thicker than normal
- **Severe:** extensive amyloid deposition with focal wall fragmentation or even double barreling of the vessel wall, microaneurysm formation, fibrinoid necrosis, and leakage of blood through the blood vessel wall

REFERENCES

- Chung KK, Anderson NE, Hutchinson D, Synek B, Barber PA. Cerebral amyloid angiopathy related inflammation: three case reports and a review. *J Neurol Neurosurg Psychiatry*. 2011;82(1):20-26. doi:10.1136/jnnp.2009.204180

- Banerjee G, Carare R, Cordonnier C, et al. The increasing impact of cerebral amyloid angiopathy: essential new insights for clinical practice. *J Neurol Neurosurg Psychiatry*. 2017;88(11):982-994. doi:10.1136/jnnp-2016-314697

- Linn J, Halpin A, Demaerel P, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. *Neurology*. 2010;74(17):1346-1350. doi:10.1212/WNL.0b013e3181dad605

- Biffi A, Halpin A, Towfighi A, et al. Aspirin and recurrent intracerebral hemorrhage in cerebral amyloid angiopathy. *Neurology*. 2010;75(8):693-698. doi:10.1212/WNL.0b013e3181eee40f

- Biffi A, Greenberg SM. Cerebral amyloid angiopathy: a systematic review. *J Clin Neurol*. 2011;7(1):1-9. doi:10.3988/jcn.2011.7.1.1

- Linn J, Herms J, Dichgans M, et al. Subarachnoid hemosiderosis and superficial cortical hemosiderosis in cerebral amyloid angiopathy. AJNR Am J Neuroradiol. 2008;29(1):184-186. doi:10.3174/ajnr.A0783

REFERENCES

- Mustapha M, Nassir CMNCM, Aminuddin N, Safri AA, Ghazali MM. Cerebral Small Vessel Disease (CSVD) - Lessons From the Animal Models. *Front Physiol*. 2019;10:1317. Published 2019 Oct 24. doi:10.3389/fphys.2019.01317

- Block F, Dafotakis M. Cerebral Amyloid Angiopathy in Stroke Medicine. *Dtsch Arztebl Int*. 2017;114(3):37-42. doi:10.3238/arztebl.2017.0037

- Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, Pruzin J, Sperling R, van Veluw SJ. Cerebral amyloid angiopathy and Alzheimer disease - one peptide, two pathways. *Nat Rev Neurol*. 2020;16(1):30-42. doi:10.1038/s41582-019-0281-2

- Rost NS, Etherton M. Cerebral Small Vessel Disease [published correction appears in Continuum (Minneap Minn). 2020 Jun;26(3):826-827]. *Continuum (Minneap Minn)*. 2020;26(2):332-352. doi:10.1212/CON.0000000000000841

- Kumar S, Goddeau RP Jr, Selim MH, et al. Atraumatic convexal subarachnoid hemorrhage: clinical presentation, imaging patterns, and etiologies. *Neurology*. 2010;74(11):893-899. doi:10.1212/WNL.0b013e3181d55efa

REFERENCES

- Sakaguchi H, Ueda A, Kosaka T, et al. Cerebral amyloid angiopathy-related inflammation presenting with steroid-responsive higher brain dysfunction: case report and review of the literature. *J Neuroinflammation*. 2011;8:116. Published 2011 Sep 14. doi:10.1186/1742-2094-8-116

- Smith EE. Cerebral amyloid angiopathy as a cause of neurodegeneration. *J Neurochem*. 2018;144(5):651-658. doi:10.1111/jnc.14157

- Viswanathan A, Greenberg SM. Cerebral amyloid angiopathy in the elderly. *Ann Neurol*. 2011;70(6):871-880. doi:10.1002/ana.22516

- Martínez-Lizana E, Carmona-Iragui M, Alcolea D, et al. Cerebral amyloid angiopathy-related atraumatic convexal subarachnoid hemorrhage: an ARIA before the tsunami. *J Cereb Blood Flow Metab*. 2015;35(5):710-717. doi:10.1038/jcbfm.2015.25

- Beitzke M, Gattringer T, Enzinger C, Wagner G, Niederkorn K, Fazekas F. Clinical presentation, etiology, and long-term prognosis in patients with nontraumatic convexal subarachnoid hemorrhage. *Stroke*. 2011;42(11):3055-3060. doi:10.1161/STROKEAHA.111.621847

REFERENCES

- PANTELAKIS S. Un type particuliar d'angiopathie sénile du systeme nerveux central: l'angiopathie congophile; topographie et fréquence [A particular type of senile angiopathy of the central nervous system: congophilic angiopathy, topography and frequency]. *Monatsschr Psychiatr Neurol*. 1954;128(4):219-256.

- Arima H, Tzourio C, Anderson C, et al. Effects of perindopril-based lowering of blood pressure on intracerebral hemorrhage related to amyloid angiopathy: the PROGRESS trial. *Stroke*. 2010;41(2):394-396. doi:10.1161/STROKEAHA.109.563932

- Amarenco P, Bogousslavsky J, Callahan A 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack [published correction appears in N Engl J Med. 2018 Jun 13;:null]. *N Engl J Med*. 2006;355(6):549-559. doi:10.1056/NEJMoa061894

- Olichney JM, Hansen LA, Hofstetter CR, Grundman M, Katzman R, Thal LJ. Cerebral infarction in Alzheimer's disease is associated with severe amyloid angiopathy and hypertension. *Arch Neurol* 1995;52:702-708.

- Vonsattel JP, Myers RH, Hedley-Whyte ET, Ropper AH, Bird ED, Richardson EP Jr. Cerebral amyloid angiopathy without and with cerebral hemorrhages: a comparative histological study. *Ann Neurol* 1991;30:637-649.