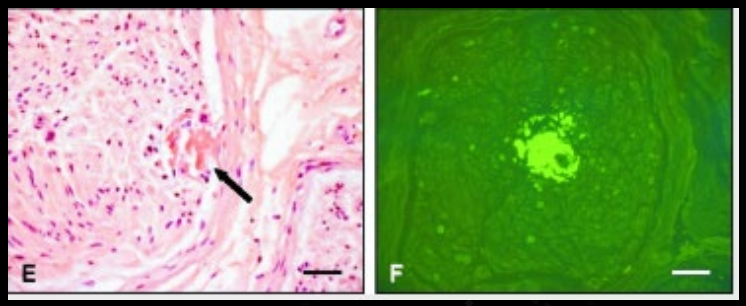
Slocum Dickson Teaching Day

Neurology

April 2025



UPSTATE
NEUROLOGICAL INSTITUTE

Patient

60 yo woman, who developed in her twenties:

- Feeling full after a small amount of food, although felt hungry approximately an hour later
- Difficulty sweating in the summer
- Difficulty gauging environmental and bodily temperature
- Burning both distal upper extremities and hands without cervical radiculopathy, brachial plexopathy, or median/ulnar/entrapment neuropathy

Patient

PMHx:

- At 40 years old, diagnosed with pulmonary sarcoid with local lymph node involvement, treated with 80 mg of oral prednisone every other day for approximately a year and a half, in remission after that

- At 49 years old, had sarcoid uveitis

- In her 50s developed non-ischemic heart failure. Cardiac MRI x2 negative for sarcoid

Patient

FHX:

- No small fiber symptoms, sarcoid, or cardiac/renal failure

Exam:

- Decreased sharp and temperature appreciation in distal upper extremities.

Patient

- Quantitative Sudomotor Axon Reflex Testing (QSART) at the Upstate autonomic lab on July 13, 2021, showed normal response in the left forearm, left proximal leg left distal leg, but was reduced in the left foot, which was suggestive of a length-dependent autonomic/small fiber neuropathy

- Skin biopsy April 2021 proximal right thigh and distal right leg, normal intraepidermal nerve fiber density. Skin biopsy is normal in 20% of patients with a small fiber neuropathy

- Negative EMG (EMG tests large fiber nerves such as motor and large fiber sensory – position and vibration. EMG does not test small fiber nerves such as autonomic or small fiber sensory – pain and temperature)

Patient

Labs:

Hemoglobin A1c mildly **prediabetic** 5.7%-5.9% (1)

Negative or normal:

serum and urine immunofixation electrophoresis
B12, B6, folate
TSH
Creatinine
ANA (including SSA, SSB), CCP, Rh factor, ANCA, cryoglobulin
tissue transglutaminase IgG and IgM
Lyme, hepatitis C, hepatitis B serologies, HIV, VDRL
urine porphyrins and heavy metal screen
Antibodies to Hu and nicotinic ganglionic AchR

Patient

- I treated her with IVIG 2 gm/kg over 5 days (which is 400 mg/kg daily for 5 days), followed 2 weeks later by 1gm/kg over 1 day, then maintenance doses of 1 gm/kg every 4 weeks, which resolved the small fiber symptoms and signs. (2) (3) (4)

- Repeat QSART in the same lab on March 6, 2024, in the left forearm, left proximal leg, left distal leg, left foot was normal

- Left superficial radial nerve biopsy, Upstate Jan 2024, showed some axonal loss and rare degenerating axons in the myelinated axonal populations, but much more axonal loss in small unmyelinated axonal populations, without inflammation or granulomas

Patient

- Superficial radial nerve biopsy was Congo Red positive at Upstate. **Amyloid**?

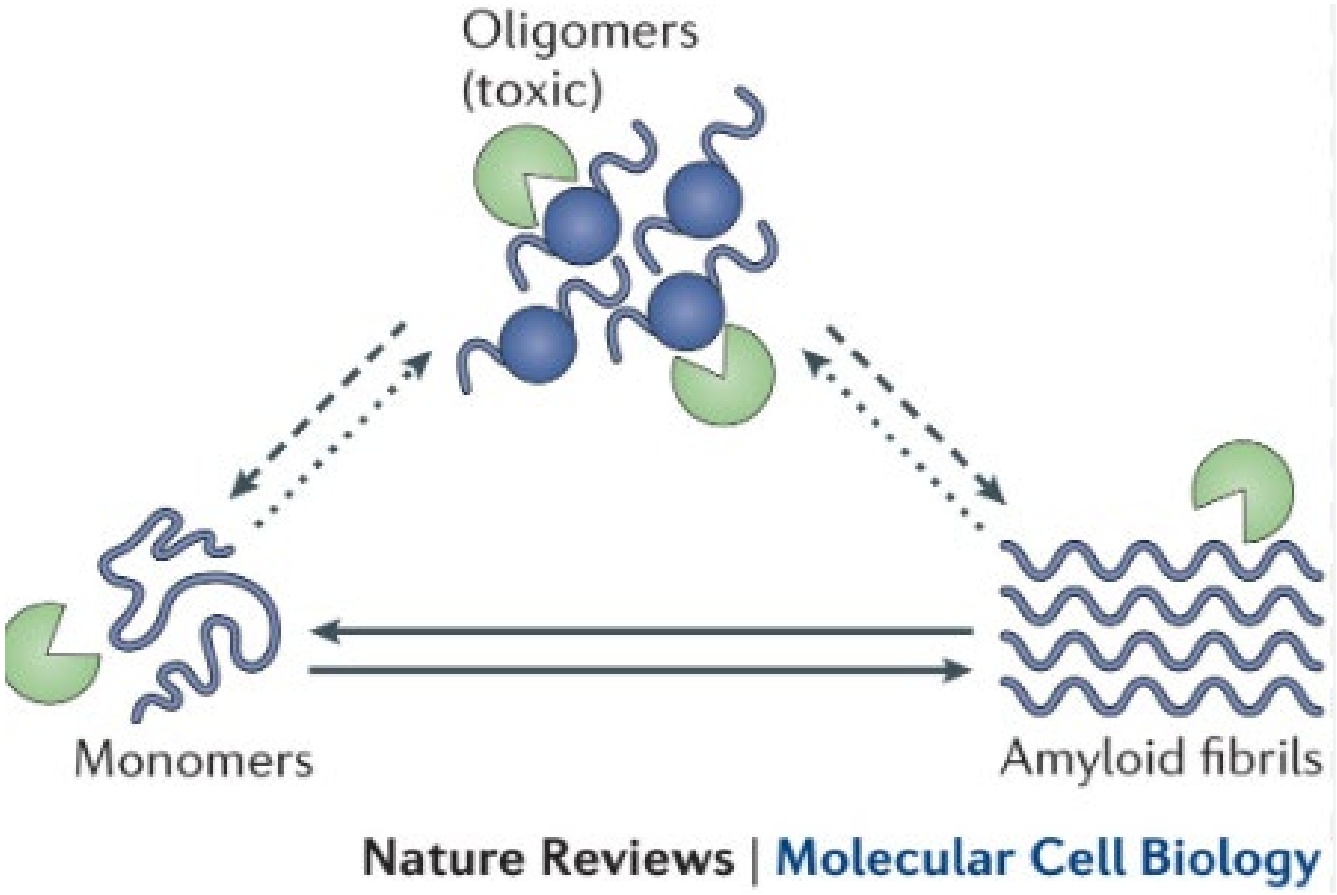
- Sample sent to Mayo Clinic, Rochester MN, for mass spectroscopy subtyping, and was found to be a false positive for amyloid (overstained)
- 13% of biopsies sent to Boston University Amyloidosis Center are false positives – artifacts can be introduced by using a cover slide, by Tefle wrapping, overstaining, etc (5)
- Genetic testing negative for hATTR (hereditary amyloid transthyretin). Immunofixation electrophoresis negative for AL Amyloid (amyloid light chain)
- So, this patient's small fiber neuropathy is likely not from amyloid (likely from sarcoid)

Amyloid is a generic term for insoluble extracellular fibrils, for which there are at least 42 different protein precursors in humans

Besides their common antiparallel beta-pleated sheet orientation that allows stacking and twisting into fibrils, different types of amyloid share common elements such as apolipoprotein and glycosaminoglycans

Amyloid can be acquired or heritable, can be produced locally in tissues or be deposited there by the blood

These proteinaceous deposits can interfere with organ function


Oligomers
(toxic)
Monomers
Amyloid fibrils
Nature Reviews | Molecular Cell Biology

How does amyloid deposition affect the neurologic system?

- Cerebral Amyloid Angiopathy
- Amyloid Beta–Related Angitis (ABRA)
- Amyloid and Alzheimer's Disease (AD)
- AL Amyloidosis (Amyloid Light Chain)
- ATTRwt and hATTR, (Amyloid transthyretin, wildtype and hereditary)

- AL Amyloid and hATTR both can present with length dependent, symmetric, sensorimotor polyneuropathy prominent small fiber sensory and/or autonomic features. hATTR neuropathy tends to be more strongly autonomic and can have CNS involvement

- For this pattern of neuropathy, always get serum and urine immunofixation electrophoresis to look for the monoclonal light chains of AL Amyloid. Don't save this for second line testing.

- Tissue subtyping with mass spectrometry for AL Amyloid and hATTR +/- genetic testing for hATTR necessary, since immunostaining can give false positives

- AL Amyloid and hATTR neuropathy prompts eval for other organ damage, including cardiomyopathy with intractable heart failure for which there are stabilizing and gene silencer meds

AL Amyloidosis and hATTR Neuropathy

Autonomic

- Orthostatic hypotension
- Early satiety/postprandial discomfort
- Sweating abnormalities
- Urinary retention
- Diarrhea, constipation
- Erectile dysfunction
- Blurred vision

If you have a patient with a predominantly small fiber sensory and/or autonomic polyneuropathy **and**:

Symmetrically numb hands?
Could be bilateral carpal tunnel syndrome

- Amyloid infiltration of flexor retinaculum (aka transverse carpal ligament) and tenosynovium causes external compression of nerve

OR

Mid-back pain radiating symmetrically down the lower extremities?
Could be lumbar stenosis

- Amyloid infiltration of the ligamentum flavum causes external compression of the lumbosacral nerves or nerve roots

Unilateral or bilateral lower extremity weakness or sensory changes without back pain?

- Could be direct infiltration of amyloid in the lumbosacral plexus

What about a patient with unilateral lower motor neuron facial droop, especially early in the course?
Could be direct infiltration of amyloid in the cranial nerve
In differential of cranial neuropathy also think of:

- Lyme
- B12 less then 400 pg/ml
- Glucose less than 50 mg/dl or greater than 400 mg/dl in a normally euglycemic person if it lasts for less than 24 hours after glucose is corrected, or diabetic or hypertensive infarct of the cranial nerve if it lasts for months
- Sarcoid
- Giant Cell Arteritis

AL Amyloidosis

- Systemic light chain (AL) amyloidosis is organ dysfunction from deposition of insoluble, misfolded immunoglobulin light chains created by a clonal plasma cell (or rarely B cell) disorder

- Prevalence is 2.5 per 100,000 in the United States (6)
- Peripheral neuropathy in 17% to 36% of AL amyloidosis (7)

Examine for signs of AL amyloid in other organs:

- Heart failure with preserved ejection fraction
- Hepatomegaly
- Macroglossia
- periorbital purpura
- Bruising (coagulopathy)
- Hypothyroid, hypogonadism

Patient may have fatigue and nephrotic range proteinuria.

AL Amyloidosis Neuropathy - Testing

Length dependent, symmetric sensorimotor polyneuropathy, with either small fiber sensory or autonomic predominance

First establish presence of a monoclonal protein: serum and urine protein immunofixation electrophoresis and serum free light chains assay (usually lambda in neuropathy)

AL Amyloidosis Neuropathy- Testing

EMG, looking for large fiber involvement or patterns consistent with **other** syndromes associated with monoclonal proteins like POEMS or CIDP

Autonomic testing (tilt table, heart rate variability with breathing, QSART)

Biopsy

- with staining (Congo red, thioflavin T for the beta pleated sheet, sulfated alcian blue for acid mucin)
- with amyloid subtyping (mass spectrometry, to confirm amyloid and to exclude transthyretin type, which has a different treatment)

AL Amyloidosis Neuropathy- Biopsy

Location	Sensitivity %	Ref
Abdominal Fat Pad	70 - 80	(8) (9)
Bone Marrow	56 - 77	(10) (11) (12)
Labial Salivary Gland	89	(12)
Skin	72	(12)

AL Amyloidosis Neuropathy - Treatment

Chemotherapy

- daratumumab+cyclophosphamide+ bortezomib +dexamethasone
- bortezomib can cause a separate sensory neuropathy but that is weighed against that 25% of patients with AL Amyloid die within 6 months of the diagnosis

Post- chemotherapy

- melphalan plus autologous stem cell transplantation

Nonspecific neuropathic pain blockers:

- Gabapentinoids - gabapentin, pregabalin
- Tricyclic Antidepressants, nortriptyline, amitriptyline
- Serotonin Norepinephrine Reuptake Inhibitors, duloxetine, venlafaxine
- Sodium channel blockers, oxcarbazepine, topiramate and lamotrigine

Autonomic dysfunction:

- pyridostigmine starting at 30 mg morning and midafternoon, to act on the autonomic nerve ganglion

Transthyretin (TTR)

TTR – transports thyroxine and retinol binding protein

Made mainly in the liver, with less than 5% made in the choroid plexus and retina

ATTRwt (wildtype) – may have heart failure, spinal stenosis and symmetric carpal tunnel syndrome (rheumatoid arthritis and hypothyroid myxedema can also cause symmetric CTS), but the heart failure may not be as severe as in AL amyloidosis and may be preceded by the CTS and spinal stenosis. Neuropathy, if present, tends to be mild (13) (14)

hATTR – hereditary transthyretin amyloidosis. These are pathogenic genetic variants.

hATTR

- Symmetric, length dependent, predominantly sensorimotor polyneuropathy with prominent small fiber sensory involvement and often very prominent autonomic involvement

- How does this differ from AL light chain neuropathy? hATTR neuropathy tends to have more prominent autonomic involvement and may involve the leptomeninges

- Distinguishing between AL amyloid and hATTR is important. Genetic testing for hATTR and/or amyloid subtyping with mass spectrometry is needful since the qualities of the neuropathy are not discriminant, and while both can cause debilitating and intractable restrictive cardiomyopathy, the treatments for this differ

hATTR

- Before the current era of oligonucleotide-based gene silencing therapies for hATTR polyneuropathy and cardiomyopathy, liver transplant was the standard, but this may not prevent cardiac amyloid progression

Noncoding, small interfering RNAs(siRNAs)

- Patisiran (Onpattro)
- Vutrisiran (Amvuttra)

Antisense oligonucleotides

- Inotersen (Tegsedi)
- Eplontersen (Wainua)

hTTR tetramer stabilizer

- Tafamidis – for cardiomyopathy (ATTRwt and hATTR) and neuropathy
- Diflunisal - NSAID, for neuropathy
- Acoramidis (ATTRibute-CM), not yet FDA approved for cardiomyopathy

Amyloid Screening During CTS Release?

Sperry BW, et al. Tenosynovial and Cardiac Amyloidosis in Patients Undergoing Carpal Tunnel Release.
Journal of the American College of Cardiology. 2018 Oct 23;72(17):2040-2050.

Objective

Identify the prevalence and type of amyloid deposits in patients undergoing carpal tunnel surgery and evaluate for cardiac involvement

Results

Of 98 patients enrolled (median age 68 years, 51% male), 10 (10.2%) had a positive biopsy for amyloid (7 ATTR, 2 light chain [AL], 1 untyped). Two patients were diagnosed with hereditary ATTR (Leu58His and Ala81Thr), 2 were found to have cardiac involvement (1 AL, 1 ATTR wild-type), and 3 were initiated on therapy. In those patients who had biopsy-diagnosed ATTR, there was no difference in plasma TTR concentration or tetramer kinetic stability

Amyloid Screening During CTS Release?

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Journal of the American College of Cardiology. 2018 Oct 23;72(17):2040-2050.

Conclusions

In a cohort of patients undergoing carpal tunnel release surgery, Congo red staining of tenosynovial tissue detected amyloid deposits in 10.2% of patients. Concomitant cardiac evaluation identified patients with involvement of the myocardium, allowing for implementation of disease-modifying therapy

Amyloid Screening During CTS Release?

Sperry BW, et al. Tenosynovial and Cardiac Amyloidosis in Patients Undergoing Carpal Tunnel Release.
Journal of the American College of Cardiology. 2018 Oct 23;72(17):2040-2050.

Methods

This was a prospective, cross-sectional, multidisciplinary study of consecutive men age ≥50 years and women ≥60 years undergoing carpal tunnel release surgery. Biopsy specimens of tenosynovial tissue were obtained and stained with Congo red; those with confirmed amyloid deposits were typed with mass spectrometry and further evaluated for cardiac involvement with biomarkers, electrocardiography, echocardiography with longitudinal strain, and technetium pyrophosphate scintigraphy. Additionally, serum TTR concentration and tetramer kinetic stability were examined

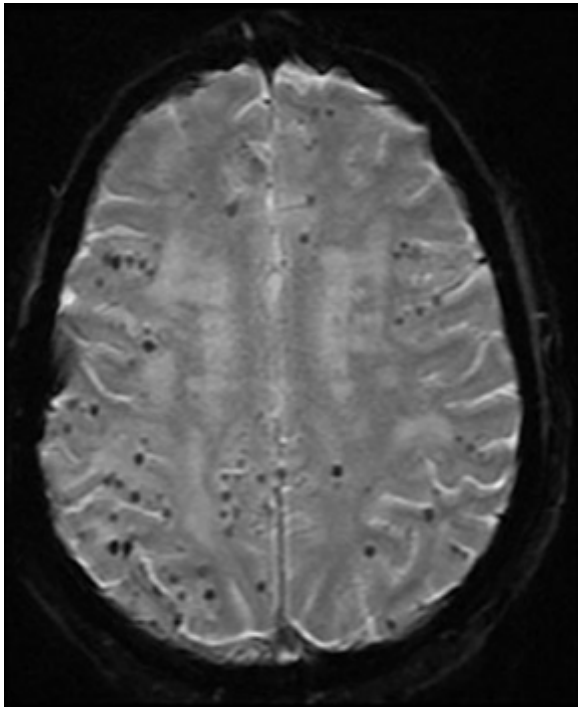
Cerebral Amyloid Angiopathy

- Amyloid beta deposition into small and medium sized cortical/subcortical/cerebellar/leptomeningeal vessels, causing increased bleeding risk and impaired local cortical function from microhemorrhages. May have perivascular inflammation (CAA-RI, aka CAA related inflammation)

- Autopsy studies show CAA increases with age 2.3% for ages 65 to 74, 12.1% over age 85 (15)

Cerebral Amyloid Angiopathy

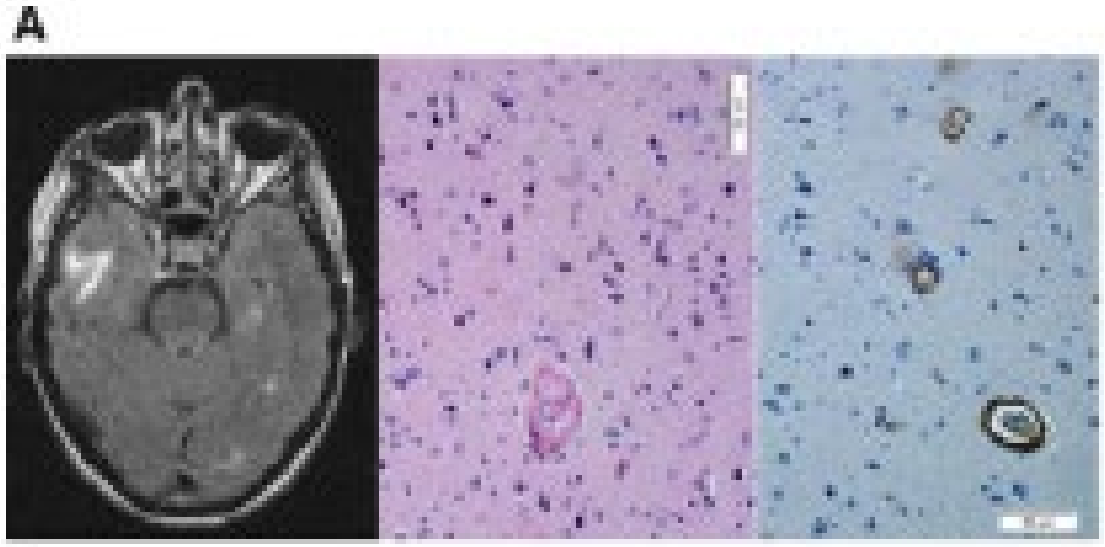
SWI axial MRI showing cortical/subcortical microhemorrhages



Greenberg SM. STROKE, 2018;(49)

Cerebral Amyloid Angiopathy

Lobar T2 hyperintensity
Perivascular inflammation
Positive amyloid B immunostaining



Aimen M. STROKE, 2015

Cerebral Amyloid Angiopathy

Can present as slowly progressive impaired executive function with relatively preserved memory

OR

Can present like TIA episodes (less than 30 minutes) with impairment in language, or vision, or movement or sensation. These episodes are associated with higher risk of lobar hemorrhages and death (16)

OR

Can present as lobar hemorrhage

Cerebral Amyloid Angiopathy

- Keep BP less than 130/80 (17)
- Avoid antiplatelets and anticoagulants if possible
- If concomitant atrial fibrillation (ischemic stroke risk) consider left atrial appendage closure vs anticoagulation (both 2b recommendations from the AHA/ASA) (17)

Amyloid Beta–Related Angitis (ABRA)

Difference from CAA related inflammation (CAA-RI) is that the vessel wall inflammation in the brain from amyloid B deposition in ABRA is intramural/transmural and destructive, sometimes granulomatous

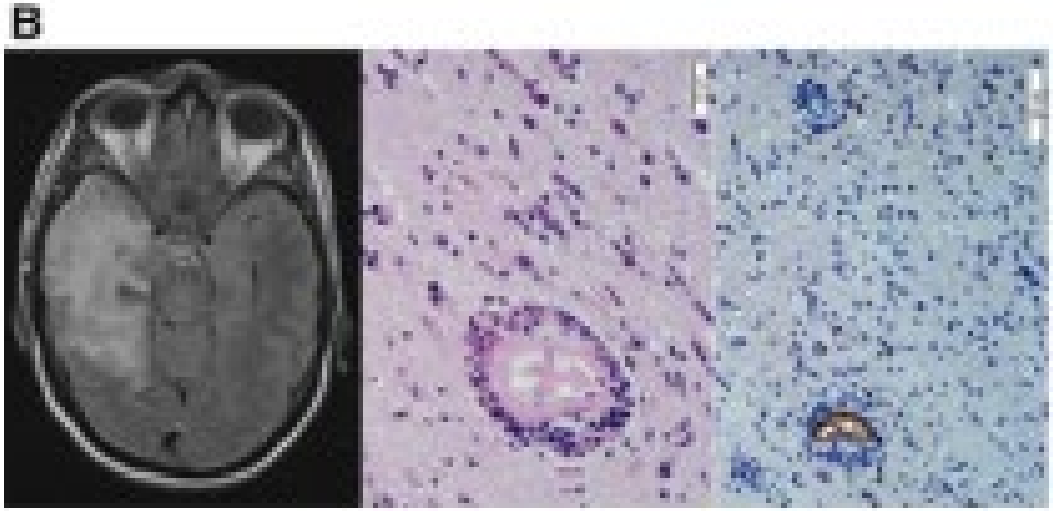
MRI brain often shows subcortical vasogenic edema

Like CAA-RI, prevalence increases with age but clinical presentation reflects the degree of inflammatory vasculitis:

- seizures
- headaches
- focal neurologic deficits
- acute to subacute cognitive deterioration
- sometimes hallucinations

Amyloid Beta–Related Angitis (ABRA)

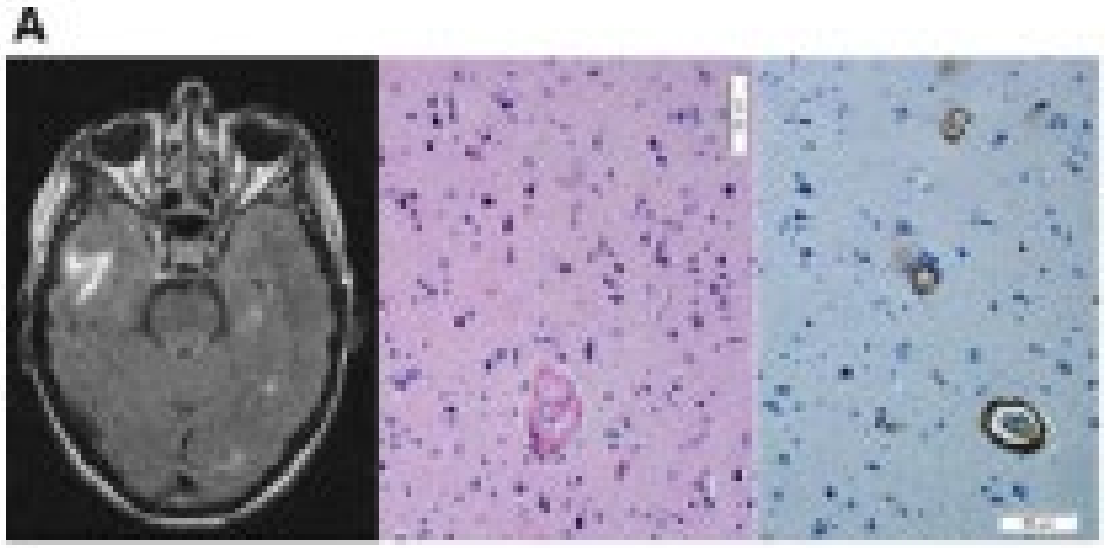
Lobar T2 hyperintensity with vasogenic edema,
Lymphocytic vascular inflammation with some fibrinoid necrosis
Positive amyloid B immunostaining



Aimen M. STROKE, 2015

Compare again to Cerebral Amyloid Angiopathy

Lobar T2 hyperintensity
Perivascular inflammation
Positive amyloid B immunostaining



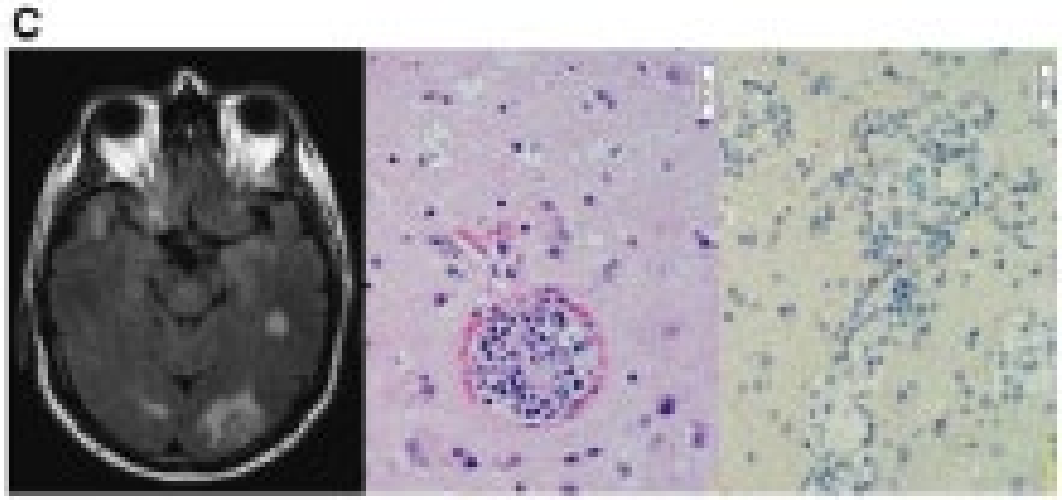
Aimen M. STROKE, 2015

Amyloid Beta–Related Angitis (ABRA)

- More inflammatory than CAA-RI
- CSF may show elevation in protein, and half the time a lymphocytic pleocytosis
- Brain biopsy shows inflammatory changes, so non-specific
- Steroids give rapid clinical and radiographic improvement (the speed of clinical and radiographic improvement mimics primary CNS lymphoma, but lymphoma has minimal vasogenic edema and ABRA often has a lot)

Primary CNS Vasculitis

Lobar T2 hyperintensity with milder vasogenic edema
Lymphocytic vascular inflammation with florid fibrinoid necrosis
No amyloid B immunostaining



Aimen M. STROKE, 2015

Amyloid and Alzheimer's Disease (AD)

- Amyloid Precursor Protein (APP) gene on chromosome 21 has an unclear physiologic function but can be cleaved into a fibrillogenic amyloid beta 42 fragment.
- A higher ratio of Aβ42 to Aβ40 has been linked to AD
- Cleavage mutations in APP associated with AD are Presenilin 1, Presenilin 2
- An extra copy of the APP gene is linked to AD developing in their 40s for patients with Trisomy 21
- APOEε4 allele is a susceptibility gene for AD, and may allow amyloid beta to sequester in the brain, due to reduced clearance through the blood

Amyloid and Alzheimer's Disease (AD)

FDA approved monoclonal antibodies against aggregated amyloid beta

- Lecanemab (Leqembi) 10 mg/kg IV once every 2 weeks
- Donanemab (Kisunla) 700 mg IV every 4 weeks for 3 doses, then 1,400 mg IV every 4 weeks)

Eligible patients are:

- amyloid positive by PET or lumbar puncture

AND

- have Mild Cognitive Impairment or mild AD

MoCA 17 or above
MMSE 22 or above
CDR clinical dementia rating 0.5 to 1

DIAN-TU Amyloid Removal Trial (ART) in Dominantly Inherited Alzheimer's Disease (DIAN-TU)

- A particularly interesting study started June 2024 at Washington University School of Medicine, recruiting now and estimated to complete in 2029

- This is a phase 3 study in patients who are asymptomatic carriers of autosomal dominant mutations for Alzheimer's, who began amyloid removal between 2 and 10 years ago with gantenerumab, and now will receive lecanemab. The study is looking at whether removing amyloid years before symptom onset, delays symptom onset

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