“Vascular Neuropathology: The Road Less Traveled”

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Disclosures

• I have no relevant financial relationships to disclose
• I sincerely wish I did
Learning Objectives

• Summarize common topics in vascular neuropathology
• Discuss uncommon clinical and pathologic characteristics associated with some common vascular neuropathology lesions
• Identify the clinical and pathologic features associated with selected rare vascular neuropathology diagnoses
Vascular neuropathology

• All adult neuropathologists are going to see vascular disease (particularly in the autopsy realm)
• Even pediatric neuropathologists may see some vascular disease like vascular malformations
Vascular neuropathology: classic topics

• Anatomy of the circle of Willis
• Vascular territories in the brain
• Risk factors for vascular disease
• Large-vessel (atherosclerosis) vs. small-vessel (arteriolosclerosis) disease
• Etiology of infarcts: thrombosis vs. embolism
• Etiology of hemorrhages: intracerebral vs. subarachnoid
Vascular neuropathology: classic topics

• Morphology and evolution of infarcts: acute, subacute, and chronic (liquefactive necrosis)
• Morphology and pathophysiology of ischemia
• Vascular malformations
  – Arteriovenous malformation (AVM)
  – Cavernous angioma/hemangioma ("cavernoma")
  – Venous angioma
  – Capillary telangiectasia
• Aneurysms: saccular, fusiform, and mycotic
Vascular neuropathology: classic topics

• Vasculitis
  – Giant-cell arteritis
  – Primary CNS angiitis/vasculitis
  – Polyarteritis nodosa

• Inherited disorders (e.g., CADASIL)

• Cerebral amyloid angiopathy

• Vascular dementia
Vascular neuropathology: classic topics

• An audience of neuropathologists will be familiar with most, if not all, of these topics
• Neuropathologists teach these topics to medical students, rotating residents, and neuropathology fellows
• Neuropathology fellows likely lecture on these topics as well
Overview of this presentation

• Five clinical cases
• Purpose in each case is to demonstrate one of the following:
  – Classic lesion with an interesting pathologic twist
  – Classic pathology with an interesting clinical twist
  – Classic pathology with a rare etiology
  – Classic, rare topics
• I’ve only seen each type of case once or very rarely
CASE #1
Prior history

- Initially presented in October 2007 as a 10-year-old boy with right basal ganglia AVM rupture causing a generalized tonic-clonic seizure and coma
- Hospitalized for a “long time” and required surgery, embolization, extraventricular drain placement, and treatment of CSF infection
- Received gamma knife treatment to residual AVM in 2008
- Saw neurology as outpatient initially in May 2016; had improved with time and could walk and talk but with residual left hemiparesis
- Got Botox every six months for leg and arm spasticity
- Also had dysarthria and cognitive/behavioral sequelae
Prior history

• Began to have breakthrough seizures after being weaned off some antiepileptic drugs he was on following the AVM rupture
• Majority of outpatient visits were to titrate epilepsy medications for breakthrough seizures and manage urinary incontinence
• 2020: presented with worsening seizures and subacute blood products on MRI at site of AVM concerning for re-rupture with increasing hydrocephalus; differential included giant cavernous angioma with repeat acute bleeding vs. very slow evolution of prior bleed; right-sided VP shunt placed; shunt revised 11/2022
• Has had multiple falls and fractures over time
Prior history

• Multiple presentations and admissions to the hospital
  – Headaches
  – Seizures
  – Hydrocephalus (including high-volume shunt tap in 6/2022)
  – Shunt infection causing constipation and ventriculitis; reimplanted on left side
  – Urinary incontinence
  – Possible colitis (2/2023)
  – Fractures
Final admission

• Presented to hospital (now age 26) on 4/7/2023 with increased headaches, right-sided head swelling, and increasingly unsteady gait
• Shunt tap 3/2023 grew *Cutibacterium acnes*; current tap negative; treated presumptively with IV penicillin
• EEG showed right hemispheric delta activity and right anterior quadrant sharp wave discharges
  – Generalized/multifocal encephalopathy
  – Structural abnormality with epileptogenic focus
  – No seizures observed
Final admission

• Head CT scan
  – Cerebellar tonsillar herniation; increased since 3/8/2023
  – Increasing cystic hypodensity extending posteriorly from the encapsulated hematoma and inferiorly, exerting mass effect upon the brainstem and cerebellum, contributing to increased herniation
  – Increased obstructive hydrocephalus since 1/24/2023

• 4/20/2023: complained of abdominal pain, vomiting, and continued headache; abdominal X-ray revealed possible kinking of shunt; baclofen added as needed; abdominal pain and nausea subsided after 4/21, but headaches continued
Final admission

• 4/24/2023: found suddenly unresponsive at 8:10 a.m.
  – No seizure per witness in room
  – In asystole; code called; CPR initiated; intubated
  – 40 cc of CSF easily aspirated from shunt valve
  – CPR continued for 55 minutes
  – Resuscitation efforts unsuccessful
  – Full autopsy requested; general autopsy unrevealing for cause of death
Final Neuropathologic Diagnosis

- Chronic encapsulated intracerebral hematoma, right basal ganglia
- Cystic degeneration, consistent with treatment sequelae of prior arteriovenous malformation
- Cerebellar tonsillar hernination
- Acute infarct, cerebellum
- Wallerian degeneration, right medullary pyramid
Chronic encapsulated intracerebral hematoma

• First described in 1981
• Presents as a subtle, slow-growing lesion exerting mass effect
• Chronic, progressive development of intracranial hypertension may occur in most cases
• CT scan: blood in various phases of degradation
• MRI with gadolinium: peripheral contrast enhancement
• May simulate a neoplasm
• Most frequent cause: AVM with rupture
• Can represent a delayed complication after stereotactic radiosurgery

Scalia, et al, Br J Neurosurg 2022 Jan 8, 1-6
Chronic encapsulated intracerebral hematoma—pathophysiology

- Brain tissue creates a fibroblastic reaction to initial hemorrhage with formation of the initial capsule membrane
- Subsequent bleeding produces granulation tissue and promotes the fibroblastic reaction to form a fibrous capsule and expand hematoma
- With radiosurgery, repetitive minor bleeding with the radionecrotic brain tissue may start the formation of the encapsulated hematoma
- Radiosurgery may cause hypoxic stress and induce transcription of VEGF with abnormal angiogenesis and vascular leakage that expands the hematoma
Cyst formation after SRS for brain AVM

- 2,619 patients across 22 studies
- 78 developed post-SRS cyst formation (3.0%)
- 64 had symptomatology and management data
- 21 (32.8%) were symptomatic and treated with surgical intervention
- 43 (67.2%) were managed conservatively
- Mean latency period to post-SRS cyst formation was 6.5 years

Cyst formation after SRS for brain AVM

• Uncommon complication with long latency period
• Majority are asymptomatic and can be managed conservatively
• Enlarging or symptomatic cysts may require surgical intervention
• Mean rates of... (based on pooled data)
  – Symptomatic radiation-induced changes: 8.6%
  – Post-SRS hemorrhage: 8.8%
  – Mortality: 6.0%

Cause of death

• Likely related to gradually worsening mass effect and rising intracranial pressure
  – Chronic encapsulated intracerebral hematoma
  – Cyst formation
• Cerebellar tonsillar herniation: finally reached the tipping point
CASE #2
History

- Consult from JFK Medical Center in Edison, NJ
- 63-year-old man who underwent a right carotid endarterectomy for stenosis and did well immediately post-op
- On post-op day #3, became unresponsive.
- Head CT showed massive right-sided intracerebral hemorrhage
- Made comfort measures-only
Final Neuropathologic Diagnosis

• Intracerebral hemorrhage, very large, right cerebral hemisphere, with extension into the ventricular system, cerebral edema, right-to-left midline shift, subfalcine and transtentorial herniation, and Duret hemorrhages

• Clinical history of recent right carotid endarterectomy
Intracerebral hemorrhage after carotid endarterectomy


Intracerebral hemorrhage after carotid endarterectomy

- 1,500 CEAs (1975-1984)—New York University
- 11 (0.7%) complicated by postop ICH
- Mortality 36%
- ICH occurred anywhere from immediately postop to 10 days later (mean 3.3 days)

Intracerebral hemorrhage after carotid endarterectomy

- 2,362 consecutive CEAs (1972-1986)—Mayo Clinic
- 14 (0.6%) postop ICHs
- All within first two weeks postop
- All ipsilateral to the side of surgery
- 8 deaths (57% mortality)

Intracerebral hemorrhage after carotid endarterectomy

- 2,747 consecutive CEAs (1990-1999)—Mayo Clinic
- 12 (0.4%) postop ICHs
- All within first 8 days postop
- All ipsilateral to the side of surgery
- 7 deaths (58% mortality)
- Of 8 patients with cerebral blood flow measurements, 5 had greater than 100% increase (“doubling”)

Intracerebral hemorrhage after carotid endarterectomy: risk factors/mechanisms

• Pre- and postoperative hypertension
• Chronic hemispheric hypoperfusion with impaired autoregulation
• Relief of high-grade carotid stenosis with subsequent hyperperfusion
• Perioperative cerebral ischemia
• Anticoagulation

CASE #3
History

• 71-year-old woman with headaches and fatigue a month prior to admission
• ESR elevated; temporal artery biopsy negative
• Continued to have throbbing headaches, confusion, disorientation, and fever as high as 102⁰
• Presented to doctor’s office and sent to E.R.
History

• Past medical history
  – Hypertension (on atenolol)
  – Hyperlipidemia (on atorvastatin)
  – Diabetes mellitus (on glipizide extended release)
  – S/P cholecystectomy, appendectomy, right total knee replacement, partial right mastectomy for presumably benign breast mass
  – No known drug allergies

• Non-focal neurologic examination
History

• Lumbar puncture: 20 WBC, protein 235
• Started on acyclovir for possible encephalitis
• MRA completely normal
• Had a brain biopsy in 2006
FINAL NEUROPATHOLOGIC DIAGNOSIS

GRANULOMATOUS ANGIITIS WITH CEREBRAL AMYLOID ANGIOPATHY (Aβ-RELATED ANGIITIS)
Cerebral amyloid angiopathy (CAA)

- Deposition of amyloid-β (Aβ) in the adventitia and media of cortical and meningeal blood vessels
- Amyloid is similar that observed in the plaques of Alzheimer disease (AD)
- Can lead to lobar intracerebral hemorrhage
- In a subset of patients, vascular inflammation is also present
  - CAA-related inflammation (CAA-RI)—perivascular and non-destructive
  - Aβ-related angiitis (ABRA)—vasculitis, transmural, often granulomatous
- Can lead to cognitive impairment without AD changes or microhemorrhages (but most often associated with them)
Study of Aβ vascular deposition and inflammation

- 62 available pathologic surgical specimens from 1987-2011 (37 open biopsy, 4 stereotactic biopsy, 21 hematoma evacuation)
- 28 cases of ABRA, 40 of CAA, and 10 of CAA-RI
- Compared to 131 consecutive cases of primary CNS vasculitis (PCNSV)—41 diagnosed by biopsy and the rest by classic angiograms; 13 were ultimately diagnosed with ABRA and placed in that group, leaving 118 cases of non-amyloid PCNSV

Comparison of ABRA, CAA-RI, CAA, and PCNSV

- ABRA: 28 cases (13 male), avg. age 66, 1.6 months to dx
- CAA-RI: 10 cases (6 male), avg. age 72, 1.2 months to dx
- CAA: 40 cases (18 male), avg. age 71, 0.7 months to dx
- PCNSV: 118 cases (50 male), avg. age 47, 1.4 months to dx
- Statistical analyses not performed on CAA-RI because of too few cases
- ABRA and CAA-RI may be part of the same pathologic spectrum, but the evidence is not definitive
Comparison of ABRA, CAA-RI, CAA, and PCNSV

• Characteristics of ABRA patients compared to CAA
  – Younger
  – Lower frequency of altered cognition
  – Less frequent neurologic deficit or stroke
  – Lower rate of intracerebral hemorrhage
  – More frequent gadolinium leptomeningeal enhancement on MRI
  – More favorable response to treatment (glucocorticoids, alone or in combination with cyclophosphamide) and better outcome

Comparison of ABRA, CAA-RI, CAA, and PCNSV

- Characteristics of ABRA patients compared to PCNSV
  - Older
  - Increased frequency of altered cognition and seizures at presentation
  - Reduced frequency of hemiparesis and visual symptoms
  - Significantly higher CSF protein levels
  - Less frequent infarcts
  - More frequent gadolinium leptomeningeal enhancement on MRI
  - Similar response to treatment and outcome

Conclusions

• ABRA and CAA-RI more closely resemble PCNSV than CAA
• ABRA forms a definable subset of PCNSV
• Vascular inflammation, more than amyloid deposition, has the most impact in causing symptoms

Follow-Up

• Treated with high-dose steroids with improvement of symptoms and discharge from hospital on taper
• Now age 87 with multiple active medical problems (HTN, hyperlipidemia, DM, CAD, chronic kidney disease, glaucoma, macular degeneration, fibromyalgia, osteoarthritis, rheumatoid arthritis)
• July 2016—total hip replacement
• Sept. 2017—invasive mucinous adenocarcinoma of sigmoid colon/rectum
• Hospitalized on inpatient psychiatric unit from 5/9 to 6/5/2023 for treatment of agitation, paranoia, and acute hallucinations in the setting of progressive dementia; on donepezil since August 2022; family looking for SNF placement
• This 2006 hospitalization/brain biopsy is never mentioned in the medical record after a discharge summary in February 2007
CASE #4
History

- Consult from Bergen County NJ medical examiner office
- 65-year-old woman found down in nursing home bed with large hematoma on forehead
- CT showed “multiple bleeds” in brain
- Bruising all throughout body
- H/O HTN, CVA, COPD, DM, CAD, dementia, cervical/uterine cancer, hypothyroidism, bipolar disorder, UTI, cardiac stents, cardiac cath, and old left temporal skull fracture (2016)
- Made CMO and died two days after presentation
Acute infarcts: right orbitofrontal cortex and substantia innominata
Acute infarct: left thalamus
Chronic infarcts: right anterior caudate/claustrum
Chronic infarcts, basis pontis and right cerebellum
Wallerian degeneration, medulla
Substantia nigra (intact)
Hippocampus and medial temporal cortex, Bielschowsky stain—minimal pathology
Final Neuropathologic Diagnosis

- Traumatic brain injury, acute (clinical history of presumed fall)
- Cerebrovascular disease, extensive
- Clinical history of dementia; no evidence of significant neurodegenerative disease pathology

- (Presumed diagnosis: vascular dementia, likely multi-infarct dementia)
Vascular dementia

• Very common to have co-existing cerebrovascular disease in decedents with neurodegenerative diseases (e.g., Alzheimer disease, dementia with Lewy bodies), resulting in an exacerbation of cognitive dysfunction
• Uncommon to have pure cerebrovascular disease as the sole cause of dementia in the absence of a genetic mutation
• How common is “vascular dementia,” really?
Vascular dementia—one study

• 1,110 consecutive autopsies of elderly decedents with dementia (1994-2008)
• Frequency of diagnoses:
  – Alzheimer disease (AD): 44.1%
  – AD + small-vessel disease: 25.7%
  – Vascular dementia (VaD): 10.8%
  – AD + Lewy pathology: 9.6%
  – “Mixed dementia” (AD + VaD): 4.8%
  – Other degenerative disorders: 3.9%
  – Other disorders (post-traumatic, alcohol, etc.): 1.6%

Jellinger KA, Attems A, J Neurol Sci 2010; 299: 150-154
Vascular dementia—one study

• Frequency of morphologic subtypes of VaD (120 cases):
  – Subcortical arteriosclerotic encephalopathy: 49.1%
  – Multi-infarct encephalopathy: 38.3%
  – Strategic-infarct dementia: 9.2%
  – Severe cerebral amyloid angiopathy without major AD pathology: 3.6%

• General autopsy findings: signs of hypertension (92%), H/O diabetes/related lesions (61.3%), myocardial infarct (52%), “cardiac decompensation” (58%)

• Gradual decreased incidence with advancing age

Jellinger KA, Attems A, J Neurol Sci 2010; 299: 150-154
Vascular dementia—clinical features

- Motor and cognitive impairment: changes in gait, behavior, and mood
- Classically a “stepwise” neurologic decline
- Usually associated with vascular risk factors (hypertension, diabetes, hyperlipidemia, smoking, etc.)
- Incidence may be declining with more aggressive treatment of hypertension and other risk factors
Vascular dementia—subtypes

- Subcortical arteriosclerotic (leuko)encephalopathy or Binswanger disease
  - Executive dysfunction with cognitive impairment
  - Severe small-vessel disease with widespread white matter demyelination without frank necrosis or pronounced infarction
- Multi-infarct dementia: results from multiple strokes of various sizes in several locations
- Strategic-infarct dementia: well-placed subcortical infarcts that disrupt specific circuits leading to executive dysfunction and personality change/apathy with relatively small overall lesion volume
- Cerebral amyloid angiopathy: microvascular ischemic changes (rare)
Considering a diagnosis of “vascular dementia”

• Clinical history of dementia
• Widespread and/or well-placed cerebrovascular disease pathology
• No significant neurodegenerative disease pathology

• (In my experience, this trifecta is very rare)
CASE #5
History

• 48-year-old man initially evaluated in the Memory Disorders Clinic on 2/13/2006
• Developed migraine in his 20’s
• Had multiple ischemic episodes; first one in 1994 where he received a diagnosis of multiple sclerosis
• Subsequent episodes in April and May of 2001
• Had skin biopsy and was diagnosed with CADASIL
• MRI appearance also consistent with CADASIL
History

- Last outpatient clinical note is dated 6/29/2017
- Lived in a nursing facility with inability to walk; falling out of wheelchair, requiring a restraint
- Progressively hypophonic speech
- Progressive dementia
- Death in December 2018 at age 61
VIRTUAL SLIDE
Final Neuropathologic Diagnosis

- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
  - Clinical history of CADASIL diagnosed by skin biopsy in May 2001
  - Lacunar infarcts: corona radiata, putamen, and thalamus, chronic
  - Arteriolosclerosis, diffuse, severe, with widespread cribriform change
  - Multiple foci of white matter pallor
  - Wallerian degeneration, corticospinal tract
CADASIL

• First described in 1955 as “familial Binswanger disease”
• Linked to chromosome 19 in 1993
• NOTCH3 gene and its protein identified in 1996
• More than 700 families worldwide
• Estimated prevalence of 4-5 per 100,000
CADASIL—clinical features

- Migraine with aura, severe (some with hemiparesis)
- Recurrent ischemic strokes
- Psychiatric symptoms
- Cognitive decline/dementia
- Seizures may be seen in late-stage disease
- Treatment is symptomatic/supportive

CADASIL—pathology

• Non-arteriosclerotic, non-amyloid arteriopathy
• Affects small- and medium-sized arteries
  – White matter
  – Leptomeninges
• Skin, skeletal muscle, and peripheral nerves also involved
• Degeneration of vascular smooth muscle cells
  – PAS-positive granules in tunica media
  – Granular osmiophilic material on electron microscopy
• Basal ganglia/thalamus/brainstem infarcts also seen
CADASIL—PAS stain (this autopsy)
Electron microscopy—2008 skin biopsy
CADASIL—genetics

- Autosomal dominant
- \textit{NOTCH3} gene on chromosome 19p13
- Functions in stem cell renewal, differentiation, proliferation, and apoptosis; required for survival and normal function of vascular smooth muscle cells
- Vast majority of abnormalities are missense point mutations
- Pathogenesis not entirely clear
Other rare, inherited, non-amyloid vascular disorders

- CARASIL/Maeda syndrome
  - Multiple infarcts with cognitive impairment
  - Orthopedic manifestations and alopecia
  - Nonsense/missense mutations of HTRA-1 on chromosome 10q
- Retinal vasculopathies with cerebral leukodystrophy
  - Hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS); cerebroretinal vasculopathy (CRV); and hereditary vascular retinopathy (HVR)
  - Central visual loss with brain infarcts and cognitive impairment
  - Mutations in TREX1 gene on chromosome 3
