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Cavernous Malformations and Telangiectasias

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Financial Disclosures

- None

Brain Capillary Telangiectasia

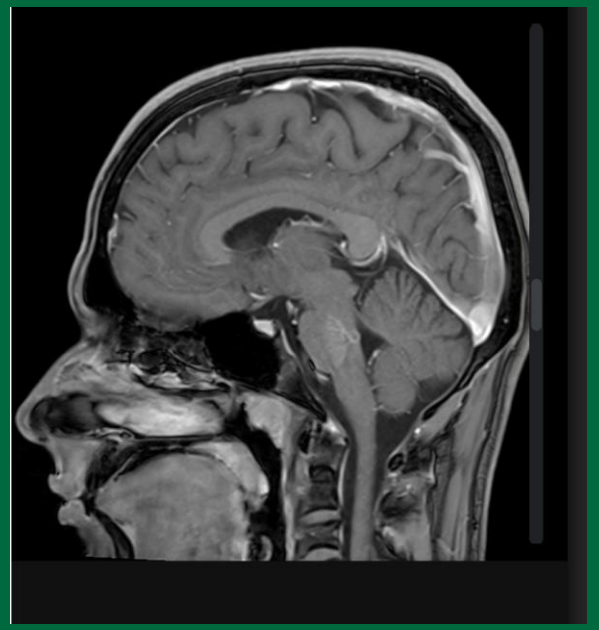
Definition & Epidemiology

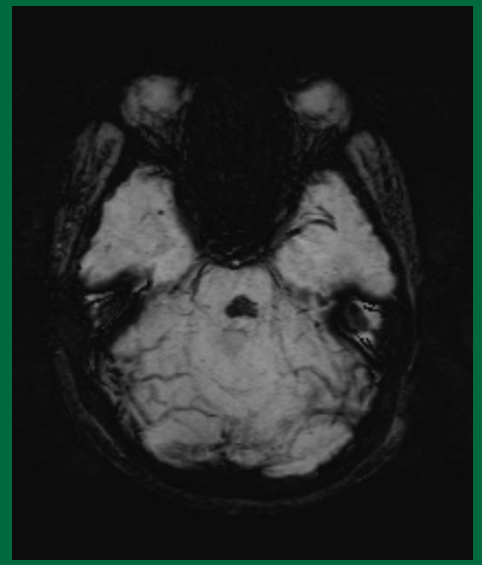
0.4-0.7%

Prevalence
on MRI

~73%

Located in
the pons





- Composed of dilated capillaries (lumen 20-500 µm) with normal interposed brain parenchyma
- Second most common vascular malformation after DVAs
- Typically asymptomatic and discovered incidentally
- Most common in pons, followed by cerebellum and spinal cord
- ~2/3 of lesions have a visible small draining vein on imaging
- Angiographically occult — not seen on conventional angiography

Larson et al., Acta Neurochir 2020; Sayama et al., J Neurosurg 2010. Radiopedia.org

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Developmental Venous Anomaly

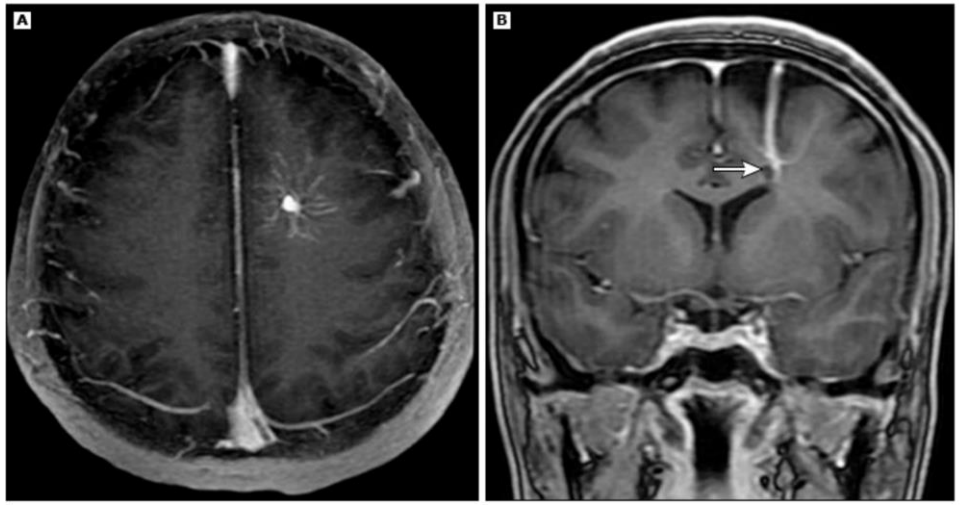
63%

Of all cerebral vascular malformations

2.6%

Prevalence in autopsy series

- **Most common cerebral vascular malformation**
- Congenital anomaly of transmedullary venous drainage
- Radially arranged dilated medullary veins converging on a single collector ("caput medusae")
- Typically discovered incidentally on neuroimaging
- 70% supratentorial, 30% infratentorial
- Rarely associated with seizure, headaches, or hemorrhage, but a causal relationship between these symptoms and the DVA is uncertain



Hsu & Krings, AJNR 2023; Hon et al., Stroke 2009; Kiyak et al., Neurol Sci 2025;

Cavernous Malformation

Cerebral Cavernous Malformation (CCM) — also known as cavernous angioma, cavernoma, or cavernous hemangioma

A vascular malformation composed of grossly enlarged, thin-walled vascular sinusoids lacking normal intervening brain parenchyma. Characterized by repeated episodes of intralesional hemorrhage.

Prevalence	0.4–0.8% of general population	**Location**	Supratentorial (75–80%), Brainstem (15–25%)
Incidence	~0.56 per 100,000 person-years	**Multiplicity**	50–84% of familial cases; <20% sporadic
Sex Distribution	Equal male-to-female ratio	**Familial Forms**	~20% of all CCM (autosomal dominant)
Age at Presentation	Peak: 3rd–5th decade	**Associated Lesions**	Developmental venous anomaly (DVA) in ~30%

Ref: Akers et al., J Neurosurg 2017; Al-Shahi Salman et al., Lancet Neurol 2012; Batra et al., Neurosurg Focus 2009

Genetics & Classification

Causative Gene Mutations (Familial CCM – Autosomal Dominant)

CCM1 / KRIT1

Locus: 7q21.2

Encodes KRIT1 protein; regulates cell-cell junction integrity via β-catenin pathway

~50% of familial

CCM2 / MGC4607

Locus: 7p13

Scaffold protein; interacts with KRIT1 and CCM3 in the CCM signaling complex

~20% of familial

CCM3 / PDCD10

Locus: 3q26.1

Promotes cellular apoptosis; mutations associated with more aggressive phenotype

More aggressive phenotype

~40% of familial

Sporadic vs. Familial Forms

Sporadic (80%)

- Single lesion in 95%

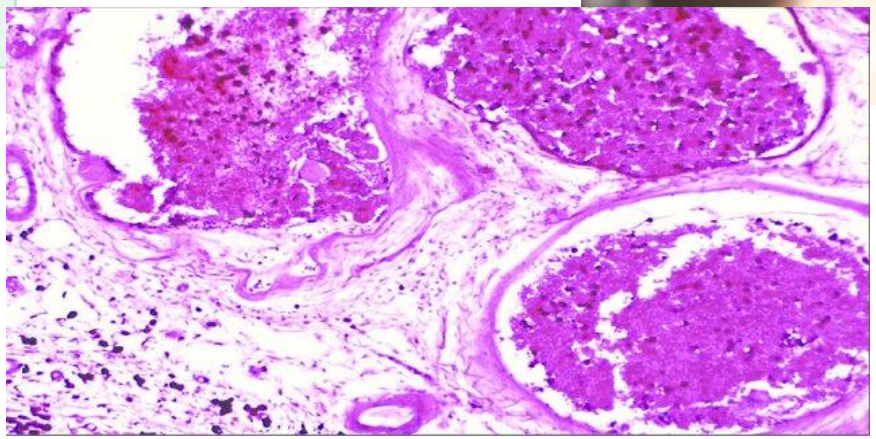
Familial (20%)

- Multiple lesions in 50–84%, can increase in number over time
- Autosomal dominant; 50% penetrance
- Hispanic CCM1 founder mutation (common)
- Screening of first-degree relatives recommended

Ref: Cavalcanti et al., Nat Rev Neurol 2012; Labauge et al., J Med Genet 2007; Denier et al., Am J Hum Genet 2004

Pathology

Gross Morphology
Mulberry appearance
Size: typically 0.5–3 cm; rarely >5 cm
Well-circumscribed, lobulated cluster of vascular cavities
Dark-red to blue-black discoloration from hemosiderin
Surrounded by hemosiderin-stained gliotic rim
Absent normal neural parenchyma between vascular cavities



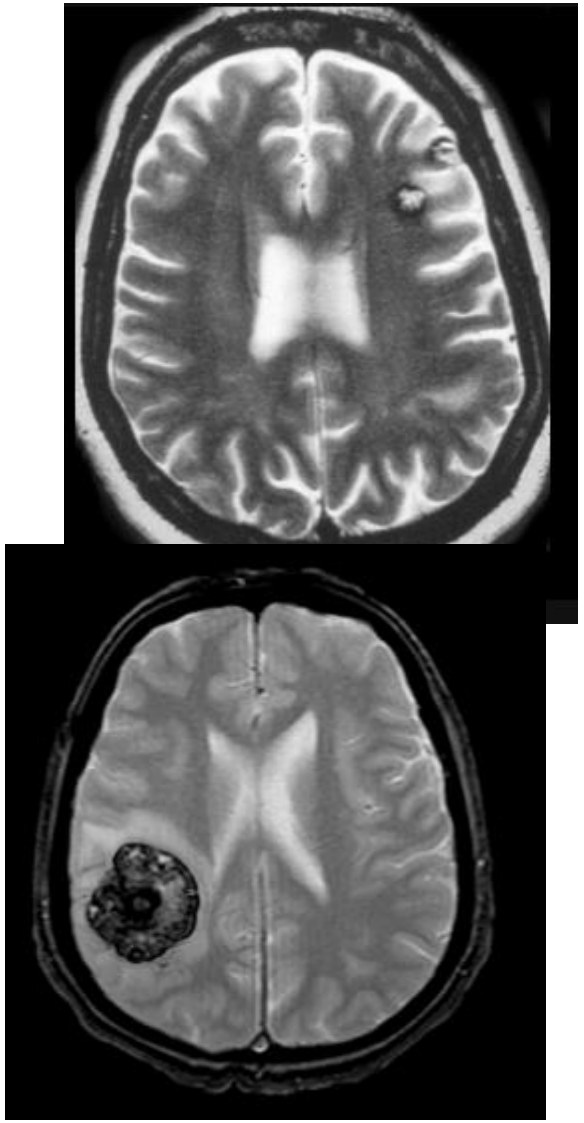
Ref: Rigamonti et al., N Engl J Med 1988; Clatterbuck et al., J Neurosurg 2001; Wong et al., Neurosurgery 2000

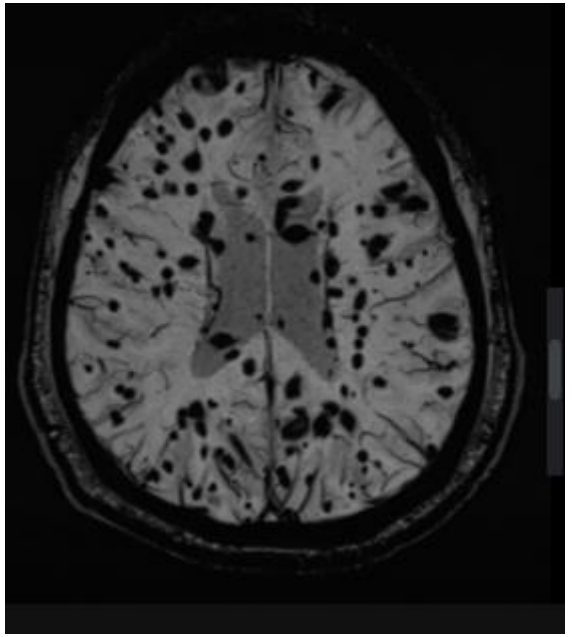
Radiology: MRI characteristics

Classic MRI Features

- **"Popcorn" or "mulberry" appearance**
- Mixed T1/T2 signal (blood products of varying ages)
- Complete hemosiderin rim (T2 hypointense)
- No surrounding edema (unless acute bleed)
- Angiographically occult

radiopaedia.org/articles/cerebral-cavernous-venous-malformation?lang=us





Clinical Presentation

Hemorrhage	Seizures	Focal Deficit	Incidental
45% *of cases*	**40%** *of cases*	**35%** *of cases*	**20%** *of cases*
Acute intralesional or perilesional bleeding; sudden symptom onset; headache, focal deficits	Most common in supratentorial CCM; focal or secondarily generalized; cortical location key risk factor	Location-dependent; brainstem CCM: cranial nerve palsies, hemiparesis, ataxia; progressive or episodic	Asymptomatic discovery on MRI for unrelated indications; annual hemorrhage risk 0.4–0.7%

Symptomatic Hemorrhage *Lancet Neurol* 2016; 15: 166–73

The 5-year estimated risk of ICH during untreated follow-up was 3·8% (95% CI 2·1–5·5) for 718 people with non-brainstem CCM presenting without ICH or FND, 18·4% (13·3–23·5) for 327 people with nonbrainstem CCM presenting with ICH or FND,
8·0% (0·1–15·9) for 80 people with brainstem CCM presenting without ICH or FND, and 30·8% (26·3–35·2) for 495 people with brainstem CCM presenting with ICH or FND.

Ref: Al-Shahi Salman et al., Lancet Neurol 2012; Zabramski et al., J Neurosurg 1994; Flemming et al., Brain 2012, Horne et al Lancet 2016

Natural History: Seizures & Epilepsy

40%

Present with seizures

4–8%

Of refractory epilepsy

Mechanism of Cavernoma-Related Epilepsy (CRE)

- Hemosiderin deposition from chronic microhemorrhage induces iron-mediated oxidative damage to surrounding cortex
- Perilesional gliosis creates an epileptogenic zone extending beyond the visible lesion
- Frontal and temporal lobe CCMs most commonly associated with seizures
- Duration of epilepsy inversely correlates with seizure-free outcomes after surgery

Seizure Management Recommendations (Alliance Guidelines, 2026)

- Antiseizure medication recommended after first CCM-related seizure
- Drug-resistant epilepsy (DRE): strong indication for surgical resection with hemosiderin rim removal
- Temporal lobe CCM: 89–90% favorable seizure outcome after surgery, even in DRE (Schuss et al., 2020)

Gao et al., Front Neurol 2020; Schuss et al., Neurosurg Focus 2020; Alliance Guidelines, Neurosurgery 2026

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Natural History: Familial vs Sporadic CCM

Feature	Sporadic (~80%)	Familial (~20%)
Number of Lesions	Usually single	Multiple (typically 6–20); increase over time
Annual Hemorrhage Rate	0.7–2.5% per patient-year	Higher overall; CCM3 especially aggressive
De Novo Lesion Formation	Rare (unless radiation-induced)	Common; new lesions appear over time
Genetic Mechanism	Somatic PIK3CA + MAP3K3; DVA-derived	Germline KRIT1/CCM2/PDCD10 + somatic 2nd hit
Seizure Profile	30–50% present with seizures	Higher cumulative risk with multiple lesions
Associated DVA	Common (20–60%); DVA is genetic primer	Less commonly associated with DVA

PDCD10 (CCM3): Most aggressive phenotype — earlier onset, greater lesion burden, more frequent hemorrhages, scoliosis, and cognitive disability. Higher penetrance and unique extraneural features distinguish CCM3 from KRIT1/CCM2 disease (Shenkar et al., 2015).

Shenkar et al., Genet Med 2015; Flemming et al., J Neurosurg 2024; Snellings et al., Nat Cardiovasc Res 2022; Sikta et al., Hum Mol Genet 2025; Alliance Guidelines, Neurosurgery 2026

Conservative Management

Observation is First-Line for Most Patients

Indications for Observation

- Asymptomatic incidental CCM (regardless of location)
- Single seizure, well-controlled with medication
- Mild deficits not impacting quality of life
- Deep/eloquent location where surgical risk > benefit
- Multiple lesions (familial) — treat symptomatic lesion only
- Patient preference after shared decision-making

Conservative Care Components

- **MRI surveillance:** Baseline, 6–12 months
- **Anti-epileptic drugs:** For seizure control (supratentorial CCM)
- **Antithrombotic caution:** Anticoagulants not absolutely contraindicated
- **Genetic counseling:** For familial forms; reproductive counseling
- **Patient education:** Symptom recognition; when to seek emergency care

Anticoagulation Controversy:

No prospective randomized data. Observational studies suggest anticoagulation (e.g., warfarin for AF) does not significantly increase CCM hemorrhage risk. Current consensus: do not withhold medically necessary anticoagulation.

Ref: Dammann et al., Neurosurgery 2017; Reinard et al., J Clin Neurosci 2016; Rosenow et al., Epilepsia 2003

Surgical Resection

Surgical Indications	Relative Contraindications
• Recurrent symptomatic hemorrhage (≥2 episodes)	• Deep eloquent location (basal ganglia, thalamus)
• Progressive neurological deficit attributable to CCM	• Single episode with minimal deficit
• Surgically accessible lesion near brain surface	• Asymptomatic patient
• Drug-refractory seizures	• Multiple lesions — target only symptomatic lesion
• Expanding lesion with mass effect	• Patient with high operative risk (medical comorbidities)

Surgical Approach & Outcomes

Seizure freedom: 60–85% seizure-free at long-term follow-up after temporal lobe resection

Re-hemorrhage: Near 0% after complete resection

Hemosiderin rim: Removal of hemosiderin rim debated; may reduce seizure recurrence

Ref: Ferroli et al., Neurosurgery 2010; Taslimi et al., World Neurosurg 2016; Abla et al., J Neurosurg 2011; Englot et al., J Neurosurg 2011

Stereotactic Radiosurgery (SRS)

SRS remains controversial for CCM. No RCT evidence. Reserved for surgically inaccessible lesions with high hemorrhage risk and significant morbidity.

Potential Benefits	Limitations & Risks
• Reduces annual hemorrhage rate ~50–75% after 2-year latency	• Latency period: 2–3 years before risk reduction
• Non-invasive; suitable for eloquent/deep locations	• Radiation-induced complications: edema (20%), necrosis (3–5%)
• Brainstem CCM: largest evidence base for SRS	• No randomized controlled trial evidence to date
• Outpatient procedure; short recovery	• Increased risk in periventricular or near-optic structures
• May achieve seizure reduction in some patients	• Re-hemorrhage risk not eliminated

SRS Technical Considerations & Patient Selection

Typical dose:	12–16 Gy at margin (brainstem: 12–13 Gy to limit toxicity)
Ideal candidate:	Deep/eloquent CCM with ≥2 symptomatic hemorrhages; not resectable
Evidence base:	Retrospective series;
SRS vs Surgery:	Surgery preferred for accessible lesions;

Ref: Sheehan et al., J Neurosurg 2012; Karaaslan et al J. Neurosurg 2021; Hasegawa et al., J Neurosurg 2002

Stereotactic Radiosurgery for CCM

Role & Indications

- Deep/eloquent CCMs not amenable to surgery
- Recurrent hemorrhage from brainstem CCM
- High surgical risk patients
- Primarily hemorrhage risk reduction (not seizure control)

Dosimetry

- Typical margin dose: 11–15 Gy
- Margin dose >13 Gy: lower rebleed risk (HR 2.57)

Evidence for Brainstem CCM SRS

14.8% → 2.3%

Hemorrhage per 100 CM –years
pre- vs post-SRS

86.6%

Symptom-free at
5 years post-SRS

5.3%

Adverse radiation
effect rate

Dayawansa et al. (2024): Multicenter study, 170 brainstem CCM patients; SRS reduced hemorrhage risk (HR 0.17, $p < 0.001$); patients >35 years had better outcomes

Dayawansa et al., Sci Rep 2024; Shi et al., Front Neurol 2025; Galvão et al., Cerebrovasc Dis 2025

Brainstem CCM: Safe Entry Zones & Surgical Timing

Safe Entry Zones (Catapano et al., 2022)

Location	BSCM Type	SEZ Used	Good Outcome (mRS ≤2)
Midbrain (22%)	15% exophytic 37% superficial 48% deep	97% of deep lesions	**80%**
Pons (66%)	Most common BSCM location	Preferred SEZ in 91%	**72–82%**
Medulla (12%)	Least common	Established SEZ	**93% stable/improved**

Optimal Surgical Timing (Qian et al., 2025)

Acute phase (8–20 days) and subacute phase (21–56 days) yield best neurological outcomes

- Hyperacute (≤7 days): higher risk due to acute edema and fragile tissues
- Chronic (>56 days): suboptimal due to gliosis and adhesions
- MRI may overestimate surface proximity (specificity 67%): prepare for SEZ use even when lesion appears superficial

Catapano et al., J Neurosurg 2022; Qian et al., Sci Rep 2025

Laser Interstitial Thermal Therapy (LITT)

Technique & Indications

- MRI-guided, minimally invasive ablation
- Real-time MR thermometry monitoring
- Primarily for epileptogenic CCMs
- Deep/eloquent lesions where craniotomy carries higher risk
- Also used for non-epileptogenic CCMs with recurrent symptoms

Key Evidence (Jimenez et al., 2024)

- Meta-analysis: 39 patients, 45 CCMs at 6 centers
- **88% seizure-free at median 30 months**
- **0% subsequent hemorrhage during follow-up**
- 73.7% volume reduction (epileptogenic CMs)
- 15.4% immediate neurological deficit (most transient)

Advantages

- Minimally invasive (single burr hole)
- Real-time thermal monitoring
- Shorter hospital stay vs craniotomy
- Access to deep/eloquent lesions

Limitations

- Small case series; no RCTs
- Thermal monitoring challenging near blood products
- No pathological specimen obtained
- Risk of cyst formation at ablation site

Jimenez et al., J Neurosurg 2024; Yousefi et al., Front Surg 2022

Emerging Medical Therapies

Table 1. Potential Pharmacologic Treatments of Clinical Relevance

Therapeutic action	Drug	Preclinical evidence	Clinical development
ROCK inhibitors	NRL-1049	Decreased lesion volume and bleeding vs placebo (murine)[56]	IND application filed and clinical program initiated[59,60]
	Atorvastatin	Decreased lesion volume and bleeding vs placebo (murine)[64]	Phase 1/2a trial in progress (DBRCT)[67,105]
	Simvastatin	Decreased lesional bleeding vs placebo; reduced VEGF-mediated permeability (murine)[64,68]	No planned clinical studies No difference in permeability of CCMs at 3 mo (RCT)[69]
β-Adrenergic receptor antagonists	Propranolol	Decreased lesion number, size, and volume vs placebo or vehicle (murine)[71,76]	Phase 2/3 trial (Treat2_CCM) is planned (DBRCT)[77] Lower risk for intracerebral hemorrhage or FND vs standard care* (phase 2, OLRCT)[77]
Superoxide dismutase mimetics	REC-994 (tempol)	Reduced vascular leakage (vs vehicle) and rescued endothelium-dependent vasodilation[78]	Phase 2 trial enrollment complete, ongoing (DBRCT)[81]

Stroke Vasc Interv Neurol. 2024;4:e001140.

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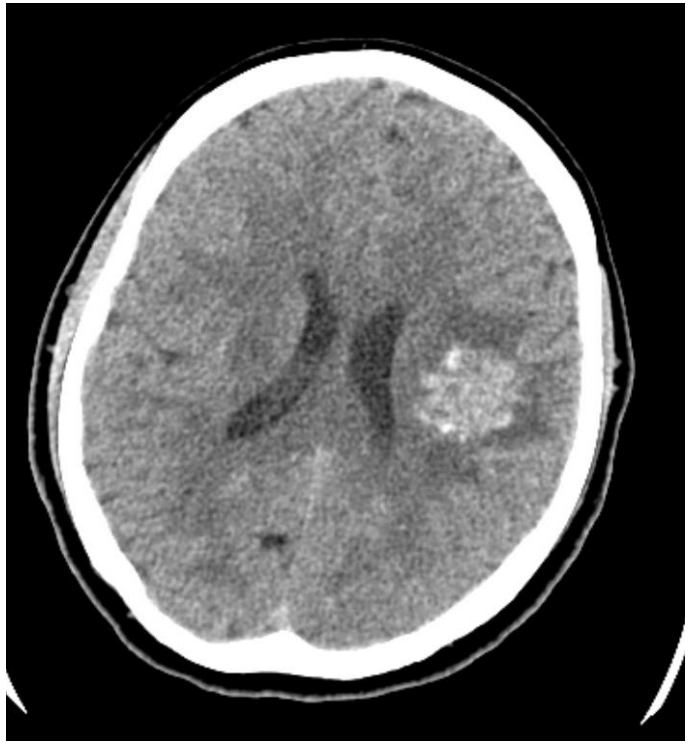
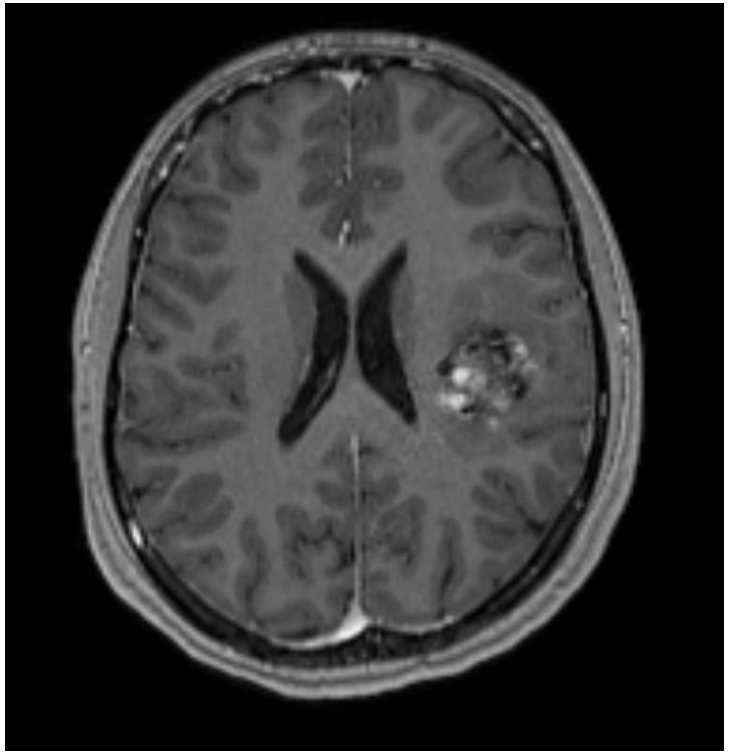
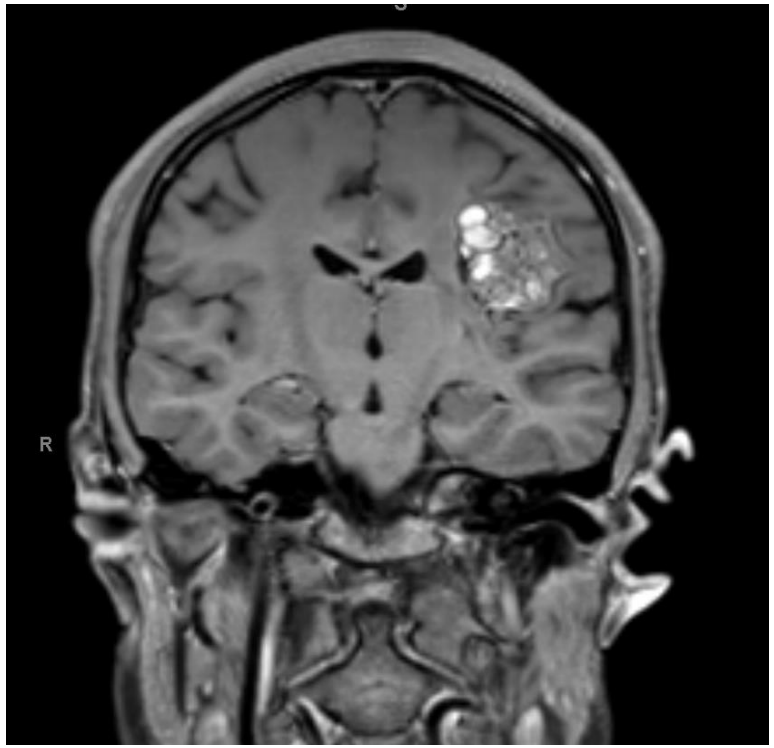
Case Illustration:

A 19-year-old lady presented with medically intractable epilepsy.







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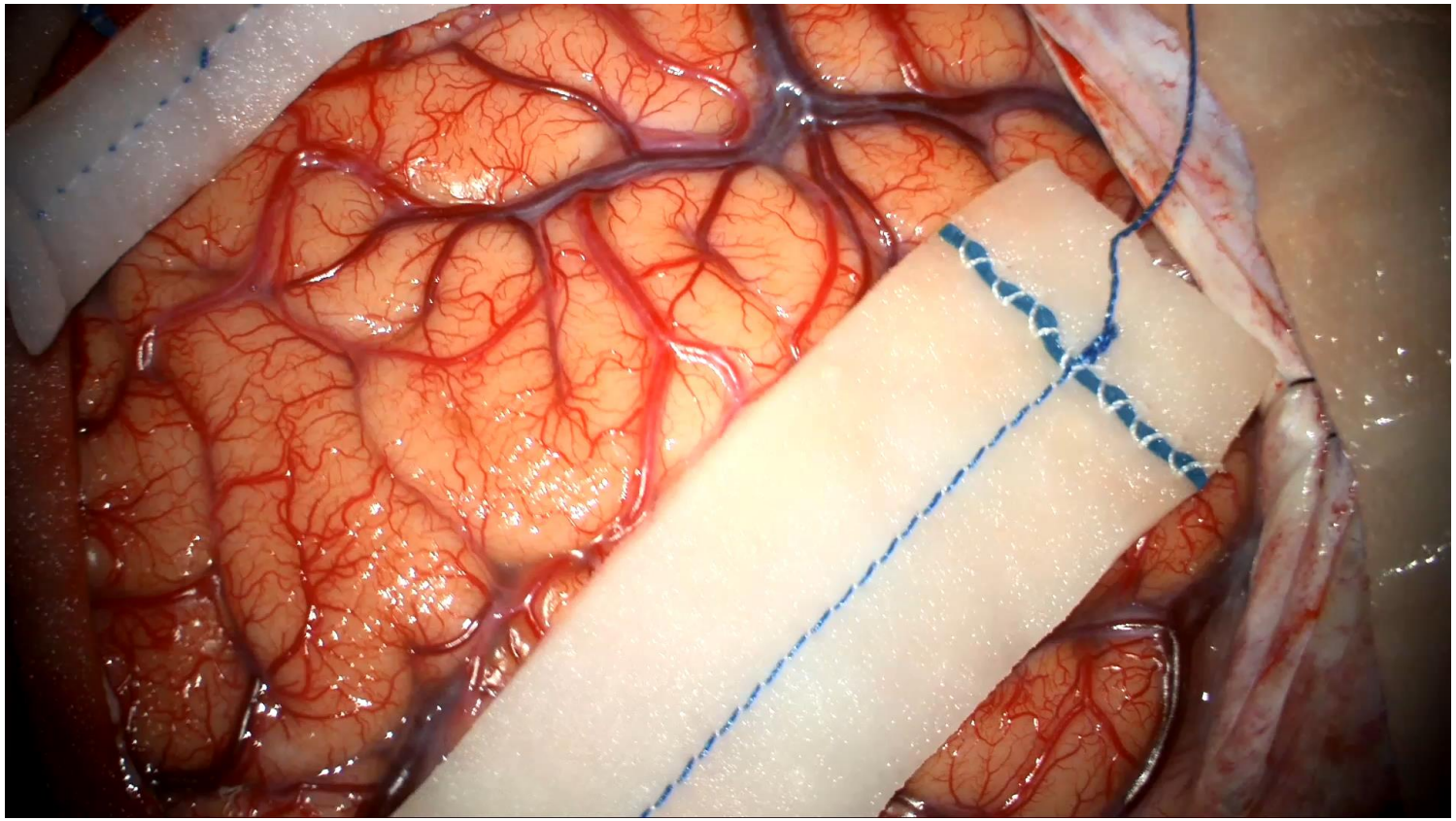

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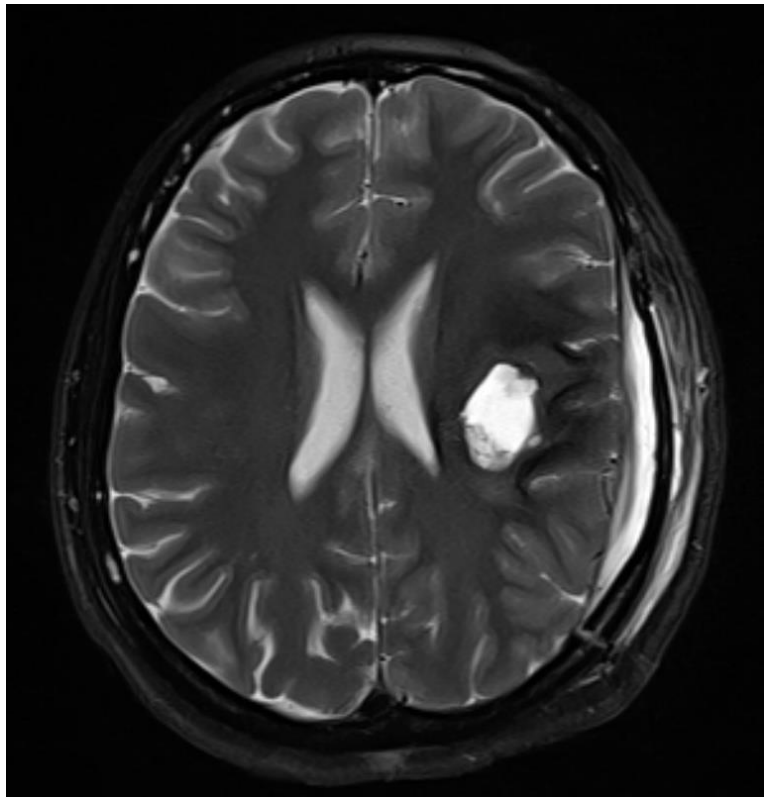
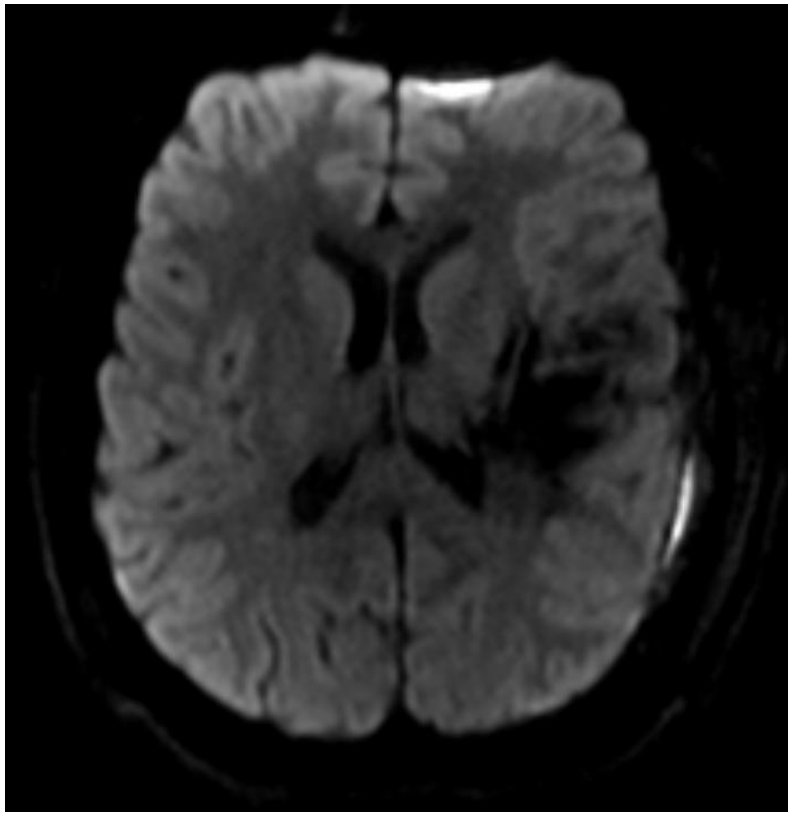
Post-op MRI:





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Discussion

Thoughts/comments/suggestions?

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Supplementary slides