

The Effect of Neuroinflammation on Development and Outcome of Aneurysmal Subarachnoid Hemorrhage

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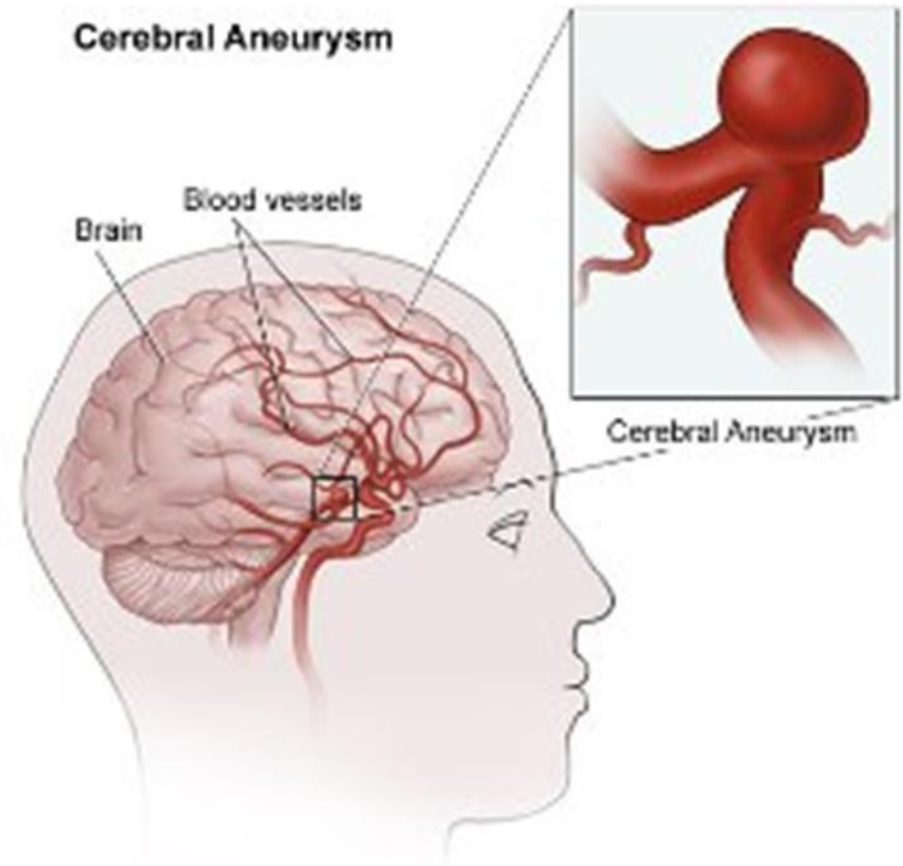
Overview

- Introduction
 - Definition of Aneurysm
 - Treatment Options
 - Risk Factors for Rupture
- Subarachnoid Hemorrhage
 - Aneurysmal SAH
- Aneurysmal SAH and Neuroinflammation
- Discussion
- Conclusion

Introduction

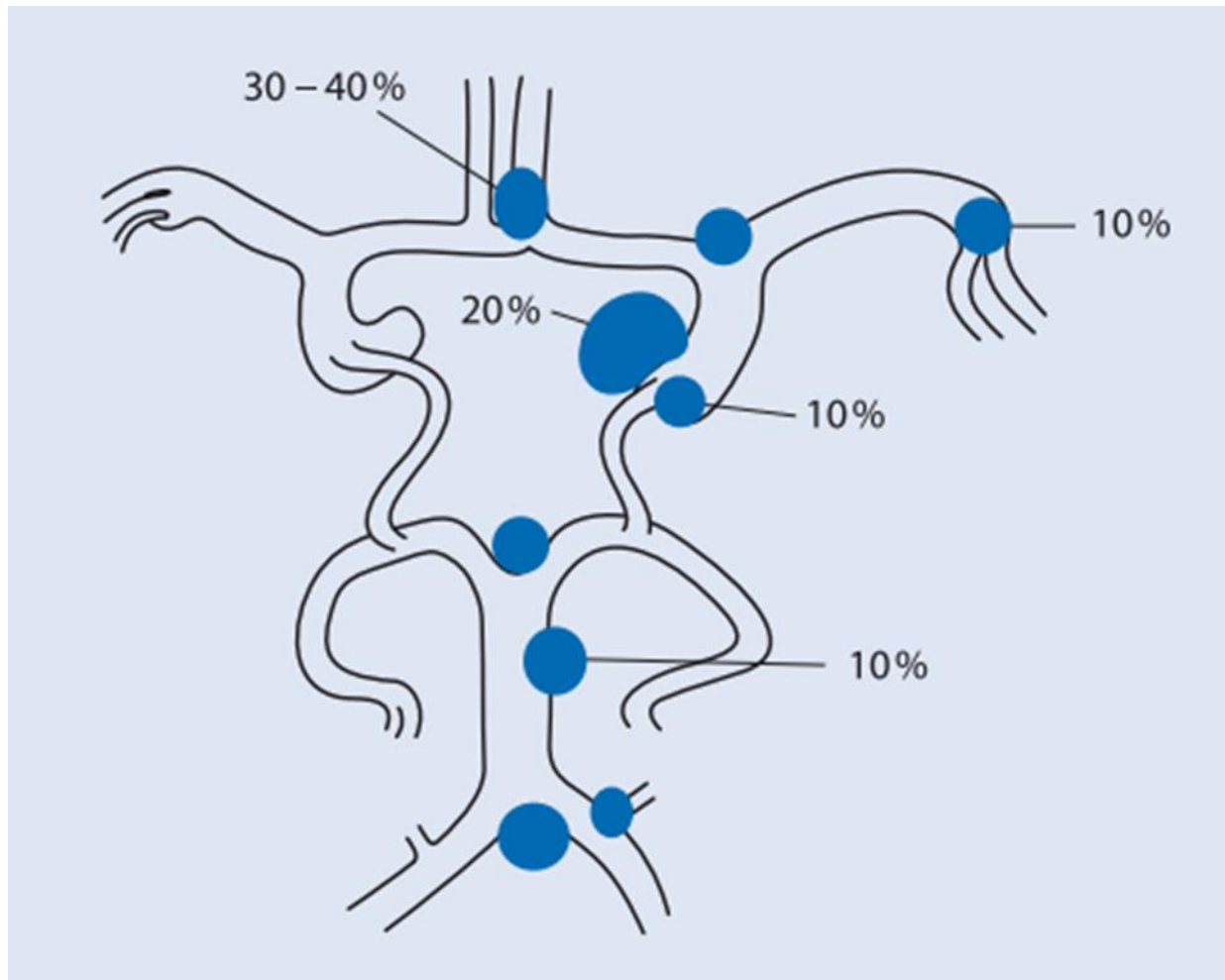
What is a cerebral aneurysm?

- Acquired dilatation of an intracranial artery.
- All the layers of the vascular wall are effected by degenerative changes.
- Typically discovered at the arterial branching sites near the skull base.



Johns Hopkins Medicine

Typical Locations of Cerebral Aneurysms



Berlit et al., Klinische Neurologie

Classification of Aneurysms

Based on their shape:

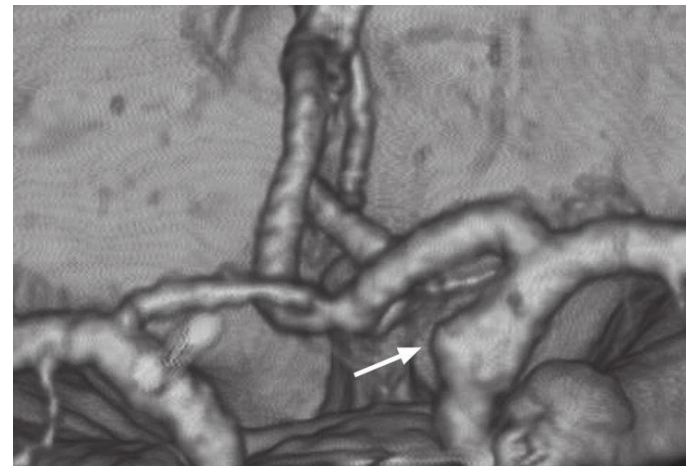
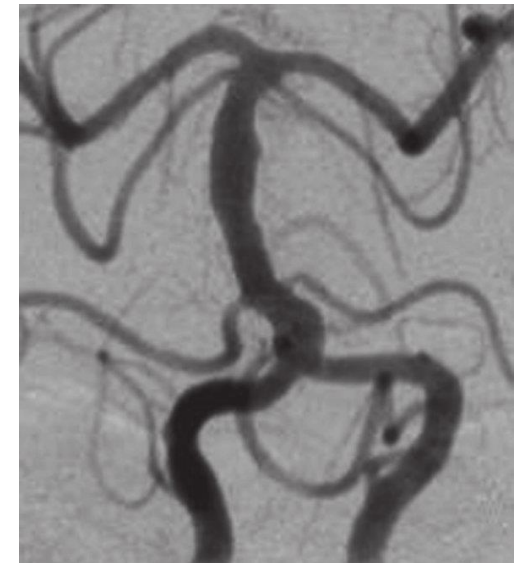
- Saccular aneurysm
- Fusiform aneurysm

Based on their size:

- Giant aneurysm
- Small-blisters type aneurysm

Based on their origin:

- Mycotic aneurysm



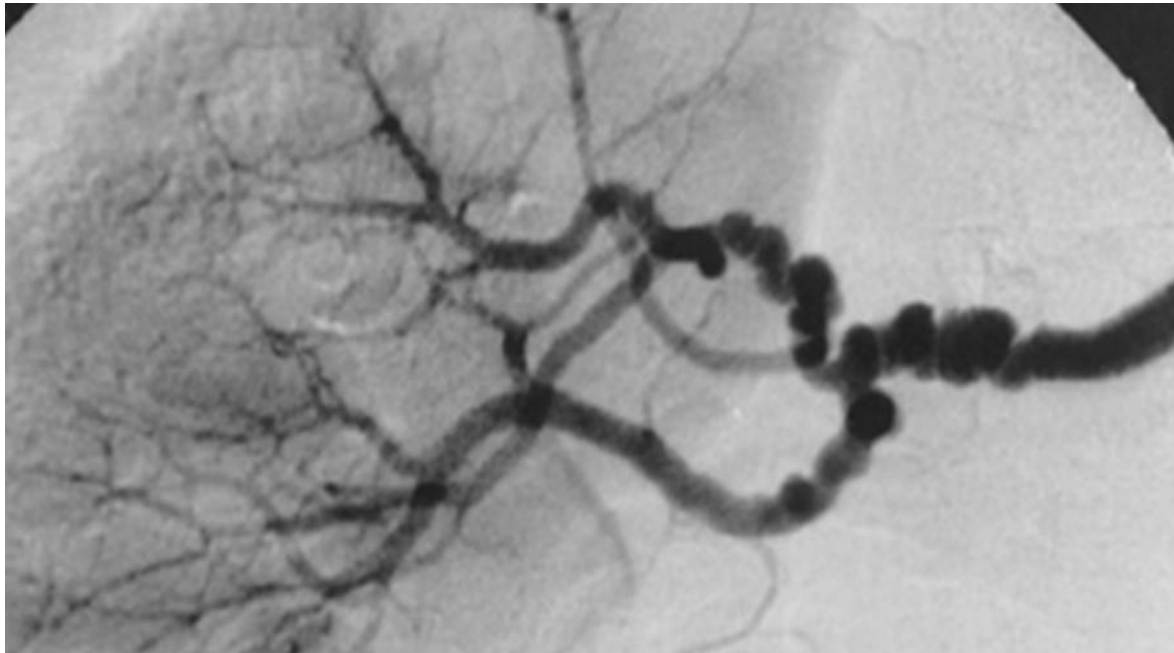
Spetzler et al., *Neurovascular Surgery, 2nd. Edition*

Epidemiology

- Overall prevalence of unruptured aneurysms: 2% of general population.
- Very rare in children, increase after 30 y.o. age.
- The prevalence is higher in female population.
- Risk factors:
 - Hypertension
 - Smoking

Diseases Associated with Aneurysms

- Autosomal polycystic kidney disease
- Fibromuscular dysplasia



Plouin et al., Orphanet Journal of Rare Diseases. 2, 28. 2007

Treatment options

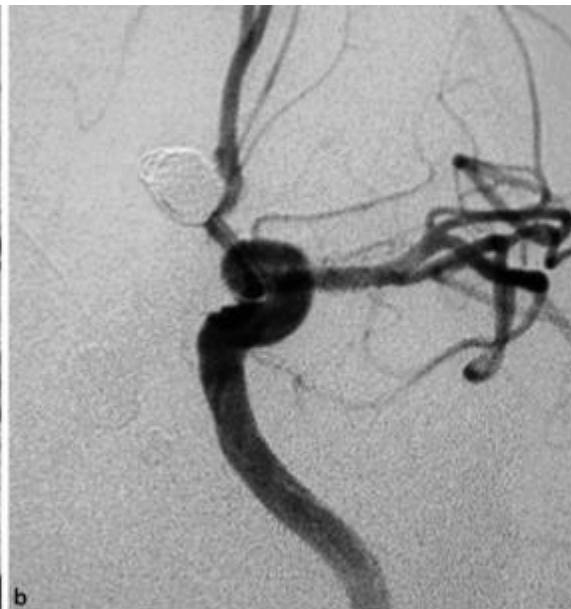
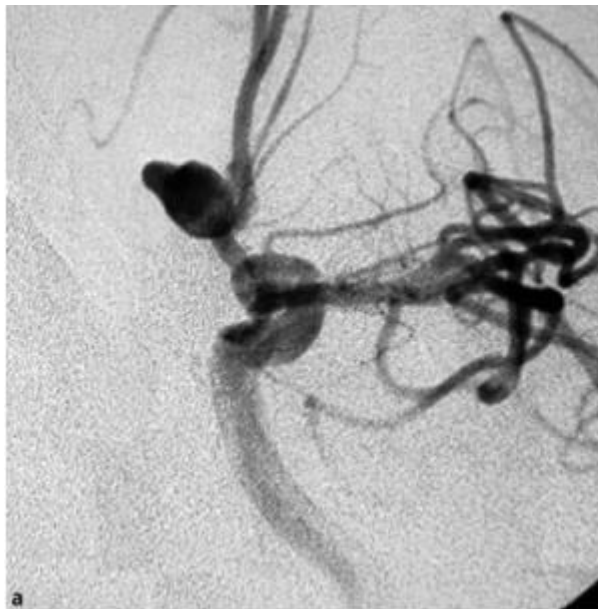
- Endovascular approach: Coiling
- Clipping

Coiling



a) Coil embolisation: insertion of first coil through the tracker catheter.

b) Insertion of further coils.



a) Digital angiogram showing anterior communicating artery aneurysm.

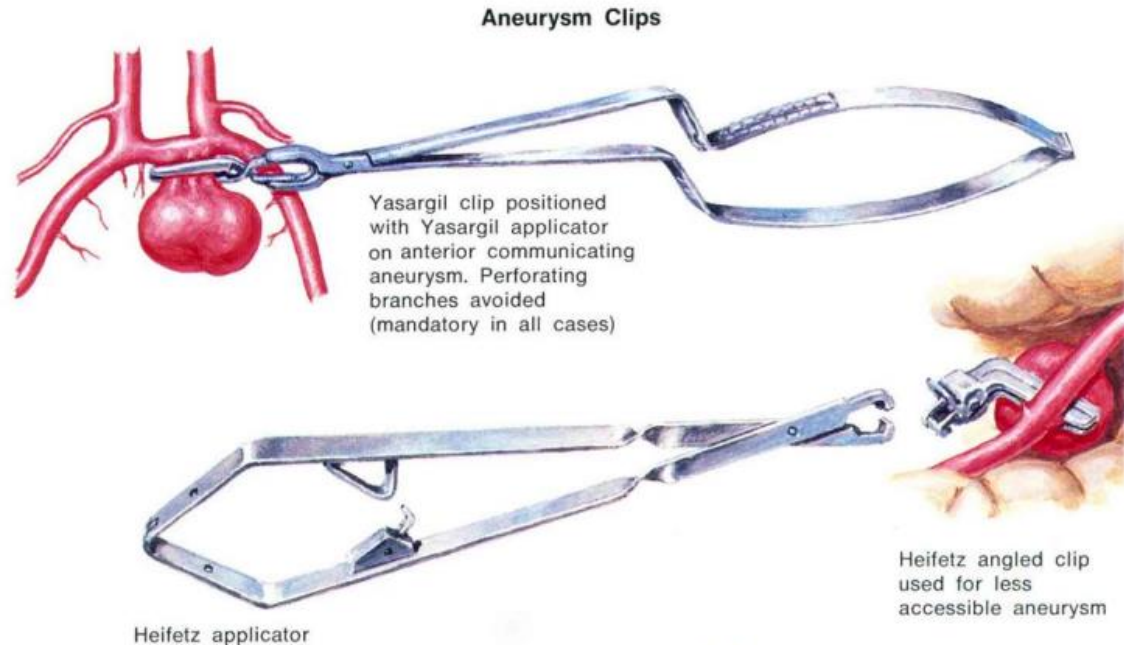
b) Final stage of coil embolisation showing fundus packed with coils.

Lumenta et al., *Neurosurgery*.

Clipping

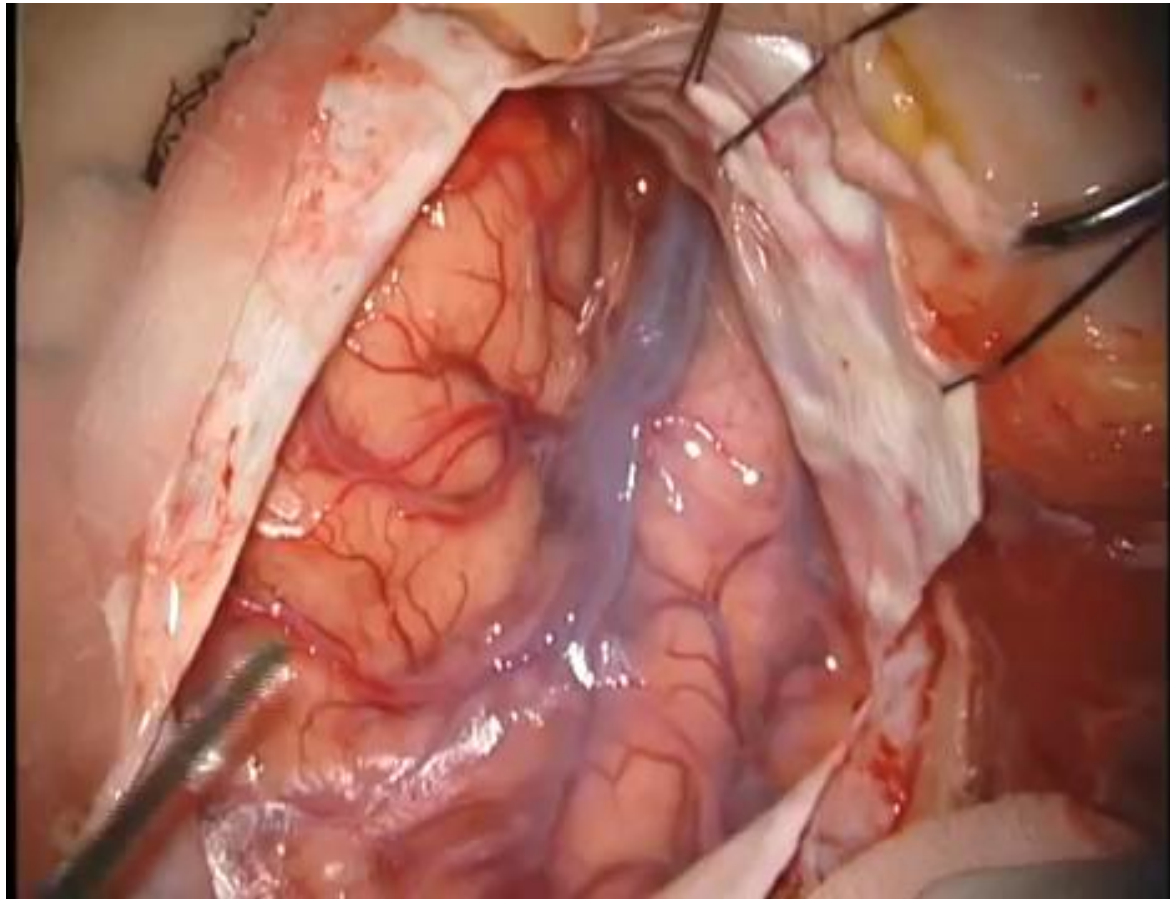


Prof. Gazi Yaşargil,
“Neurosurgery’s Man of
the Century”



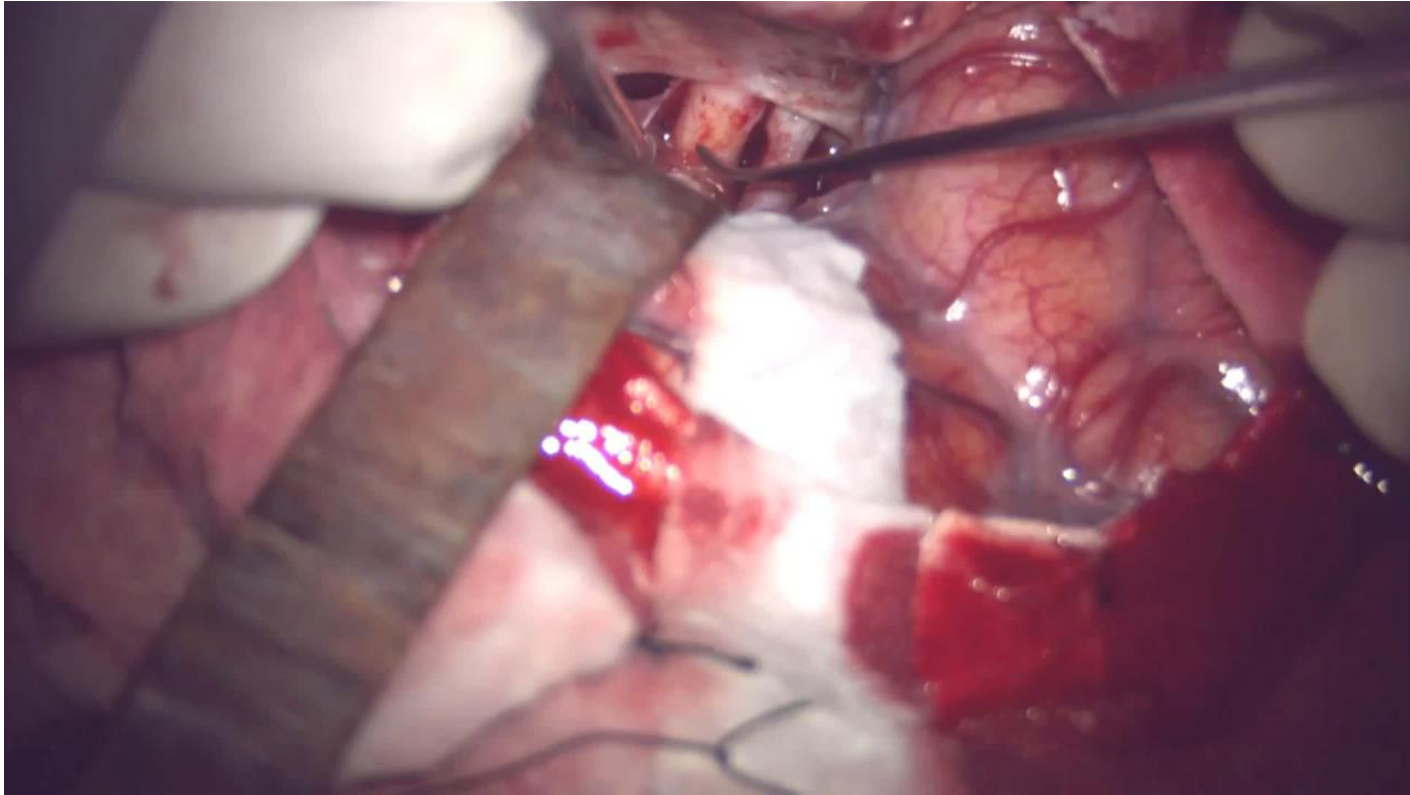
Netter Atlas of Human Anatomy

Clipping of a MCA-Aneurysm



www.youtube.com, 02.01.2019

Clipping of an ACoA-Aneurysm



www.youtube.com, 02.01.2019

Patient-related Risk Factors for IA Rupture

- Older age
- Female gender
- Smoking
- Hypertension
- Previous history of aneurysmal SAH

Aneurysm-related Risk Factors for IA Rupture

- Larger aneurysm size
- Location

Table 38.1 Size and Location of 6,163 Aneurysms Found in 4,257 Patients Admitted to the Department of Neurosurgery in Helsinki Between 1989 and 2008

	Ruptured	Unruptured
N	3,062	3,101
Location		
ICA	622 (20%)	741 (24%)
ICA-PCoA	396 (13%)	200 (6%)
ACoA	945 (31%)	318 (10%)
MCA	1,020 (33%)	1,577 (51%)
MCA-MbifA	810 (26%)	917 (30%)
DACA	143 (5%)	168 (5%)
VBA	332 (11%)	297 (10%)
VBA-Bas bif	127 (4%)	111 (4%)
Size, median (range)	8 (1–70)	4 (1–60)
< 7 mm	1,123 (37%)	2,256 (74%)
7–14 mm	1,616 (53%)	609 (20%)
15–24 mm	281 (9%)	103 (3%)
> 24 mm	42 (1%)	94 (3%)

Abbreviations: ICA, internal carotid artery; ICA-PCoA, origin of posterior communicating artery; ACoA, anterior communicating artery; MCA, middle cerebral artery; MbifA, middle cerebral artery bifurcation; DACA, distal anterior cerebral artery; VBA, vertebrobasilar area (posterior circulation); Bas bif, basilar artery bifurcation.

Spetzler et al., *Neurovascular Surgery, 2nd. Edition*

Subarachnoid Hemorrhage

- Presence of blood in subarachnoid space
- Classification:
 - Traumatic
 - Spontaneous

About 15 % of SAH patients die before reaching medical attention.

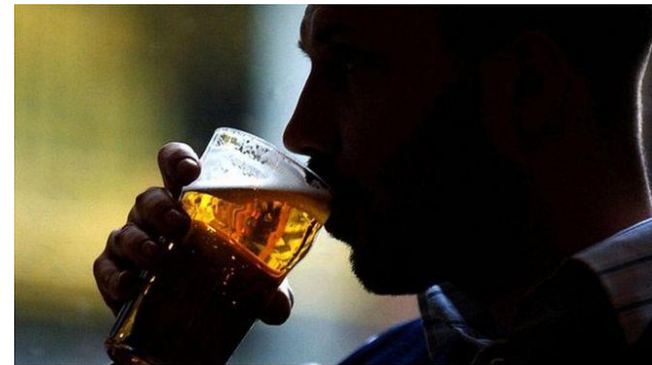
Even with modern treatment, case fatality rates are still close to 50 % at 1 month after SAH.

Incidence of SAH

- Overall incidence: 9 per 100000 person-years.
- Variations across countries with different racial and ethnic compositions.
- Higher in men in the 25- to 45-year age group, but is significantly higher in women in the 55- to 85-year age group.

Modifiable Risk Factors for aSAH

- Systolic blood pressure
- Current and former smoking
- Alcohol consumption?



Clinical Presentation of aSAH

- “The worst headache of my life!”
- Sudden onset
- Characteristically diffuse headache that persists for a few days after onset
- Neck stiffness
- Nausea
- Vomiting
- Transient loss of consciousness
- Early neurological deterioration

Aneurysmal Subarachnoid Hemorrhage

Diagnosis:

- CT scan within 6 hours
- Negative CT but strong clinical history → lumbar puncture

Delayed rehemorrhage from an incompletely treated aneurysm. 71 y.o. woman with a history of smoking, family history of aSAH, and poor pulmonary function requiring chronic oxygen therapy presented with a decreased level of consciousness and diffuse high-grade SAH.



Spetzler et al., *Neurovascular Surgery*, 2nd. Edition

Clinical Assessment of SAH

Table 39.1 Clinical Scales to Assess Severity of Presentation in Aneurysmal Subarachnoid Hemorrhage

Grade	Hunt and Hess Scale	WFNS Scale
I	Asymptomatic or mild headache	GCS sum score 15 without hemiparesis
II	Moderate to severe headache, nuchal rigidity, no focal deficits other than cranial nerve palsy	GCS sum score 13–14 without hemiparesis
III	Confusion, lethargy, or mild focal deficits other than cranial nerve palsy	GCS sum score 13–14 with hemiparesis
IV	Stupor or moderate to severe hemiparesis	GCS sum score 7–12 with or without hemiparesis
V	Coma, extensor posturing, moribund appearance	GCS sum score 3–6 with or without hemiparesis

Abbreviations: WFNS, World Federation of Neurosurgical Societies; GCS, Glasgow Coma Scale.

Spetzler et al., *Neurovascular Surgery, 2nd. Edition*

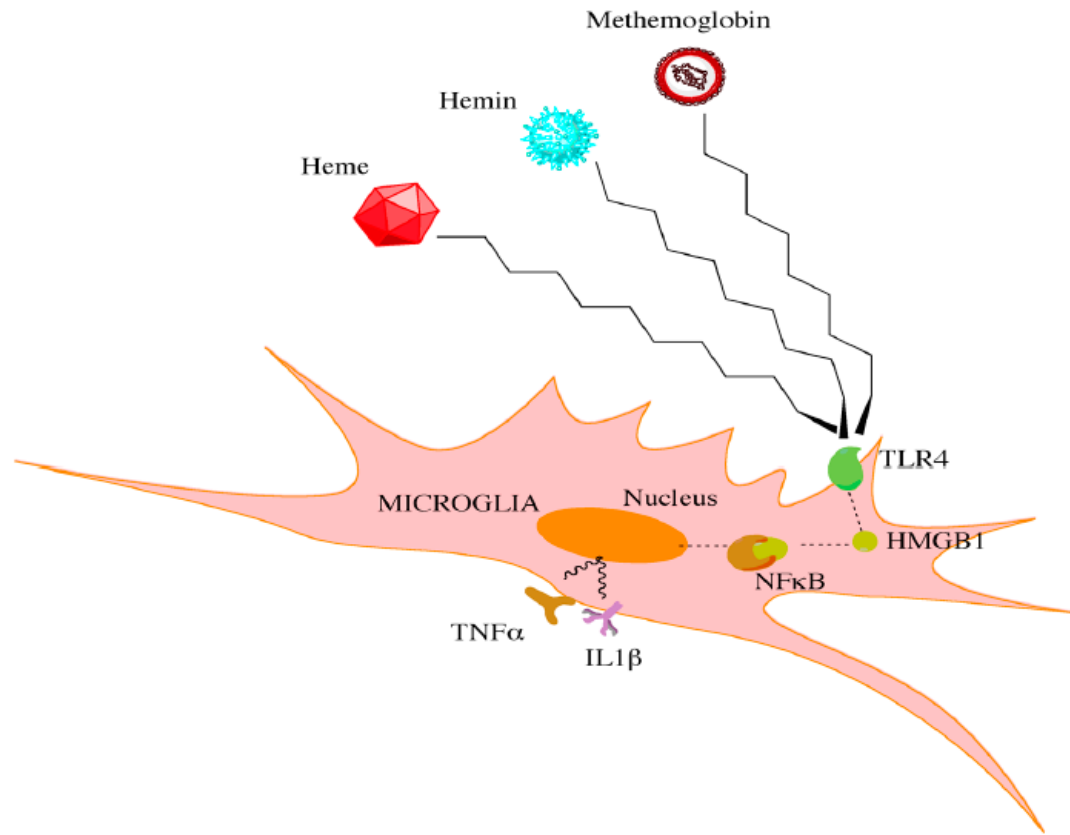
Aneurysmal SAH and Neuroinflammation

SAH Pathophysiology: Acute events

- Blood deposition after initial aneurysmal rupture within the subarachnoid space.
- Red blood cell breakdown and degradation overtime → Deposition of hemoglobin.
- Methemoglobin, heme, and hemin → Activation of TLR4
→ Activation of inflammatory cascades → Neuron and white matter damage.
- Release of redox-active iron.

SAH Pathophysiology: Acute events

- Microglia activation
- Macrophage and neutrophil recruitment



Lucke-Wolde et al., 2016

SAH Pathophysiology: Subacute-Chronic events

- Alterations in cerebral spinal fluid flow and restoration of the endothelial tight junction barrier → Trapped peripheral immune cells.
- Degranulation → Release of inflammatory factors (Endothelin, oxidative radicals).
- Inflammation induced vasoconstriction, arterial narrowing, meningitis, and cerebritis.

Inflammatory Mediators in SAH

- IL-1 beta, IL-6, and TNF alpha released into both the serum and cerebrospinal fluid following SAH.
- In animal models of SAH also increased in the cerebral artery.
- Inflammation → Cerebral vasospasm (Beginning no earlier than day three and peak at one week) → Cerebral ischemia and infarction.
- Accumulation of inflammatory cells → Closely related with neuronal cell death → Depletion of inflammatory cells → Reduction of cell death.
- B and T cell lymphocyte infiltration into the vessel of aneurysms.

Proteases in SAH

- Matrix metalloproteinase 9 (MMP9) : Responsible for the degradation of tight junction proteins (BBB integrity).
 - Elevated levels in brain tissue, serum, and cerebrospinal fluid after SAH.
 - Not only in serum but also in the vessel wall.
- A new target to restore BBB integrity or to prevent BBB disruption?

Discussion

- Neuroinflammation as a new target in the treatment of patients after aneurysmal SAH.
- The role of neuroinflammation in the formation of aneurysms.

Conclusion

- Aneurysmal SAH remains a difficult clinical paradigm to treat.
- Understanding the exact pathophysiology of aneurysmal SAH can open up new frontiers in the treatment.

Thanks for listening!