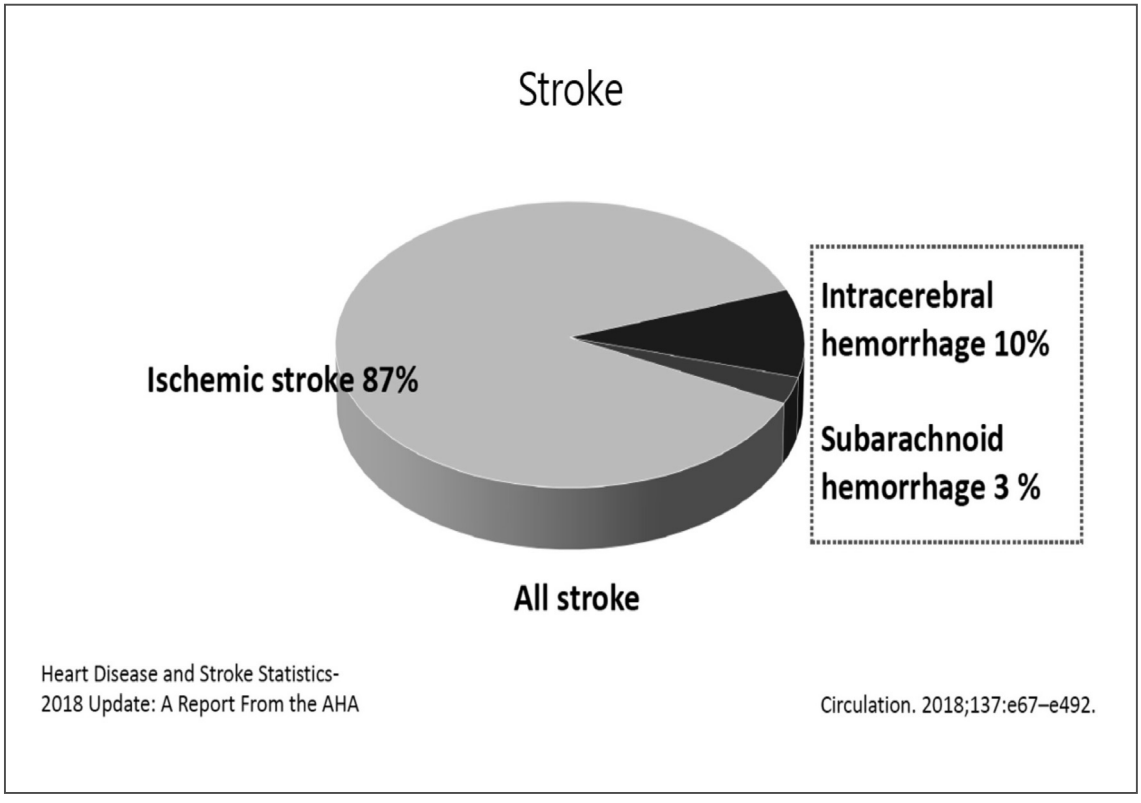
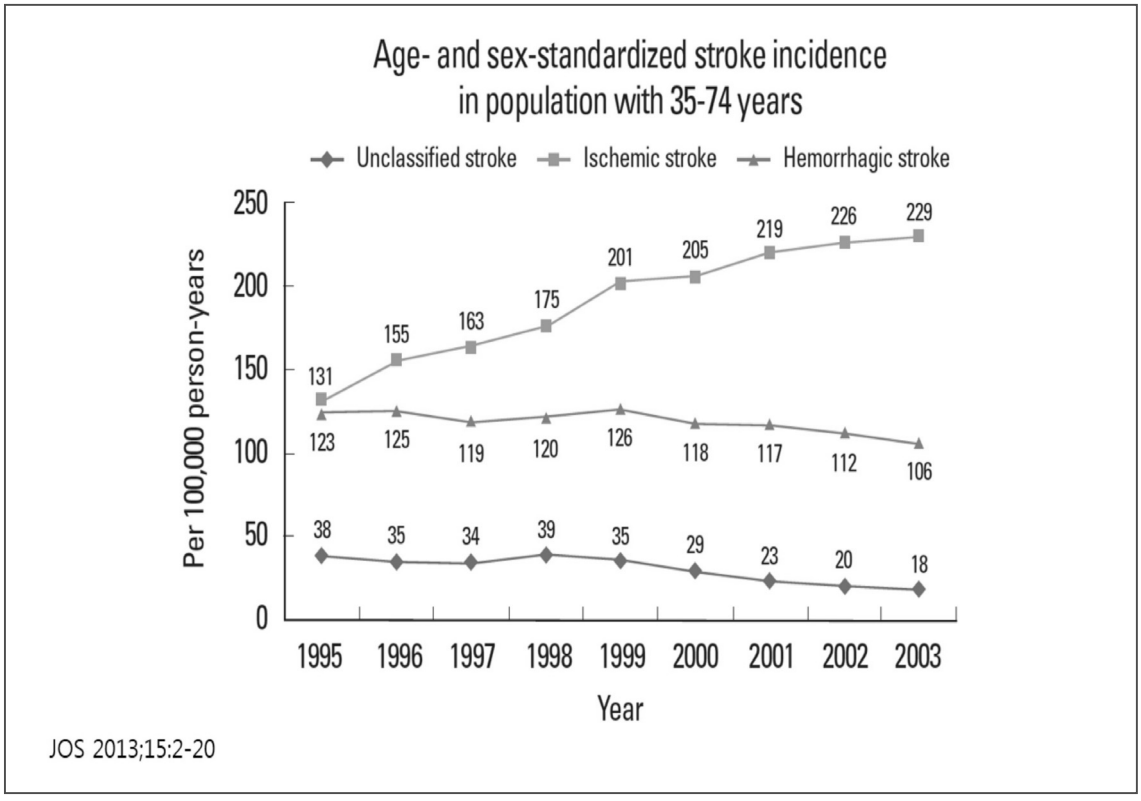
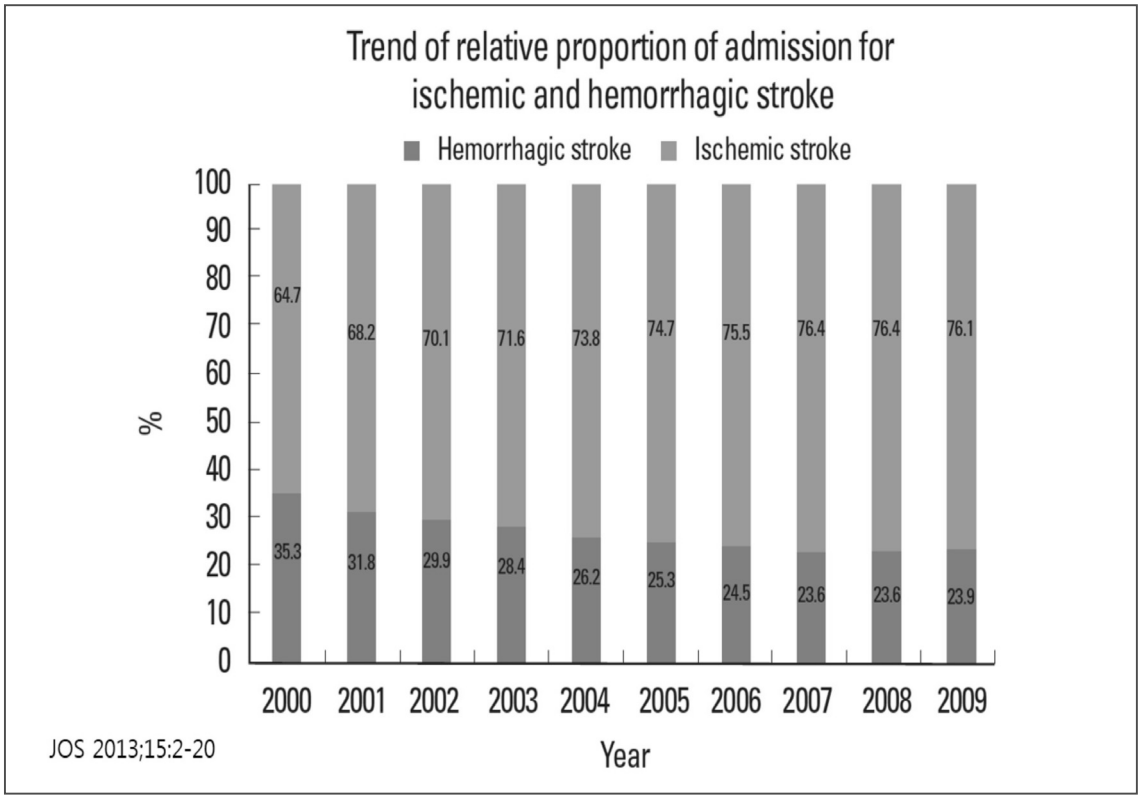
Intracranial hemorrhage

송 희 정
충남의대

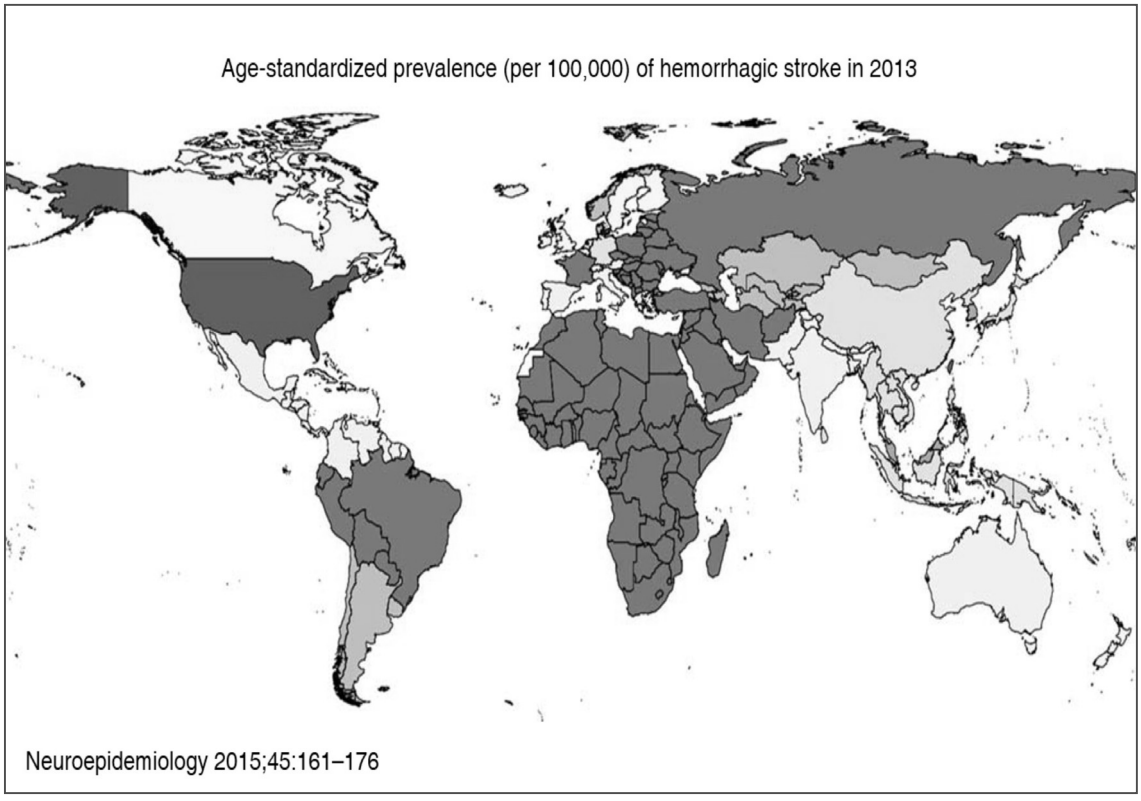


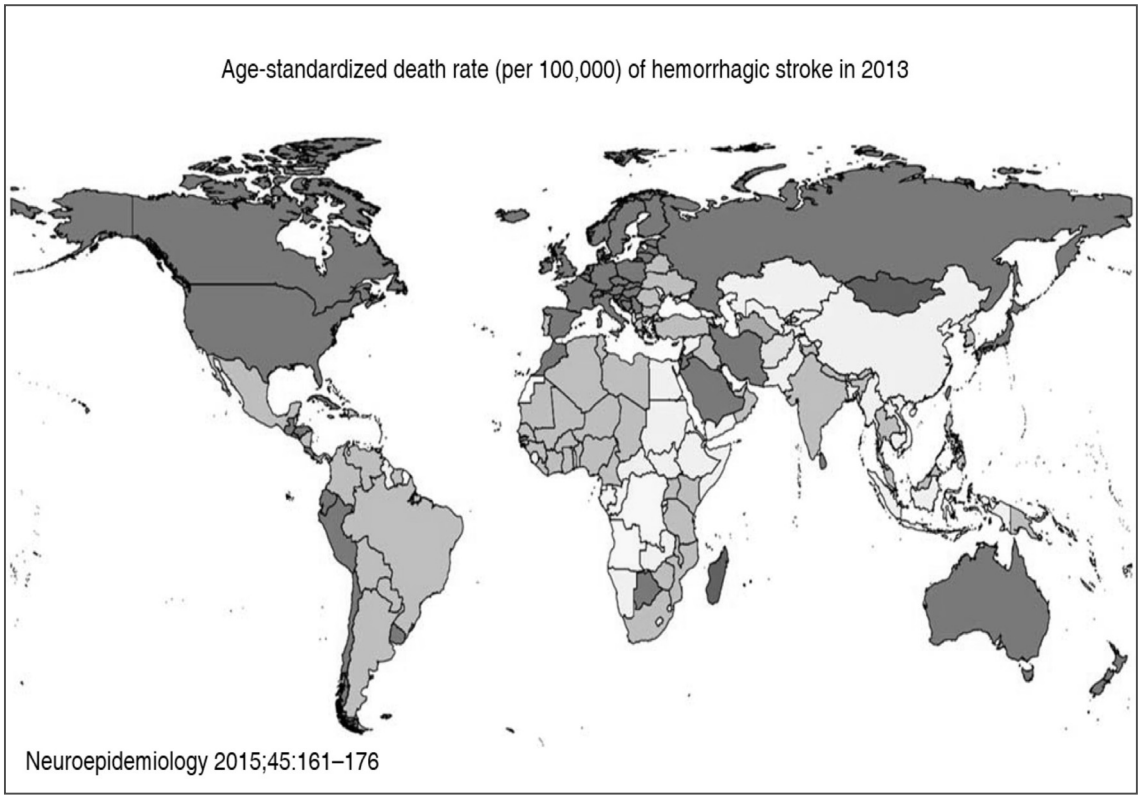


JOS 2013;15:2-20



JOS 2013;15:2-20


Age-standardized prevalence (per 100,000) of hemorrhagic stroke in 2013
Neuroepidemiology 2015;45:161–176


Age-standardized death rate (per 100,000) of hemorrhagic stroke in 2013
Neuroepidemiology 2015;45:161–176

Intracranial Hemorrhage

- Intracerebral hemorrhage
- Intraventricular hemorrhage
- Subarachnoid hemorrhage
- Cerebral venous thrombosis
- Subdual hemorrhage
- Epidural hemorrhage

Spontaneous Intracerebral hemorrhage

- 10-15% of the ~700,000 annual strokes in U.S.
- Incidence 12-15/100,000
- <1/3 –functionally independent after ICH
- High mortality
  - 40% survive first 30 days
  - 1 year mortality—50%
- Increases with age, ethnicity(Non-white race)
- Risk factors: Advanced age, HTN, kidney disease, Excessive alcohol use, very low cholesterol, genetics (apoε2, ε4), drug abuse

Etiology of s-ICH

Primary ICH	Secondary ICH
Hypertension	Vascular malformations
Cerebral amyloid angiopathy	Arteriovenous malformation
Sympathomimetic	Cavernous malformation
Drugs of abuse	Saccular aneurysm
Cocaine	Mycotic aneurysm
Methamphetamine	Dural arteriovenous fistula
Coagulopathy	Moyamoya
	Ischemic stroke (hemorrhagic conversion)
	Cerebral venous sinus thrombosis (hemorrhagic conversion)
	Tumor (primary or metastatic)
	Cerebral vasculitis

Risk factors of ICH

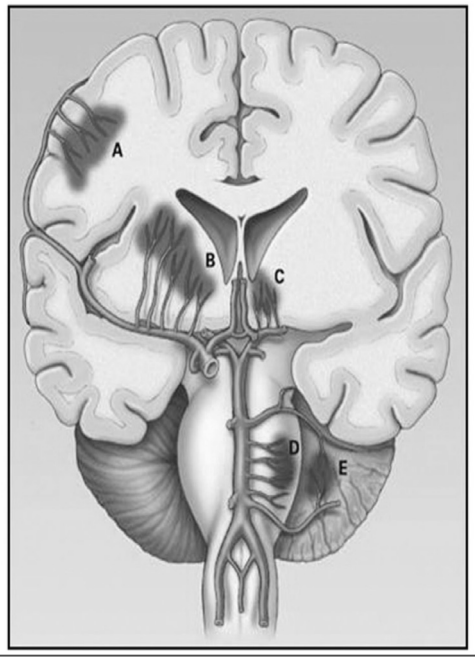
Modifiable risk factors	Non-modifiable risk factors
Hypertension	Old age
Current smoking	Male
Excessive alcohol consumption	Asian
Decreased LDL-cholesterol, low TG	Cerebral amyloid angiopathy
Anticoagulation	Chronic kidney disease
Use the antiplatelet agent	
Sympathomimetic drugs (cocaine, heroin, amphetamine, PPA and ephedrine)	
Other factors suggested to be related the risk	
Multi-parity	
Poor working conditions (blue-color occupation, longer w orking time)	
Long sleep duration	

Journal of Stroke 2017;19(1):3-10

Primary ICH

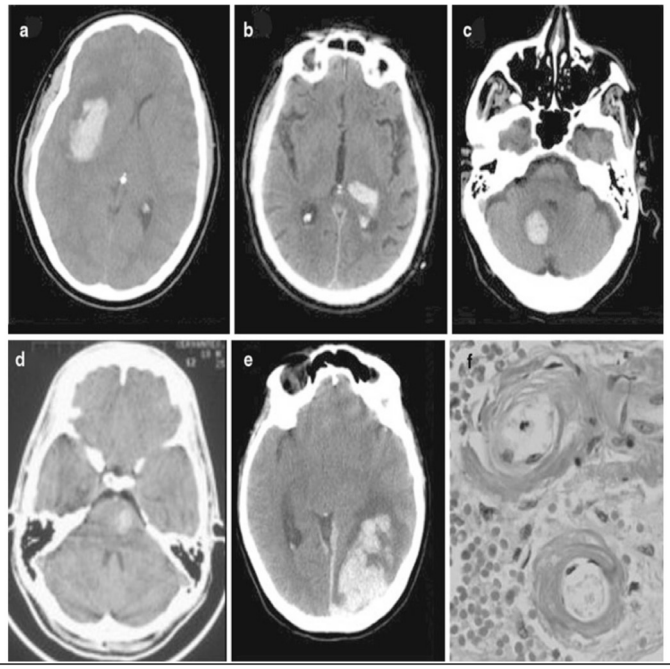
- Due to the rupture of small arterioles (<100μm)
  - effects of longstanding hypertension on these small vessels
  - ~60 to 70% of all ICH
- Cerebral amyloid angiopathy
  - particularly in elderly patients
  - presence of the ε2 and ε4 alleles of the apoEgene
    → Recurrent hemorrhage risk 3 times

Typical locations for hypertensive ICH



Continuum
Lifelong Learning Neurol
2009;15(3):121–137.

Typical locations for hypertensive ICH



Emergency Neurology,
DOI 10.1007/978-0-387-88585-8_9

Lipohyalinosis of small penetrating arteries

Prognostic factors of ICH

Table 2. Poor prognostic factors of intracerebral hemorrhage

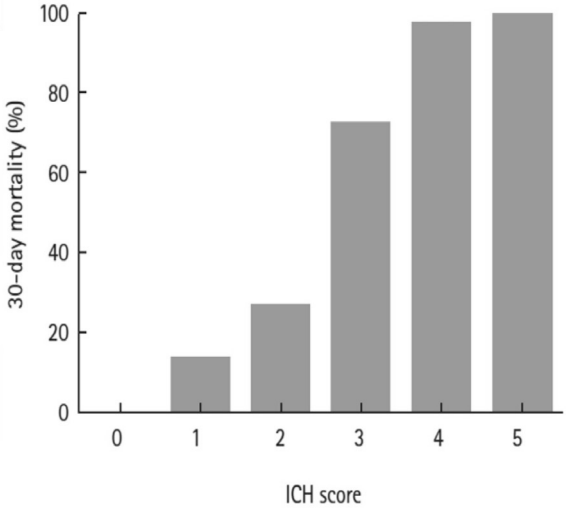
Low score of Glasgow coma scale
Intracerebral hemorrhage volume (≥ 30 cm^3)
Intraventricular extension of hemorrhage
Infra-tentorial origin of Intracerebral hemorrhage
Old age (≥ 80)
Advanced white matter lesions
Underweight at admission
Hyperglycemia at admission
Chronic kidney disease (estimated glomerular filtration rate < 60 mL/minute/m^2)

Journal of Stroke 2017;19(1):3-10

ICH score and 30-day mortality

Table 1. Determination of the ICH score

Component	ICH Score Points
GCS score	
3–4	2
5–12	1
13–15	0
ICH volume (cm^3)	
≥ 30	1
< 30	0
IVH	
Yes	1
No	0
Infratentorial origin of ICH	
Yes	1
No	0
Age (year)	
≥ 80	1
< 80	0
Total ICH Score	0–6



Journal of Stroke 2017;19(1):28-39

Location of ICH and prognosis

- Important for determination of outcome and potential Tx.
- Pontine hemorrhages - the highest mortality
- Superficial hemorrhages might be more amenable to surgical removal
- Bleeding from an ICH could extend into the ventricular system

  → **IVH** arise in ~ 40% of cases and predict a poor outcome

ICH location and outcome

		Death or major disability		Major disability		Death	
	No.	OR	95% CI	OR	95% CI	OR	95% CI
Caudate head	42	0.42	0.16-1.14	0.24	0.09-0.62[a]	2.19	0.77-6.26
Thalamus	640	2.24	1.40-3.57[b]	1.18	0.82-1.71	1.97	1.18-3.29[a]
Putamen/globus pallidus	1,161	1.36	0.87-2.14	0.86	0.60-1.22	1.11	0.68-1.82
External capsule	553	1.05	0.78-1.40	0.96	0.74-1.25	1.23	0.81-1.87
Anterior limb of internal capsule	102	1.03	0.56-1.91	1.00	0.59-1.71	0.94	0.45-1.97
Posterior limb of internal capsule	957	2.10	1.65-2.68[b]	1.81	1.45-2.26[b]	1.04	0.72-1.51
Lobar	297	1.34	0.86-2.08	0.61	0.43-0.88[a]	1.95	1.21-3.15[a]
Infratentorial	141	3.04	1.68-5.50[b]	1.27	0.77-2.11	2.45	1.09-5.50[c]

[a] $0.01 \leq p \leq 0.05$
[b] $0.001 \leq p < 0.01$
[c] $p < 0.001$

Neurology 2017;88:1408–1414.

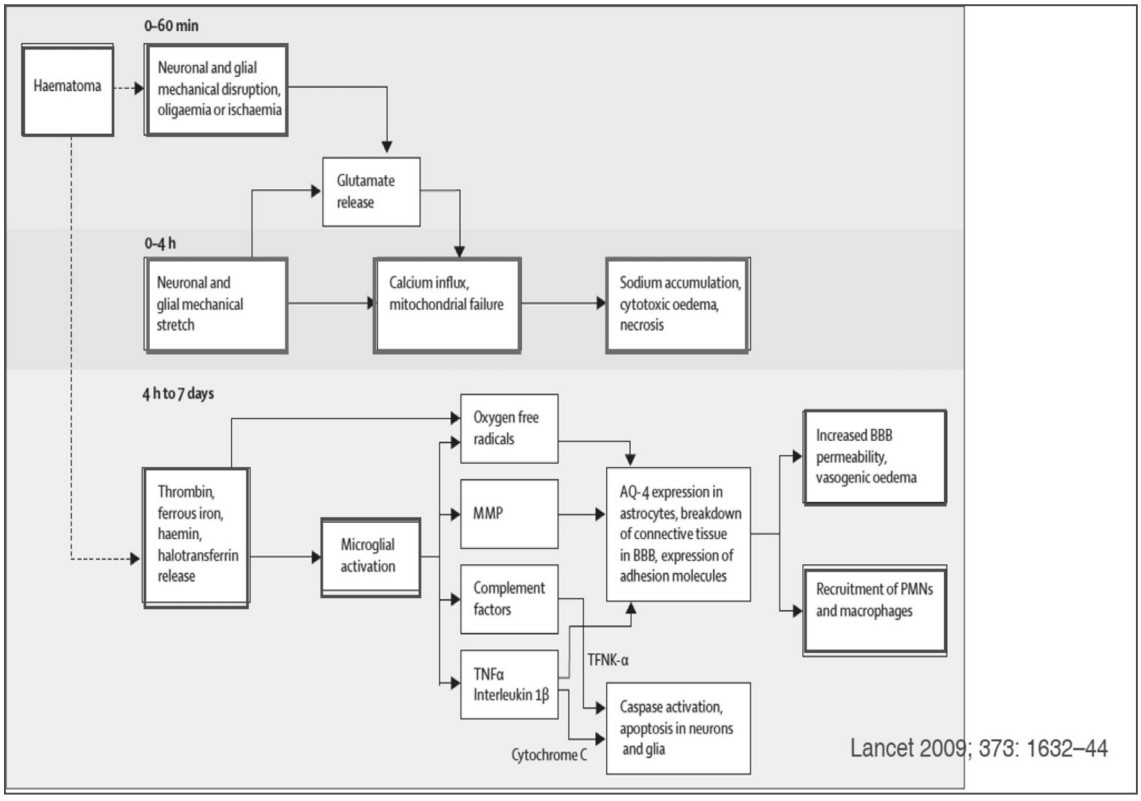
ICH location and outcome

		Utility score		Mobility		Self-care		Usual activity		Pain/discomfort		Anxiety/depression	
	No.	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Thalamus	181	1.63	1.00-2.66	1.04	0.63-1.73	1.13	0.68-1.88	1.75	1.04-2.95[a]	1.58	1.00-2.49[a]	1.43	0.90-2.29
Putamen	342	0.53	0.35-0.81[b]	0.53	0.35-0.80[b]	0.49	0.32-0.75[b]	0.67	0.43-1.03	1.08	0.74-1.58	0.70	0.47-1.04
Infratentorial	138	1.55	0.89-2.69	1.78	1.02-3.10[a]	1.27	0.72-2.25	1.86	1.06-3.26[a]	1.57	0.94-2.60	1.17	0.68-2.01
Lobar	181	0.55	0.33-0.91[a]	0.44	0.26-0.74[b]	0.43	0.25-0.73[a]	0.63	0.37-1.08	0.97	0.61-1.54	0.77	0.48-1.23
Thalamus and posterior limb of internal capsule	339	1.71	1.12-2.60[a]	1.55	0.99-2.43	2.08	1.34-3.22[a]	2.26	1.42-3.60[c]	1.78	1.21-2.62[b]	1.34	0.90-1.99
Putamen/globus pallidus and posterior limb of internal capsule	177	1.48	0.92-2.39	0.85	0.52-1.41	1.30	0.79-2.14	1.41	0.84-2.38	1.73	1.12-2.67[a]	1.60	1.03-2.49[a]

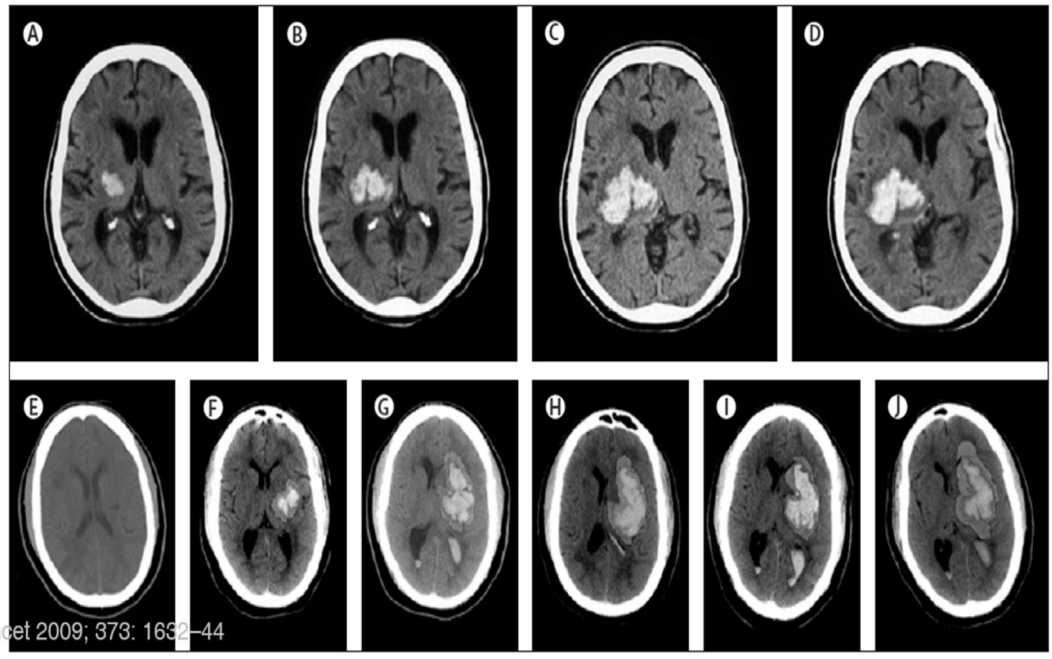
- Poor clinical outcomes -ICH affecting the posterior limb of internal capsule, thalamus, and infratentorial sites
- Death or major disability and poor EQ-5D utility score ← ICH encompassing the thalamus and posterior limb of internal capsule

Chronological change of ICH

Time	Macroscopic change	Microscopic change
Seconds		Rupture of vessel wall
Minutes	Hematoma (red color)	Blood leakage
< 1 hr	Space occlupying lesion Compression of surrounding tissue Structural distortion	Hemolysis
Several hours	Perihematoma edema & ischemia Mass effect	Brain edema/Cerebral ischemia/PMN infiltration
2-3 days ~ weeks	Brownish discoloration of hematoma	Hemosiderin formation Hemophagocytosis Astrocytes enlargement Neovascularization
Weeks ~ months	Fragile brownish hematoma	Phagocytosis of hematoma and necrotic tissue Organization of hematoma
Months ~ Years	Cavity formation including concentrated blood	Persistent absorption of hematoma
Months ~ Years	Cavity formation including clear fluid	Cavity surrounded by hypertrophic astrocytes



Progression of hematoma and edema on CT



Lancet 2009; 373: 1632–44

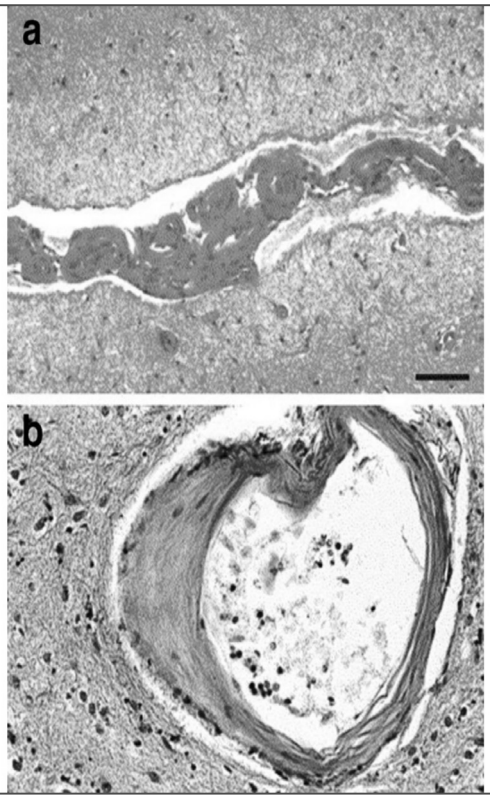
Pathophysiology of ICH

- Vessel rupture
- Initial hematoma growth
- Secondary hematoma expansion

Hematoma expansion

- Definition: relative (>33%) or absolute change (>12.5 mL) comparing with hematoma volume from initial to following CT slide
- Early HE occurs in 18–38% of patients scanned within 3 h of ICH onset
- >70% at least some extent of HE within the first 24 h without coagulopathy
- Independent predictor of early neurological deterioration and poor long-term clinical outcomes

N Engl J Med 2005;352:777-85



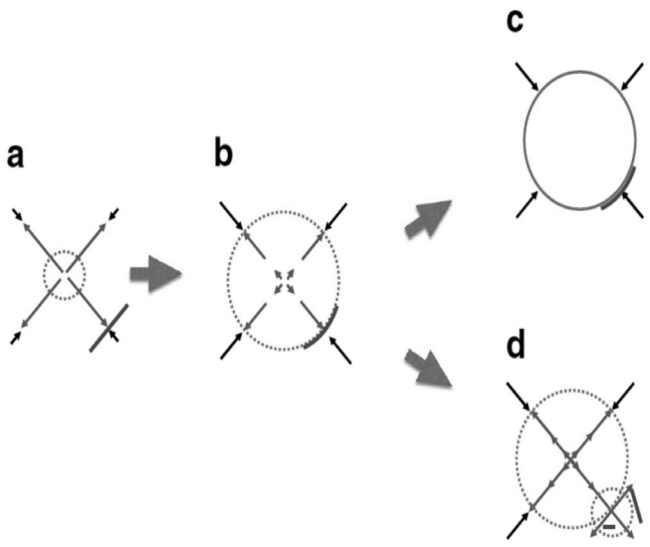
Vessel rupture

smooth muscle cell proliferation
→ Medial hyperplasia in a cerebral arteriole (a)

smooth muscle cell death
→ Collagenization of the tunica media (b)
→ Ectasia
→ Charcot-Bouchard aneurysm.

Transl. Stroke Res. (2015) 6:257–263

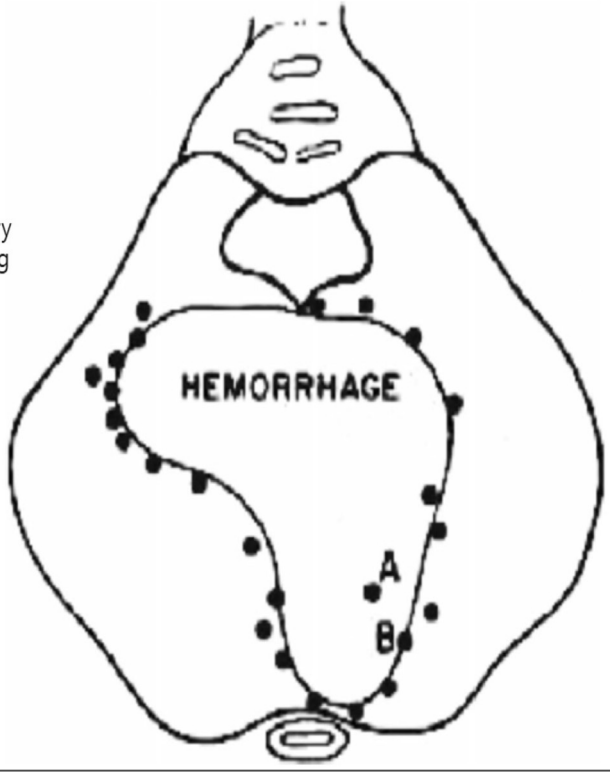
Initial hematoma growth



Transl. Stroke Res. (2015) 6:257–263

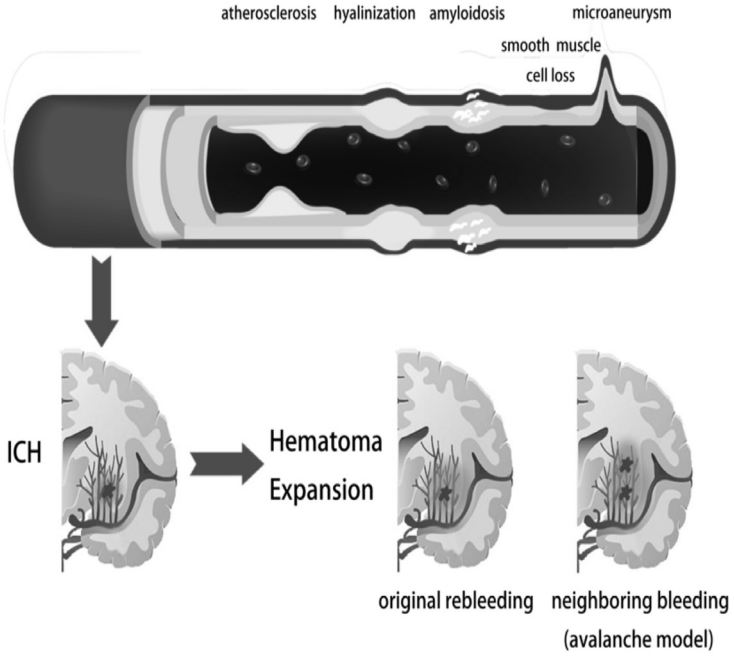
Secondary hemorrhage

bleeding arteries mainly lay in the boundary zone between hemorrhage and surrounding brain tissue.



Transl. Stroke Res. (2015) 6:257–263

Mechanism of ICH & hematoma expansion

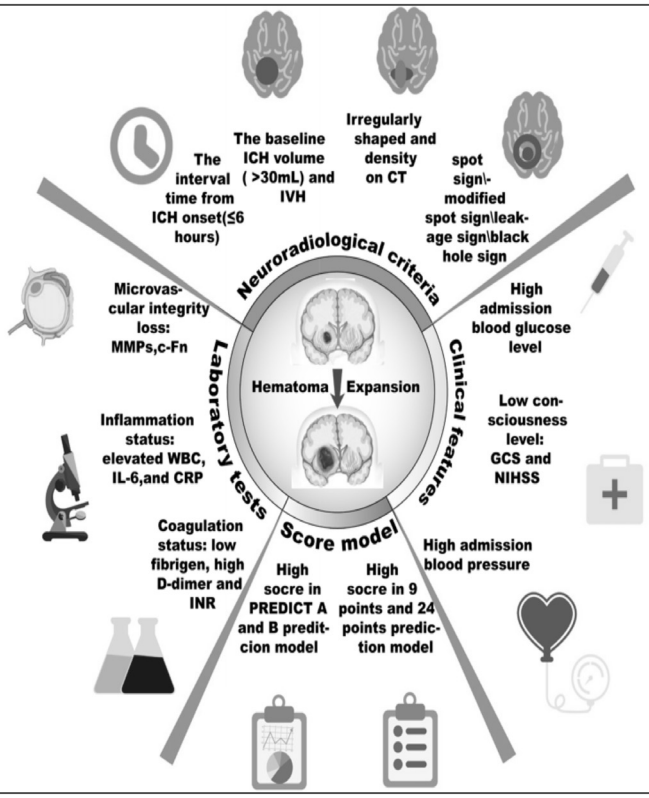


Mechanisms of hematoma expansion

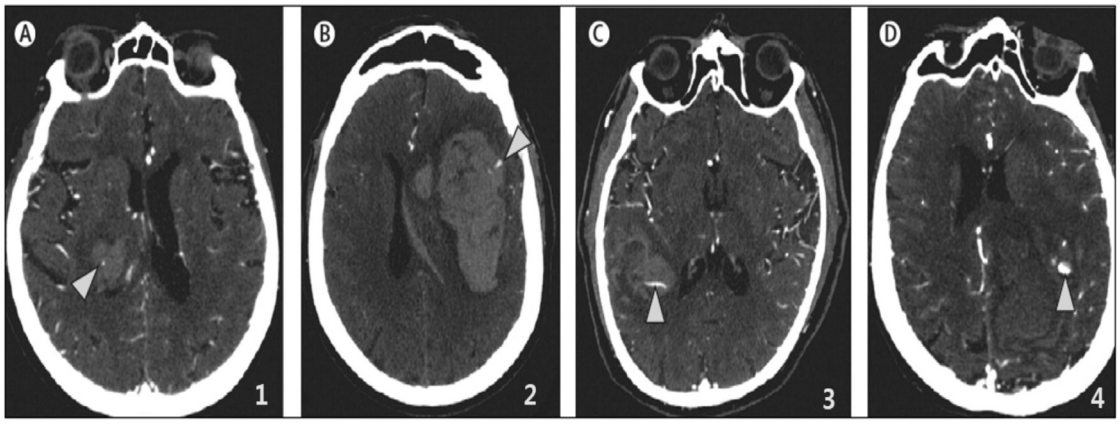
Early HE during the acute phase

- dysregulation of hemostasis via inflammatory cascade activation
- matrix metalloproteinase (MMP) overexpression
- breakdown of the blood–brain barrier
- a sudden increase in ICP leading to local tissue distortion and disruption
- vascular engorgement due to reduced venous outflow
- increased plasma concentration of cellular fibronectin (c-FN) and the inflammatory mediator IL-6

Scheme diagram of predictors for hematoma expansion after ICH



Contrast extravasation (spot sign)

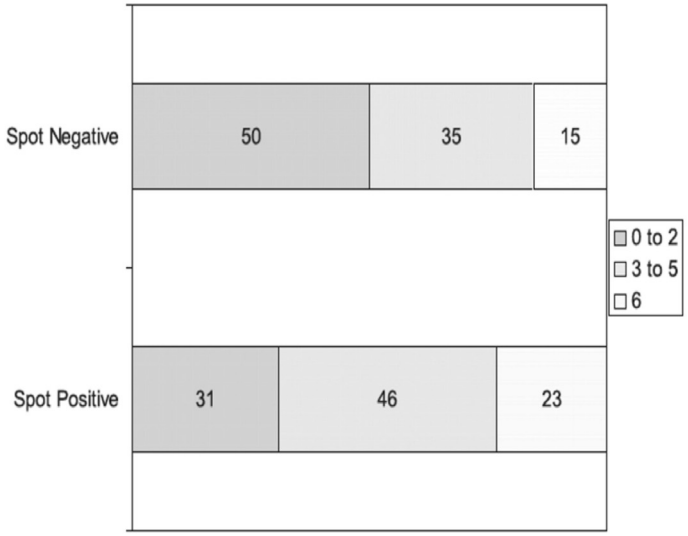


Lancet Neurol 2012; 11: 101–18

Spot-sign score

- Grade the number of spot signs and their maximum dimensions and attenuation
- Strongest predictor of HE
- Independent predictor of in-hospital mortality and poor outcome in people with ICH

Contrast extravasation (spot sign)



The computed tomography angiography spot sign is associated with the presence and extent of hematoma progression

Stroke. 2007;38:1257-1262

Black hole sign

(1) relatively hypoattenuated area (black hole) encapsulated within the hyperattenuating hematoma.

(2) The black hole could be round, oval, or rod-like but was not connected with the adjacent brain tissue.

(3) The relatively hypoattenuated area should have an identifiable border.

(4) The hematoma should have at least a 28 Hounsfield unit (HU) difference between the 2 density regions

Stroke . 2016;47:1777-1781

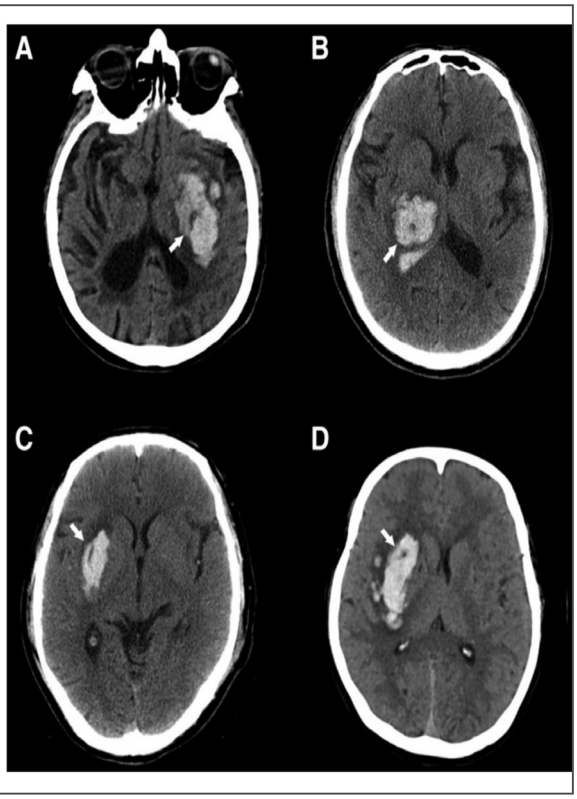


Table 2. Univariate Analysis of Predictors for Early Hematoma Growth

Variable	Odds Ratio	95% Confidence Interval	*P* Value
Age	1.01	0.99–1.04	0.291
Gender	0.62	0.33–1.17	0.139
Current smoking	1.21	0.68–2.16	0.519
Alcohol consumption	1.11	0.62–1.99	0.725
Hypertension	1.08	0.57–2.04	0.805
Systolic blood pressure	1.01	0.99–1.02	0.121
Diastolic blood pressure	1.01	0.99–1.03	0.346
Diabetes mellitus	1.32	0.54–3.22	0.544
Intraventricular hemorrhage	1.20	0.65–2.21	0.555
Glasgow Coma Scale score	0.857	0.79–0.94	0.001
Time to baseline CT	0.68	0.55–0.83	<0.001
Baseline ICH volume	1.08	1.05–1.11	<0.001
Black hole sign on baseline CT	7.55	3.15–18.11	<0.001

CT indicates computed tomography; and ICH, intracerebral hemorrhage.

Table 3. Multivariate Analysis of Predictors for Early Hematoma Growth

Variable	Odds Ratio	95% Confidence Interval	*P* Value
Glasgow Coma Scale score	0.95	0.86–1.06	0.371
Time to baseline CT	0.62	0.49–0.79	<0.001
Baseline hematoma volume	1.07	1.03–1.11	<0.001
Black hole sign on baseline CT	4.12	1.44–11.77	0.008

CT indicates computed tomography.

Blend sign

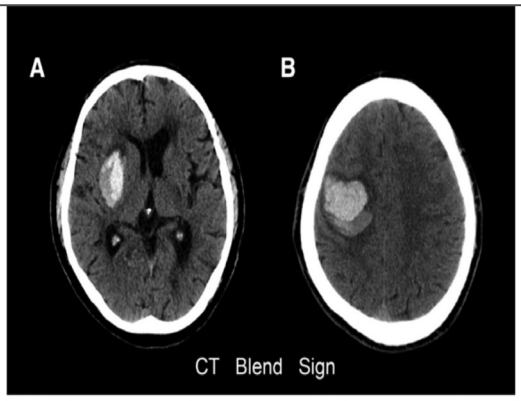
(1) blending of relatively hypoattenuating area with adjacent hyperattenuating region within a hematoma

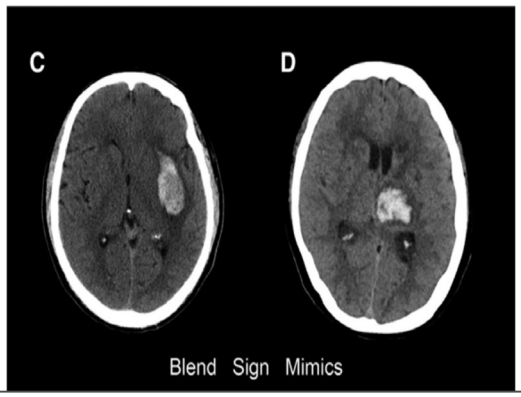
(2) there is a well-defined margin between the hypoattenuating area and adjacent hyperattenuating region that is easily recognized by the naked eye

(3) the hematoma should have at least a 18 Hounsfield unit difference between the 2 density regions

(4) the relatively hypoattenuating area was not encapsulated by the hyperattenuating region

Stroke. 2015;46:2119-2123





Blend sign

Table 3. Univariate Analysis of Predictors for Early Hematoma Growth

Variable	Odds Ratio	95% Confidence Interval	*P* Value
		0.99–1.05	0.164
		0.29–1.17	0.126
		0.34–1.20	0.166
		0.54–1.88	0.992
		0.41–1.58	0.527
		0.99–1.02	0.153
		0.98–1.03	0.415
		0.34–2.06	0.693
		0.40–1.55	0.48
Time to baseline CT	0.61	0.47–0.78	<0.001
Baseline ICH volume	1.06	1.03–1.09	<0.001
Blend sign on baseline CT	13.75	4.89–38.66	<0.001

ICH indicates intracerebral hemorrhage; and CT, computed tomography.

Table 4. Multivariate Analysis of Predictors for Early Hematoma Growth

Variable	Odds Ratio	95% Confidence Interval	*P* Value
Time to baseline CT	0.46	0.32–0.66	<0.001
Baseline hematoma volume	1.06	1.02–1.09	<0.001
Blend sign on baseline CT	20.23	5.13–79.77	<0.001

CT indicates computed tomography.

The BAT score

Table 4. Individual Components of the BAT Score

Variable	Points
Blend sign	
Present	1
Absent	0
Any hypodensity	
Present	2
Absent	0
Time from onset to NCCT	
<2.5 h	2
≥2.5 h or unknown	0

NCCT indicates noncontrast computed tomography.

Stroke . 2018;49:1163-1169

Table 5. Hematoma Expansion Rate by BAT Score

	Hematoma Expansion, n (%)		
	Development Cohort	Validation Cohort No. 1	Validation Cohort No. 2
C-statistics (95% CI)	0.77 (0.70–0.83)	0.65 (0.61–0.68)	0.70 (0.64–0.77)
Score			
0–1	14/193 (7.3)	15/145 (10.3)	3/46 (6.5)
2	17/90 (18.9)	114/541 (21.1)	18/83 (21.7)
3	10/22 (45.5)	14/44 (31.8)	8/17 (47.1)
4	18/35 (51.4)	74/192 (38.5)	26/65 (40.0)
5	3/4 (75.0)	19/32 (59.4)	16/30 (53.3)
Dichotomized			
<3	31/283 (11.0)	129/686 (18.8)	21/129 (16.3)
≥3	31/61 (50.8)	107/268 (39.9)	50/112 (44.6)
Dichotomized test characteristics (95% CI)			
Sensitivity	0.50 (0.37–0.63)	0.45 (0.38–0.51)	0.70 (0.58–0.81)
Specificity	0.89 (0.85–0.93)	0.78 (0.74–0.81)	0.64 (0.56–0.71)
PPV	0.51 (0.38–0.64)	0.40 (0.34–0.46)	0.45 (0.35–0.54)
NPV	0.89 (0.85–0.92)	0.81 (0.78–0.84)	0.84 (0.76–0.90)
Overall accuracy	0.82 (0.78–0.86)	0.70 (0.66–0.72)	0.66 (0.59–0.72)

CI indicates confidence interval; NPV, negative predictive value; and PPV, positive predictive value.

Important predictors of hematoma expansion

- Large hematoma volume on presentation
- Early presentation (especially within 3 h of onset)
- Heterogeneity of hematoma density on admission CT
- Prior use of warfarin
- Blood biomarkers
  - -increased IL-6, MMP-9, c-FN, and tumor necrosis factor
  - -reducedplatelet activity, reduced fibrinogen concentrations
  - -increased serum creatinine
- Controversial –D-dimer, systolic BP, prior use of antiplatelet drugs

Lancet Neurol 2012; 11: 101–18

Putative risk factors for early hematoma growth

1. Shorter time from symptom onset to first CT
2. Large hematoma size; hematoma volume on first CT <25 mm3
3. Irregular hematoma shape
4. Mean arterial blood pressure (MAP) >120 mm Hg; SBP ≥200 mm Hg; highest SBP
5. GCS score ≤8; the presence of consciousness disturbance
6. History of cerebral infarction
7. Liver disease
8. Fasting plasma glucose ≥141 mg/dl and hemoglobin A1c ≥5.1%; hyperglycemia
9. Hypocholesterolemia
10. Alcohol consumption (46.3 g/d);
11. Reduced fibrinogen level (<87 mg/dl); elevated serum fibrinogen levels>523 mg/dl
12. Body temperature>37.5 °C;
13. Neutrophil count (by 1000-unit increase);
14. Intraventricular hemorrhage
15. Admission cellular fibronectin level >6 μg/ml, admission interleukin-6 level >24 pg/ml

J Neuro Sci2007;261: 99–107.

Hematoma growth is a determinant of mortality and poor outcome after ICH

- A meta-analysis of 218 patients with ICH
- CT scans within 3 h of onset and follow-up scans within 24 h
- Every **10% increase in ICH** growth
- 5% increased risk of **death**
- 16% increased risk of **worsening outcome**as measured with the mRS
- 18% increased likelihood of **being dependent or of a poor outcome** on the Barthelindex

Neurology 2006; 66: 1175–81.

Perihematomal edema

- Increased mass effect and END
- Edema volume can exceed that of the original hematoma
  → Predictor of poor functional outcome and mortality
- PHE develops early in the hyperacutephase (increasing in volume by 75% in the first 24 h)
  → evolves over many days
  → increases strongly during the first week
  → reaches maximum during the second week

Cerebrovasc Dis 2016;42:155–169.
Lancet Neurol 2012;11:720–

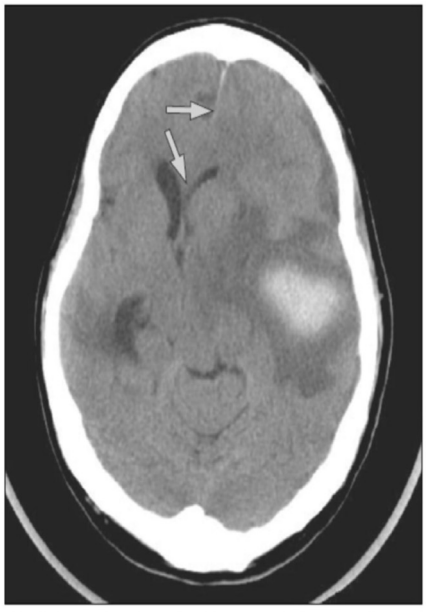


Figure 1: CT scan of a patient with perihaematomal oedema (hypodensity zone) 14 days after intracerebral haemorrhage

Mechanism of PHE

- Hyperacutefirst phase (immediately)
  → Vasogeniceffect of pro-osmotic substances (protein, electrolytes) from the clot; development of hydrostatic pressure during hematoma formation and clot retraction □ leakage of serum proteins from the clot into the surrounding tissue
- Second phase (a few days post ictus)
  →Activation of the coagulation cascade and thrombin production
- Third, delayed PHE (days~ weeks post ictus)
  → Erythrocyte lysis and haemoglobin-mediated toxic effects caused by the iron-catalyzed production of reactive oxygen species

Lancet Neurol 2012;11:101–18

Factors related with PHE

- Hyperglycemia
- Coagulation factors
- increased serum concentrations of MMP-9
- persistently increased SBP

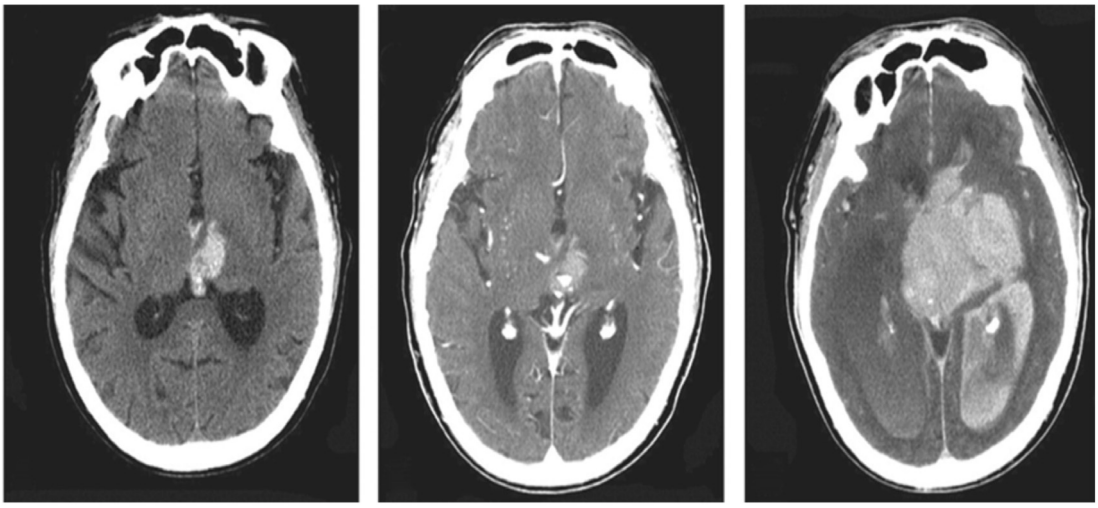
Effect of PHE on clinical outcome and mortality

- Unclear -poor outcome vs. no clear association
- Absolute edema volume growth-decrease in neurological status at 48 h after ICH, but not with 3 month functional outcome
- The INTERACT trial

  → both absolute and relative growth in PHE volume were associated with mortality or dependency at 90 days after adjustment for age, sex, and randomized treatment, but not when further adjusted for baseline hematoma volume

Neurology 2009;73:1963–68

Intraventricular extension of hemorrhage & hydrocephalus



Lancet Neurol 2012; 11: 101–18

Intraventricular extension of hemorrhage & hydrocephalus

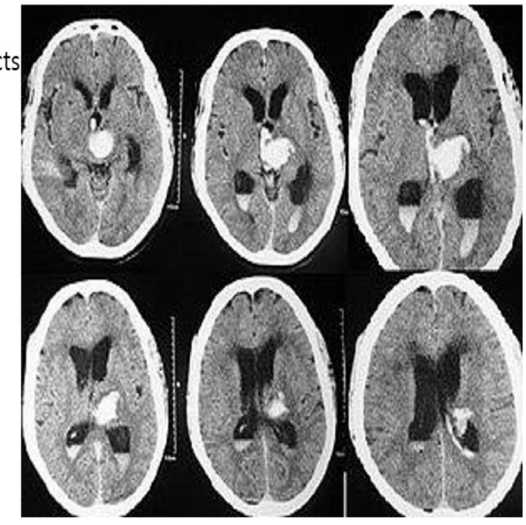
- Extension of hemorrhage into the ventricles can impede normal CSF flow and, with direct mass effects of ventricular blood

  → acute obstructive hydrocephalus

- Acute hydrocephalus

~50% of patients with IVH secondary to ICH due to obstruction of 3rd & 4th ventricle

- more common in patients with high IVH volume (Graebscore ≥6)
- more with thalamic than with putaminal, almost absent in lobar hemorrhages



BMC Neurol. 2007; 7: 1.

Graeb score

- Components
- **Each lateral ventricle**
  1: trace of blood
  2: less than 50% filled
  3: more than 50% filled
  4: completely filled and expanded
- **3rd and 4th ventricles**
  0: no blood
  1: blood present, size normal
  2: filled with blood and expanded

J Neurosurg. 2012;116(1):185-92

Graeb score = scores of (right ventricle + left ventricle + 3rd ventricle + 4th ventricle

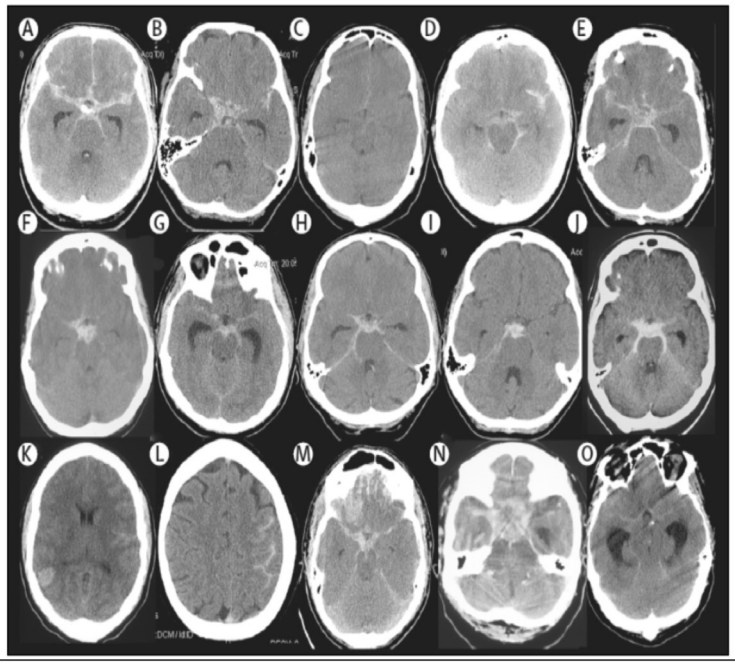
IVH and hydrocephalus after s-ICH (STICH trial)

- Favorable outcomes -more frequent when IVH absent
  (31.4% vs. 15.1%; p < 0.00001)
- Presence of hydrocephalus -11.5% lowered favorable outcome
  (p = 0.031)
- Presence of IVH + hydrocephalus -independent predictors of poor outcome
- In IVH -more favorable outcome in early surgical intervention (17.8%) vs. conservative management (12.4%) (p = 0.141)

Acta Neurochir Suppl 2006;96:65–68

Subarachnoid hemorrhage

Lancet 2017; 389: 655–66



Epidemiology

- Incidence of SAH in population-based studies, including out-of-hospital deaths
  - 9.1/100 000 people per year (95% CI 8.8–9.5)
- Finland (19.7 cases per 100 000 people per year, 18.1–21.3)
- Japan (22.7 cases per 100 000 people per year, 21.9–23.5)

- Spontaneous cases

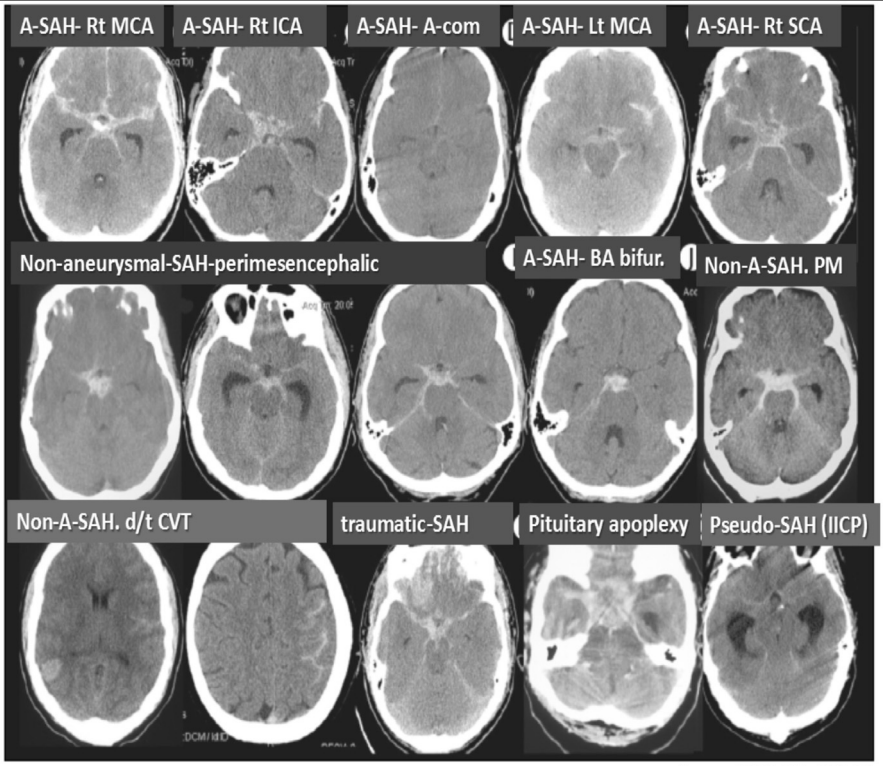
  : **85% are aneurysmal**/ 10% are non-aneurysmal perimesencephalic /

  5% -diverse causes

Different types of SAH

Criteria for NAPM- SAH

- SAH in peri-mesencephalic cisterns anterior to midbrain
- If, SAH extension into the anterior interhemispheric fissure, not extending into all of the fissure
- If, SAH extension into the medial Sylvian fissures, not extending into the lateral fissure
- If layering interventricular extension, no frank IVH
- No intraparenchymal hemorrhage



Lancet 2017; 389: 655–66

Causes of SAH

Category	Causes
1. Idiopathic	Nonaneurysmal perimesencephalic SAH
2. Infections	Bacterial, tuberculous, and fungal meningitis, syphilis, herpes simplex or other viral encephalitis, leptospirosis, listeriosis, brucellosis, yellow fever, typhoid fever, dengue, malaria, anthrax
3. Trauma	Closed head injury, electrical injury, gunshot wounds and other penetrating cranial trauma, heat injury, strangulation, high altitude, caisson disease, radiation, germinal matrix haemorrhage in neonates
4. Toxins	Amphetamines, cocaine, monoamine oxidase inhibitors, epinephrine, alcohol, ether, carbon monoxide, morphine, nicotine, lead, quinine, phosphorus, pentylenetetrazol, hydrocyanic acid, insulin, snake venoms
5. Vascular	Intracranial saccular, fusiform or dissecting aneurysm, reversible cerebral vasoconstriction syndrome, rupture of hypertensive, amyloid or other type of intracerebral haemorrhage into the cerebrospinal fluid, hemorrhagic transformation of ischemic infarction, ruptured arteriovenous or other vascular malformation, vasculitis from systemic lupus erythematosis, polyarteritis nodosa or other cause, eclampsia, intracranial venous thrombosis, oral contraceptives, volume depletion, hypercoagulable states, trauma, infection
6. Blood diseases	Leukaemia, hemophilia, sickle cell anaemia, pernicious anaemia, aplastic anaemia, agranulocytosis, thrombocytopenic purpura, polycythaemia vera, Waldenström's macroglobulinaemia, lymphoma, myeloma, hereditary spherocytosis, afibrinogenaemia, liver diseases associated with coagulopathy, disseminated intravascular coagulation, acquired coagulopathies due to anticoagulant drugs, other congenital or acquired platelet vessel or coagulation disorders
7. Neoplasms	Glioma, meningioma, hemangioblastoma, choroid plexus papilloma, chordoma, hemangioma, pituitary adenoma, sarcoma, osteochondroma, ependymoma, neurofibroma, schwannoma, bronchogenic carcinoma, choriocarcinoma, melanoma, numerous other cranial and spinal tumors

http://dx.doi.org/10.1016/S0140-6736(16)30668-7

Risk factors

- Peaks between age 50 and 60 years
- 1.6times more common in women than man (only after 5th decade)
  - Maybe Protective effects of estrogen ?

- Risk factors are similar in Unruptured aneurysm, rupture of aneurysm, &SAH
  - **Smoking (↑)**
  - **Hypertension (↑)**
  - Alcohol intake (↑)
  - Regular physical exercise (↓), but high intensity exercise (↑ SAH)
  - hypercholesterolemia (↓)
  - Unmodifiable – **increased age (↑)**/ Female sex (↑)/ Family Hx (↑) / **ADPKD (↑)**
  - Aneurysm location/size/ shape/growth/ Hx. of SAH

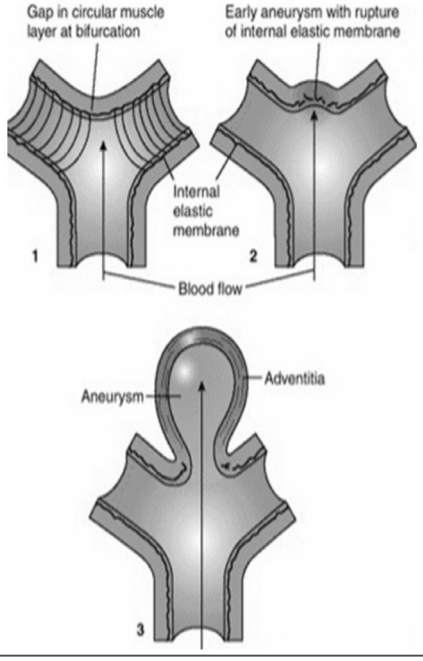
Pathophysiology

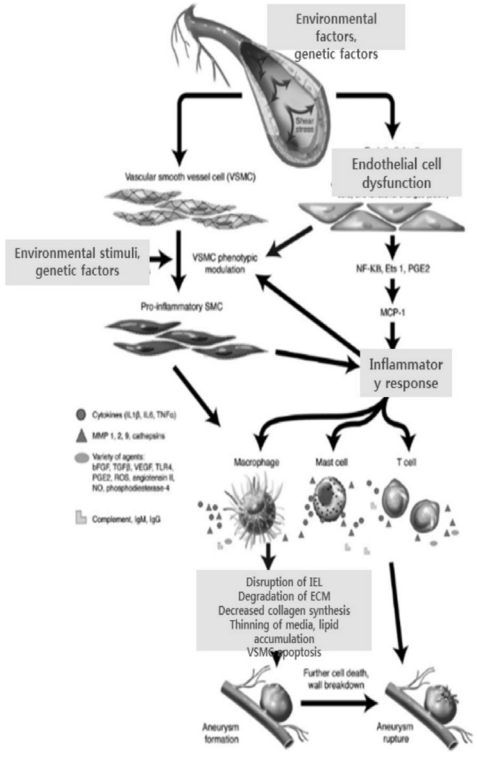
- Saccular cerebral aneurysm

  - Acquired lesions that develop at branch points of major arteries of the circle of Willis

  - Develop in response to hemodynamic stress-induced degeneration of the internal elastic lamina with secondary thinning and loss of the tunica media

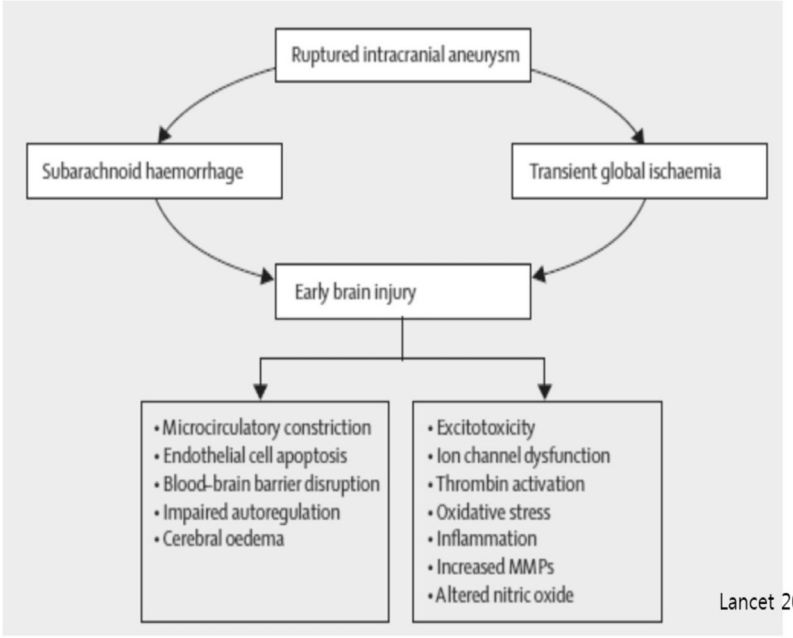
- average size of a **ruptured aneurysm is 6–7 mm**



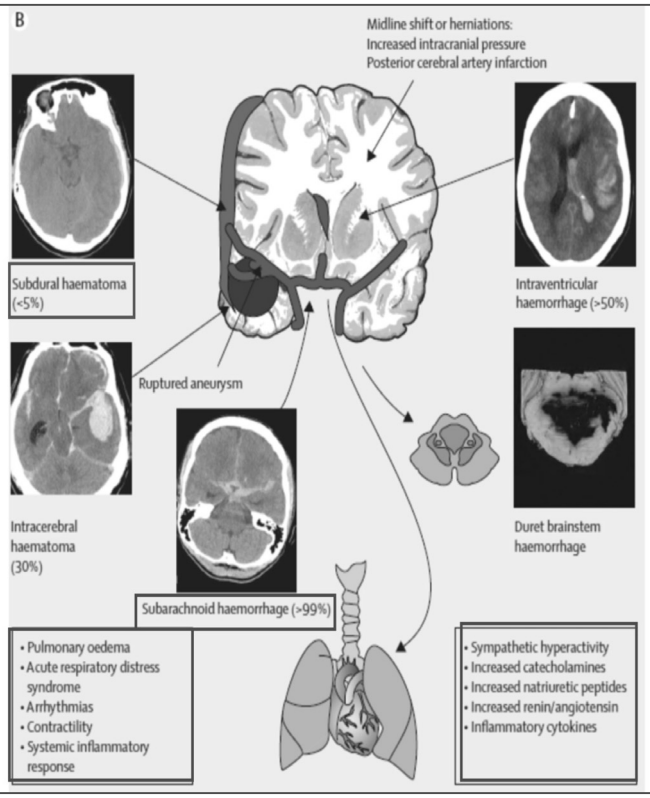


Journal of Cerebral Blood Flow & Metabolism
2012; 32: 1659-1676

Pathophysiology



Lancet 2017; 389: 655–66



Lancet 2017; 389: 655–66

Diagnosis - symptom

- **Sudden onset** of the "**most severe headache of a person's life**"
- 70% of patients present with HA, which is of **sudden onset in 50%** (thunderclap HA, defined as reaching maximum severity within 1 min of onset)
- **"Sudden onset"** is a more important than "**severity"**
- Nausea, vomiting, transient or ongoing loss of consciousness, or focal neurological deficits
- 56 (12%) of 482 patients with SAH 1996 and 2001 were initially misdiagnosed

JAMA 2004; 291: 866–69

Ottawa SAH rule

- age ≥40 years
- neck pain or stiffness
- witnessed loss of consciousness
- onset of headache during exertion
- instantaneous onset of headache
- limited neck flexion on examination

→Diagnosis with a **sensitivity of 100%** (95% CI 97–100%)
& a specificity of 15% (14–17%)

Diagnosis - non-contrast CT

- Diagnostic test of choice

- A prospective multicenter study assessed CT scans on 3132 neurologically normal patients reaching maximum severity within 1 h

  - 953 patients scanned **within 6 h, the sensitivity** of CT for SAH **was 100%,**

    but declined with increasing time from headache onset

- Multi-detector CT scanners

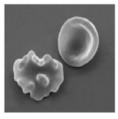
  - In the **first 72 h**, sensitivity is **>97%**, only 50% after 5 days

Diagnosis – Lumbar puncture

- support the diagnosis of SAH if erythrocytes or **xanthochromia** in the CSF
- If, CT scan does not result in a definitive diagnosis→ lumbar puncture is recommended
- But,, T-tap…
- If SAH cannot be excluded , a CT angiogram can be useful to exclude an aneurysm

http://dx.doi.org/10.1016/S0140-6736(16)30668-7

Differentiating SAH from traumatic lumbar puncture



Criteria	SAH	Traumatic puncture
Erythrocyte count	No change from first to subsequent tubes, some suggest > 5 x 10^6 erythrocytes/L although any erythrocytes are technically abnormal	Decreasing number of erythrocytes, although no specific decline has been shown to rule out SAH
Clotting	Does not clot	May clot
Xanthochromia, free hemoglobin, bilirubin [33]	Present > 12 hours after ictus in supernatant fluid of a centrifuged tube that has been kept refrigerated in the dark, processed expeditiously and subjected to spectrophotometry, free hemoglobin > 0.04 AU, bilirubin > 350 nmol/L	No xanthochromia, free hemoglobin < 0.04 AU, bilirubin < 350 nmol/L
Crenated erythrocytes	Present	Absent
Erythrocyte / leucocyte ratio	May be decreased due to inflammation	Same as peripheral blood
D-dimer	Present	Absent
Protein	May be increased	Normal in relation to number of erythrocytes
Hemosiderin-laden macrophages	Present weeks after an SAH	Not present
Cerebrospinal fluid pressure	Normal or increased in 60% of cases	Normal
Repeat lumbar puncture	SAH	Usually clear

Diagnosis – MRI and MRA

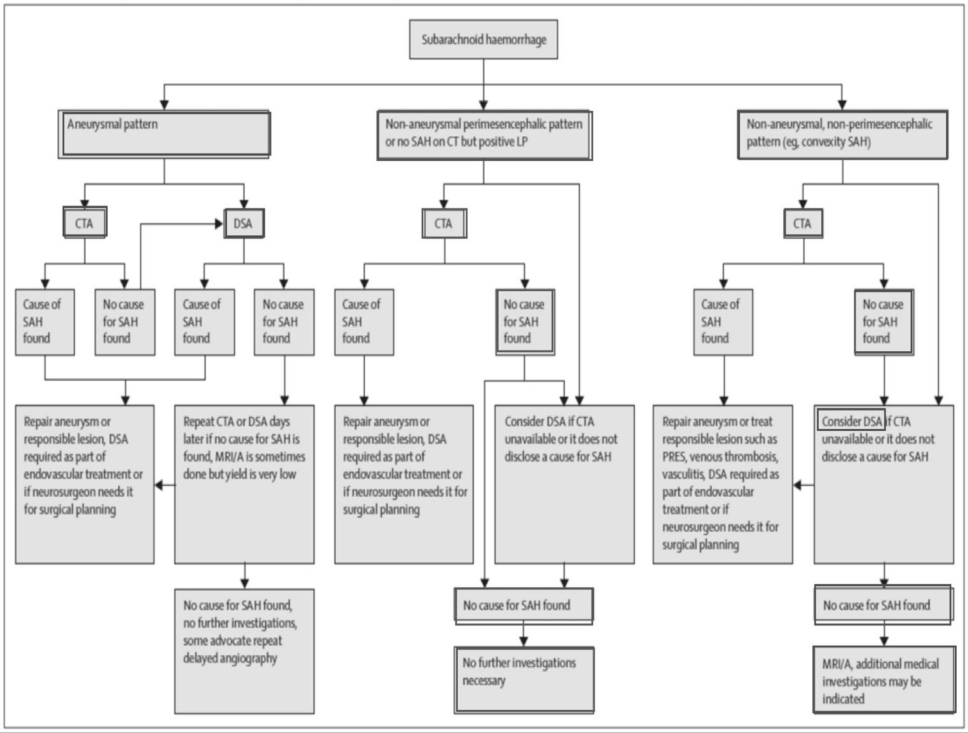
- Detection of aneurysms: sensitivity was 95% (95% CI 89–98)
  & pooled specificity was 89% (80–95)

- Hemosiderin-sensitive MRI sequences, such as GRE T2*-weighted and SWI
  - useful to detect SAH in patients who present weeks after a possible hemorrhage

- Other usage
  - investigation of SAH with unknown cause
  - follow-up of coiled aneurysms to assess for recanalization
  - Research method to examine brain structure and function after SAH

Algorithm for investigation of patients with SAH with CT or lumbar puncture

Lancet 2017; 389: 655–66



Clinical course of SAH

Causes of neurological deterioration after SAH

Neurological	
Secondary to SAH	Delayed cerebral ischaemia
	Hydrocephalus
	Rebleeding
	Seizures
	Intracranial haematoma (subdural, intracerebral)
	Cerebral oedema/increased intracranial pressure
	Enlargement/thrombosis of aneurysm

Postoperative complications	Major arterial occlusion
	Venous infarction
	Perforator injury
	Intracranial haematoma
	Cerebral oedema/increased intracranial pressure
	Retraction injury
	Hypotension, hypoxic brain injury
	Aseptic or infectious meningitis
	Seizures
Complications of angiography	Thromboembolism

http://dx.doi.org/10.1016/S0140-6736(16)30668-7

Clinical course of SAH

Causes of neurological deterioration after SAH

Systemic	
Systemic infection	
Hepatic, renal failure	
Drugs	Corticosteroids
	Sedation
	Alcohol withdrawal
Other drug reactions	Anticonvulsants
Metabolic	Hyponatraemia, syndrome of inappropriate antidiuretic hormone, cerebral salt wasting
	Hypernatraemia, diabetes insipidus
	Metabolic acidosis or alkalosis
	Hypocalcaemia
	Hypomagnesaemia

Pulmonary	Hypoxaemia
	Respiratory acidosis or alkalosis
	Venous thromboembolism
Cardiovascular	Hypotension
	Hypertension
	Arryhthmias
	Takotsubo cardiomyopathy/low cardiac output

http://dx.doi.org/10.1016/S0140-6736(16)30668-7

Prognosis of SAH

- Short term outcome
  - **overall case fatality of 8.3–66.7**% in patients with SAH
    - 55% of patients regain independent function
    - 19% remain dependent
    - 26% die

Lancet Neurol 2009; 8: 635–42

- Absolute annual reduction rate in 30 day mortality of 0.9% (95% CI 0.3–1.5) between 1980 and 2005, for an **overall 50% reduction**

Neurology 2010; 74: 1494–501

Factors at hospital admission associated with **unfavorable outcome**

- Glasgow outcome score
- modified Rankin score
- worse admission neurological condition
- older age
- aneurysm repair by clipping rather than coiling
- more severe SAH on CT scan
- history of hypertension
- Larger aneurysm
- posterior circulation aneurysm

Only 25% of the outcome explained by these variables

Other factors (genetic, epigenetic, disease-related factors…) have substantial effect on outcome

Neurocrit Care. 2013;18(1):143-53

Stroke 2010;41: e519–36.
Lancet Neurol 2011; 10: 349–56.
Stroke 2015; 46: 1813–18.

Prognosis of SAH

Long term outcome of survived SAH pts.

- Continue to have the deficits in cognition, quality of life, mood, and fatigue

- **15 times higher risk** of a second hemorrhagic event than general population

→ Long-term standardized mortality ratio is **1.5**, in excess of the general population,

(C.O.D.- Cardio-V and Cerebro-VD)

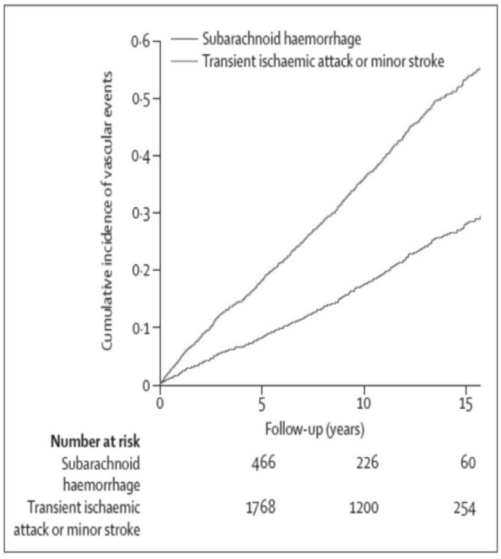


Figure 2: Age and sex-adjusted cumulative incidence of vascular events after aneurysmal subarachnoid haemorrhage and transient ischaemic attack or minor ischaemic stroke

Cerebral Venous Thrombosis

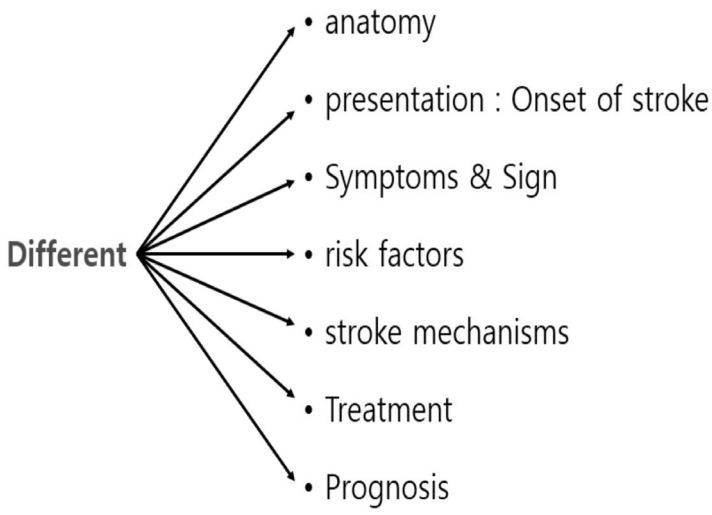
Epidemiology

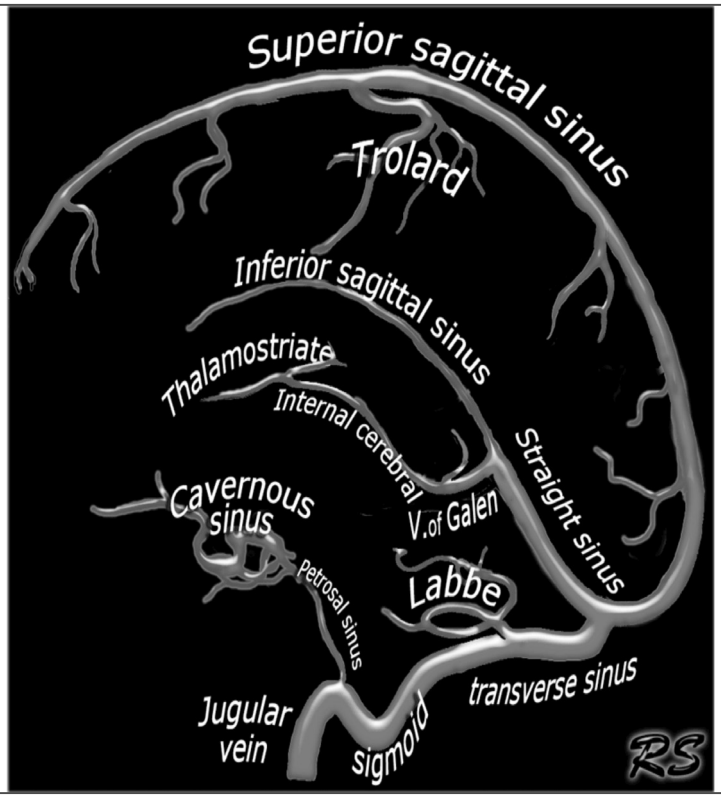
- 0.5% of all stroke

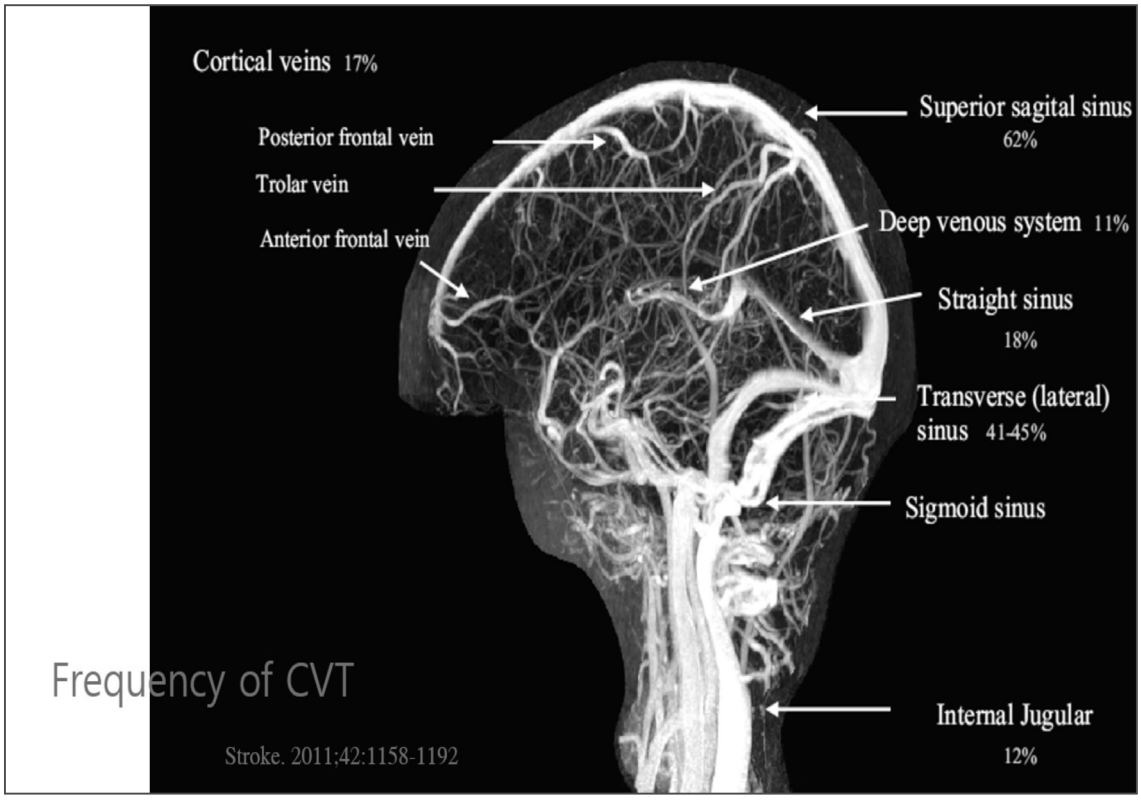
- 70% of total cerebral blood volume in cerebral vein
- 1000 times less often than arterial stroke

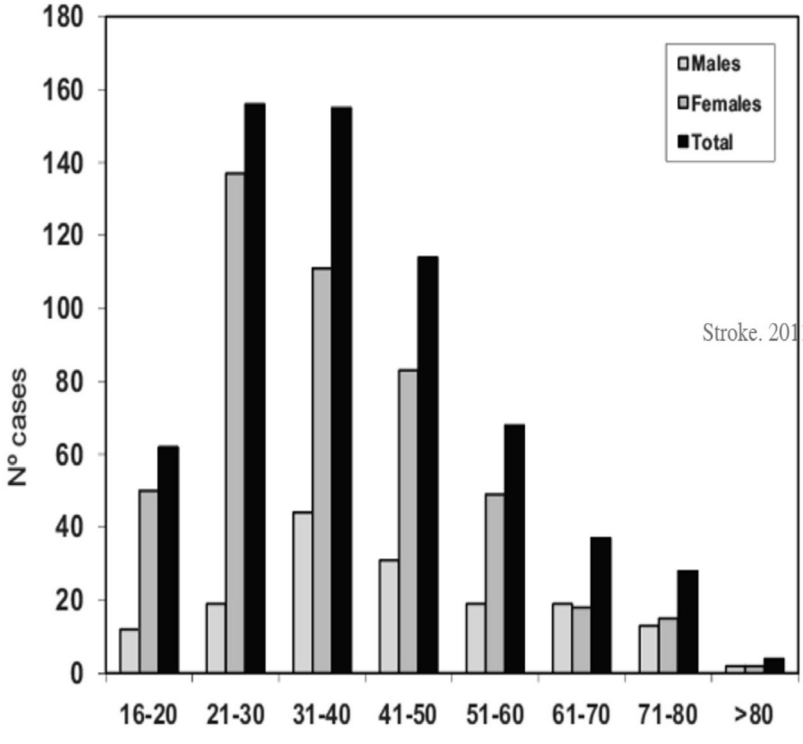
- 3-4 case/ 1 milion
- Young adults
- 3:1 female dominance

Different Stroke




Superior sagittal sinus
Trolard
Inferior sagittal sinus
Thalamostriate
Internal cerebral
Straight sinus
Cavernous sinus
V.of Galen
Petrosal sinus
Labbe
Jugular vein
sigmoid
transverse sinus
RS


Cortical veins 17%
Posterior frontal vein
Trolar vein
Anterior frontal vein
Superior sagital sinus 62%
Deep venous system 11%
Straight sinus 18%
Transverse (lateral) sinus 41-45%
Sigmoid sinus
Internal Jugular 12%
Frequency of CVT
Stroke. 2011;42:1158-1192



Stroke. 2011;42:1158-1192

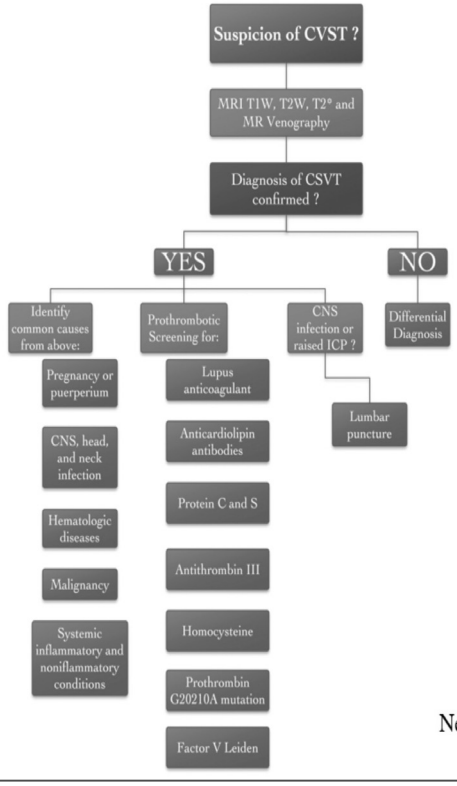
Causes and Risk factors

Genetic Prothrombotic States	Hematology
antithrombin deficiency	polycythemia
protein C and S deficiency	thrombotic thrombocytopenic purpura
resistance to activated protein C	thrombocythemia
factor V Leiden mutation	severe anemia and autoimmune hemolytic
prothrombin mutation (A–G at position 20210)	anemia
methylenetetrahydrofolate reductase (MTHFR)	paroxysmal nocturnal hemoglobinuria
mutations leading to homocysteinemia	heparin-induced thrombocytopenia
Acquired Prothrombotic States	**Drugs**
pregnancy	oral contraceptives
puerperium	lithium, androgens
homocysteinemia	sumatriptan
antiphospholipid antibody	intravenous immunoglobulin
nephrotic syndrome	hormone replacement therapy
	asparaginase
	steroids
	illicit drugs (such as ecstasy)
Infection	**Mechanical Causes**
meningitis	head trauma
otitis	neurosurgical procedures
mastoiditis	jugular vein catheterization
sinusitis	lumbar puncture
neck, face, mouth infection	injury to cerebral sinuses
systemic infectious diseases	intravenous drug abuse
AIDS	
Inflammatory and Autoimmune Diseases	**Other Causes**
systemic lupus erythematosus	dehydration, especially in children
Adamantiades-Behçet disease	thyrotoxicosis
Wegener granulomatosis	arteriovenous malformations
sarcoidosis	dural fistulae
inflammatory bowel disease	congenital heart disease
thromboangiitis obliterans	postradiation
Malignancy	
CNS tumors	
systemic malignancies	
solid tumors outside CNS	

Neurosurg Focus 27 (5):E3, 2009

Pathology

- BBB disruption
- Vasogenic edema
- Cytotoxic edema due to reduced capillary perfusion pressure
- Obstructive hydrocephalus
- Perivascular hemorrhage
- Ischemic venous infarction



Neurosurg Focus 27 (5):E3, 2009

Panel 1: Presenting symptoms of CVT

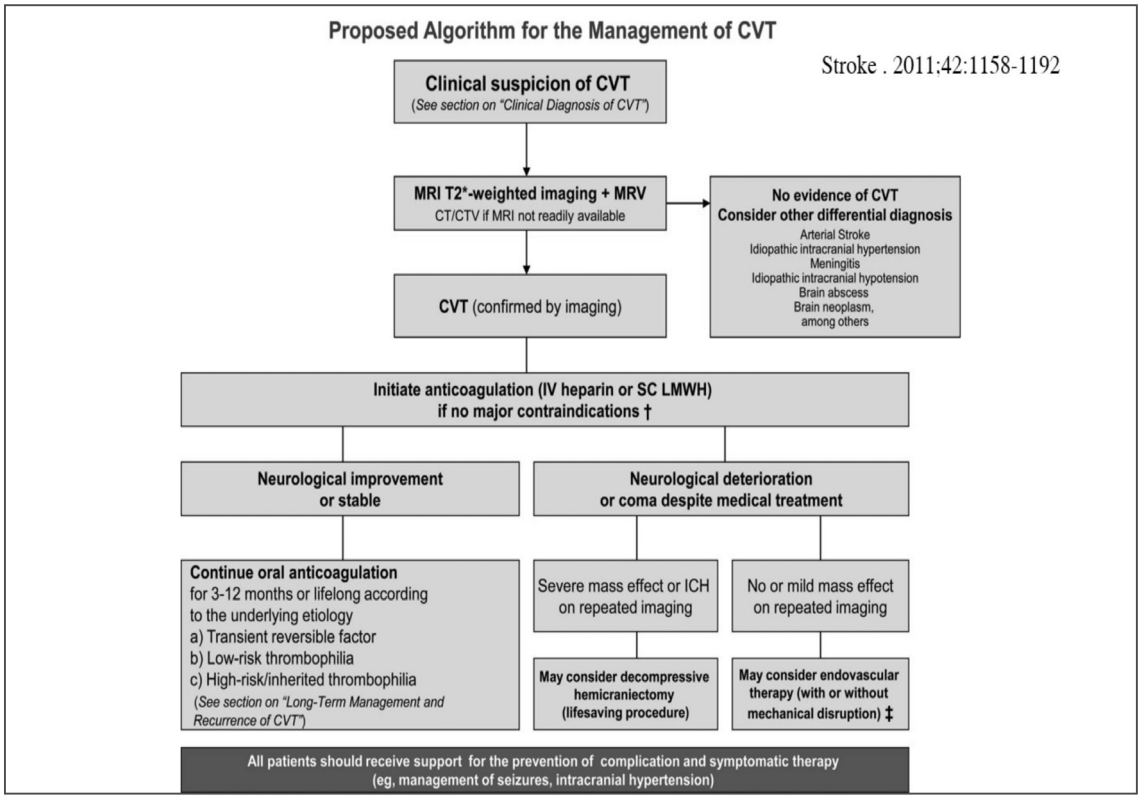
Common symptoms

Isolated intracranial hypertension
Focal syndrome (deficit and/or seizure)
Diffuse encephalopathy
Any combination of the above

Rare symptoms

Cavernous sinus syndrome
Subarachnoid haemorrhage
Thunderclap headache
Attacks of migraine with aura
Isolated headache
Transient ischaemic attacks
Tinnitus
Isolated psychiatric symptoms
Isolated or multiple cranial nerve palsies

Lancet Neurol 2007;6:162–70



Panel 2: Summary of CVT treatment following European Federation of Neurological Societies guidelines[65]

Antithrombotic treatment

Acute phase

No contraindication for anticoagulation:

- Body-weighted subcutaneous low-molecular-weight heparin in full therapeutic dosage or APPT (two times above normal values) dose-adjusted intravenous heparin

Worsening despite best medical treatment, other causes of deterioration excluded:

- Local intravenous thrombolysis*, or mechanical thrombectomy*

Prevention of recurrent thrombotic events with oral anticoagulants

CVT related to a transient risk factor, 3–6months

Idiopathic CVT or related to mild hereditary thrombophilia, 6–12 months

Recurrent CVT or severe hereditary thrombophilia, indefinite

Symptomatic treatment

Antiepileptics

Acute phase

- Patients with acute seizures
- Patients with focal parenchymal lesions*
- Patients with focal neurological deficits*

Prevention of seizures after the acute phase

- Patients with acute seizures
- Patients with focal haemorrhagic lesions*

Treatment of intracranial hypertension

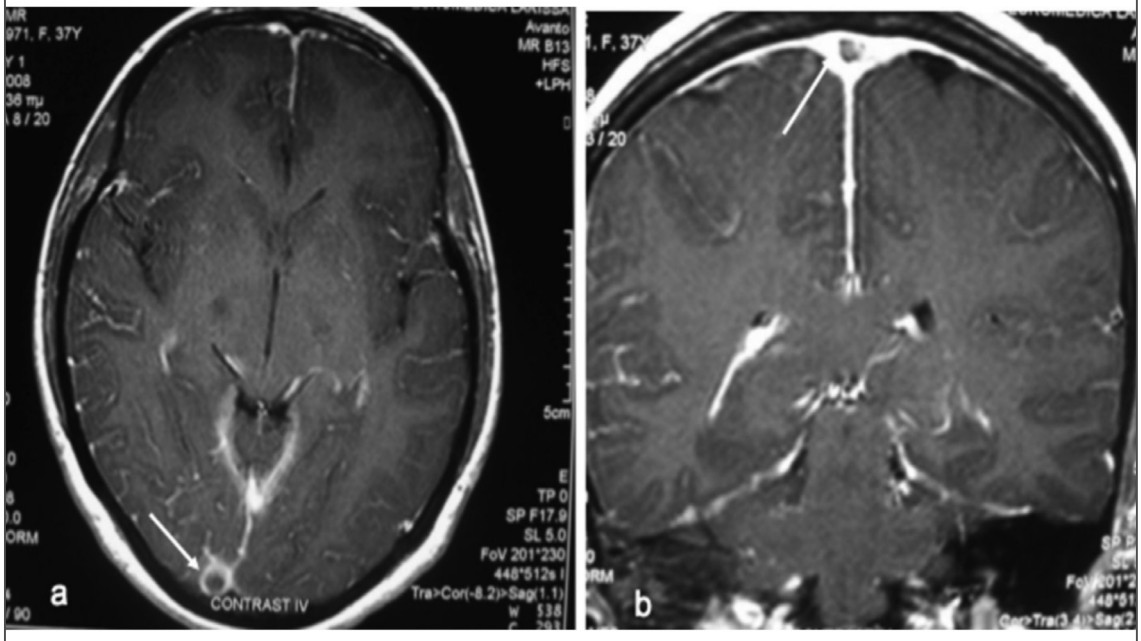
Threatened vision

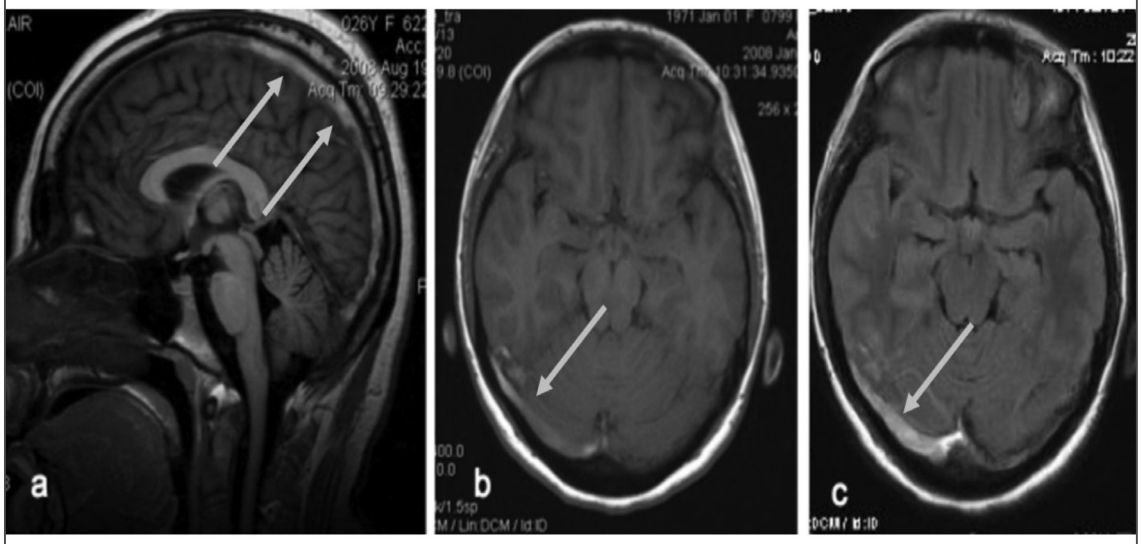
- Lumbar puncture (if no parenchymal lesions)
- Acetazolamide
- Surgical procedures (lumboperitoneal shunt, ventriculoperitoneal shunt, optic nerve fenestration)

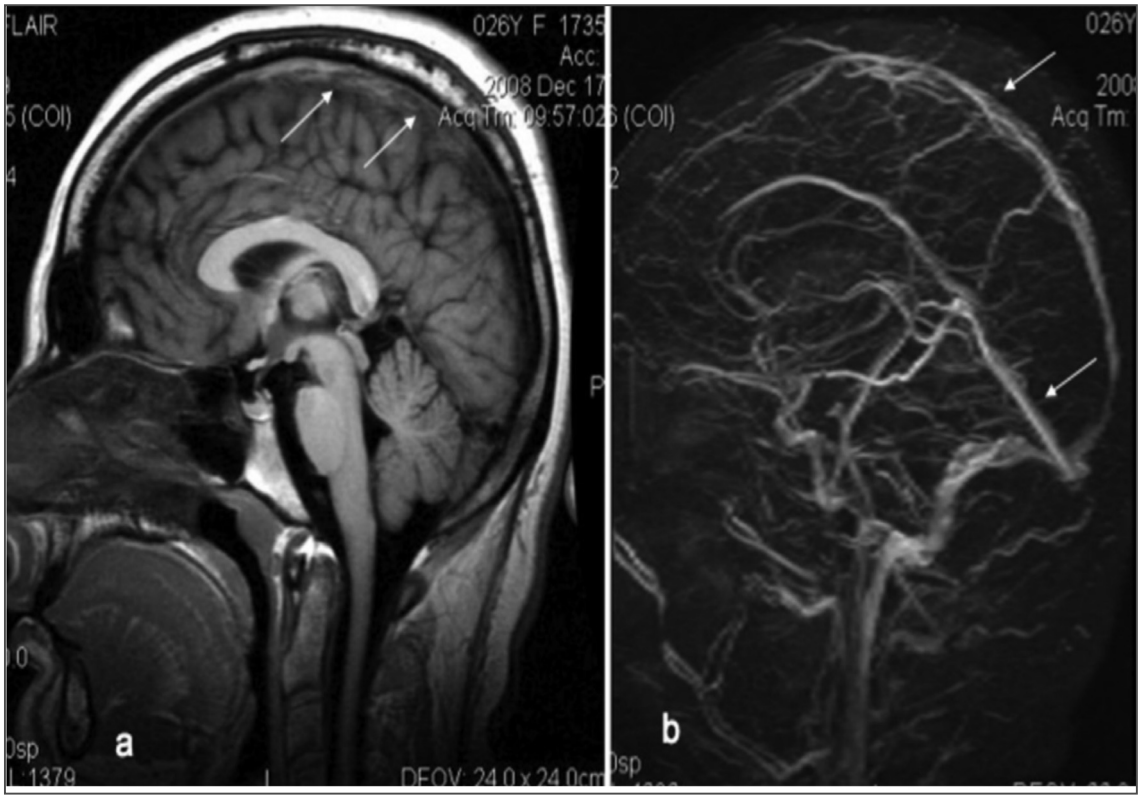
Impairment of consciousness or herniation

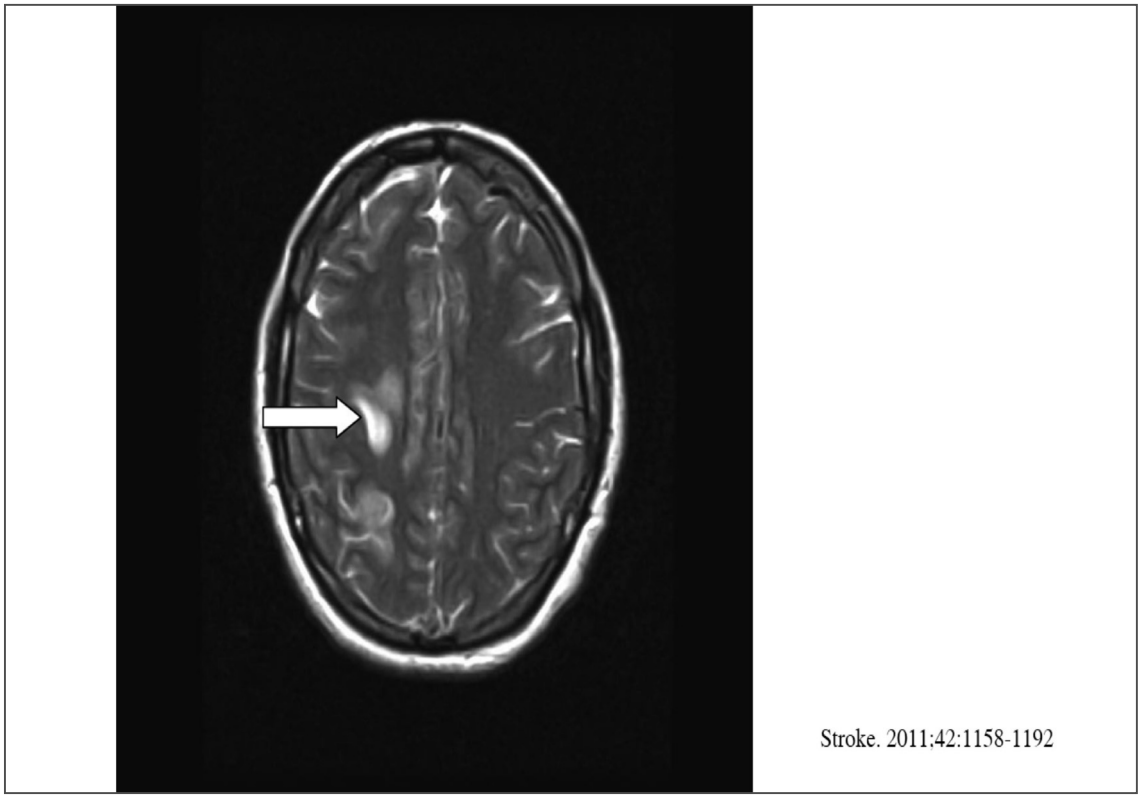
- Osmotic therapy
- Sedation and hyperventilation
- Hemicraniectomy*

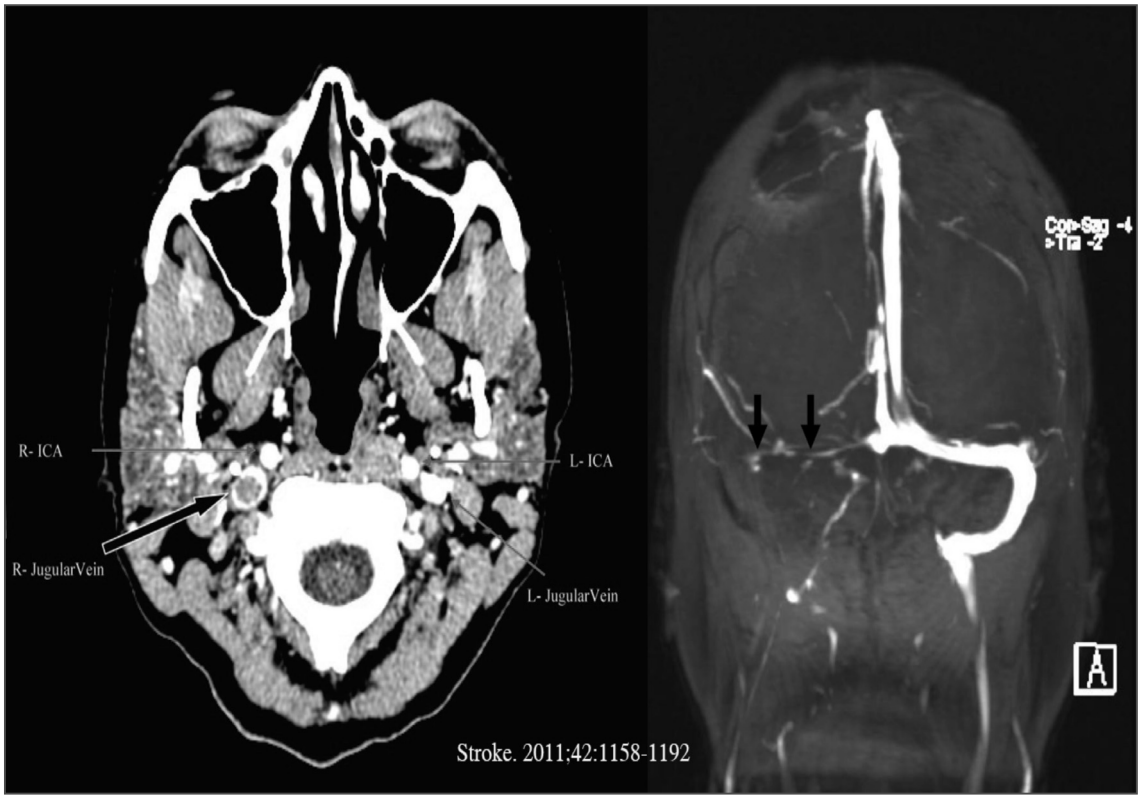
Lancet Neurol 2007;6:162–70

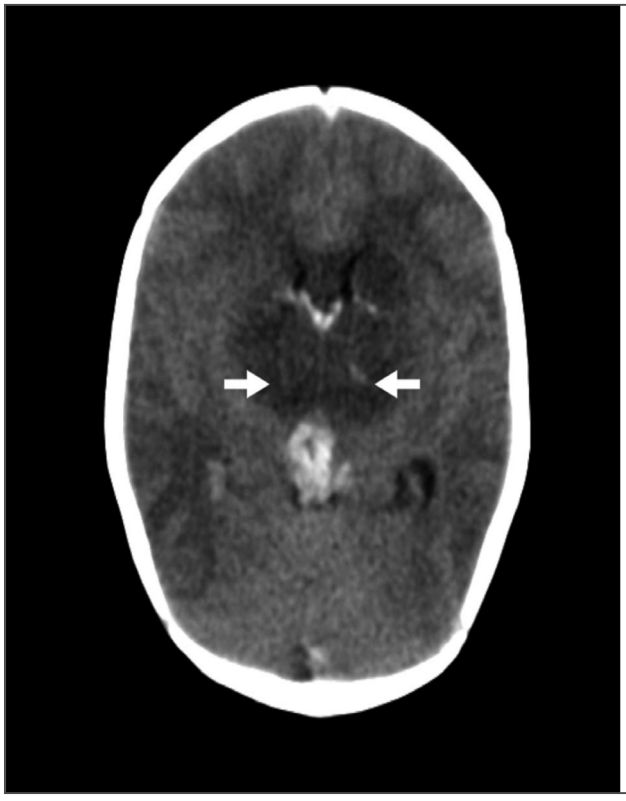



a
b
c


FLAIR
026Y F 1735
Acc:
2008 Dec 17
(COI)
a
b
DFOV: 24.0 x 24.0cm

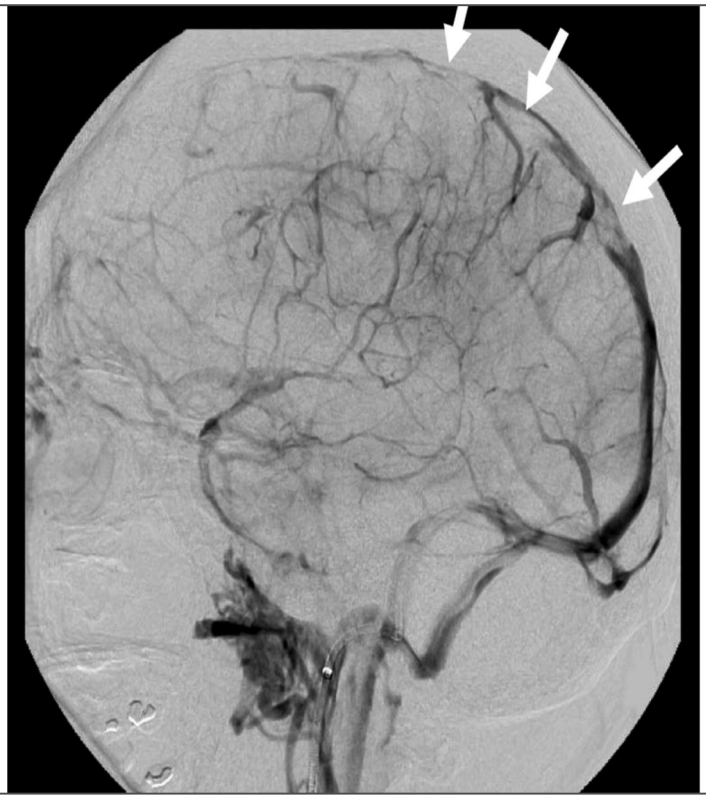

Stroke. 2011;42:1158-1192


R- ICA
L- ICA
R- JugularVein
L- JugularVein
Stroke. 2011;42:1158-1192



Stroke. 2011;42:1158-1192

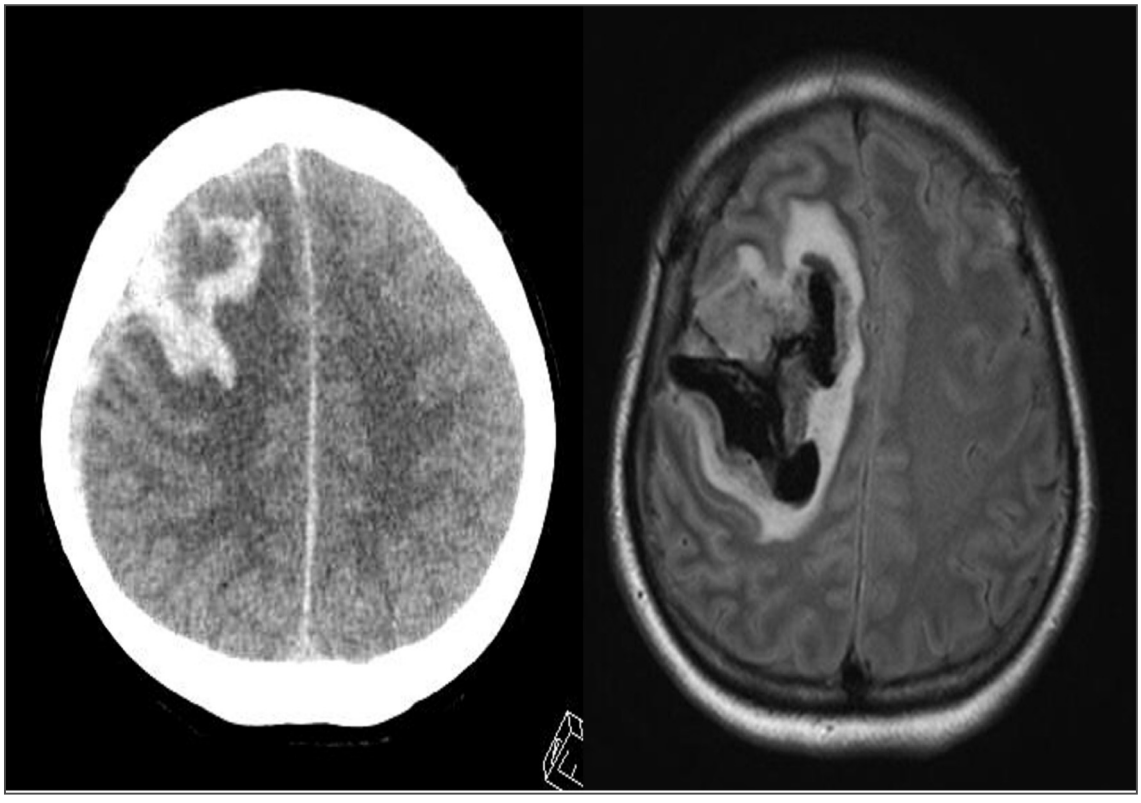
Newborn with deep cerebral venous thrombosis and bilateral thalamic (white arrows) infarcts.

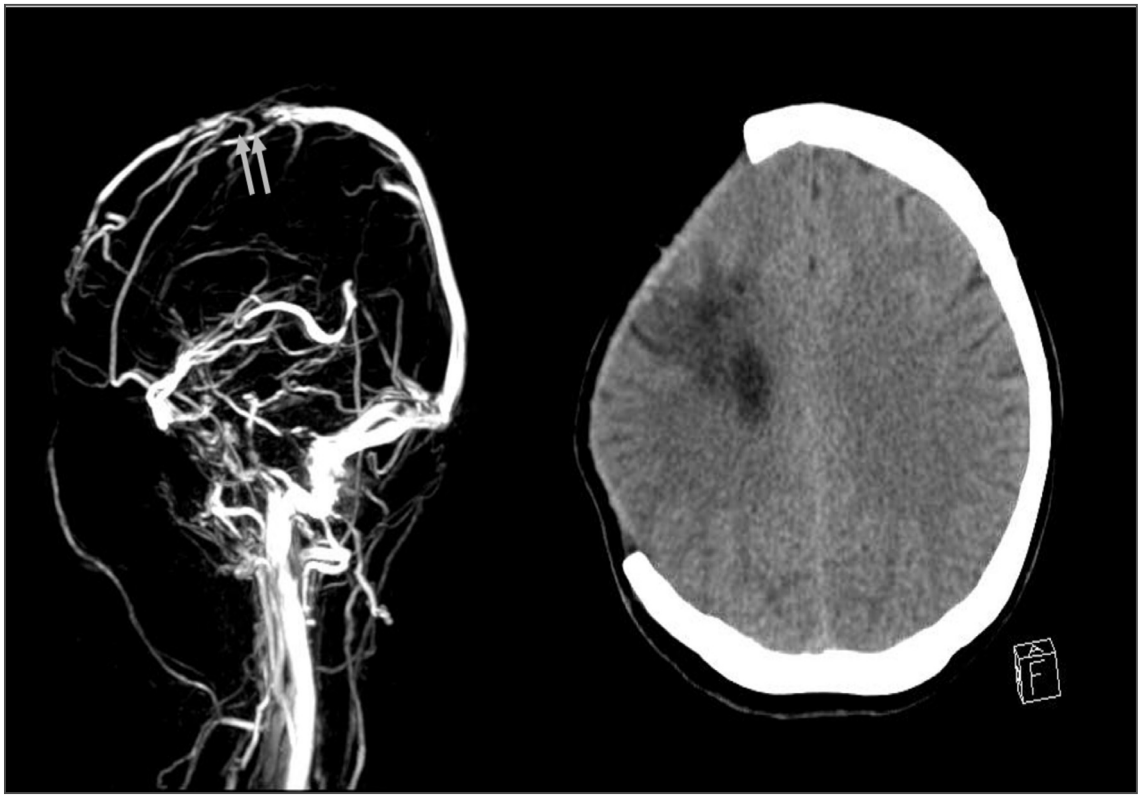


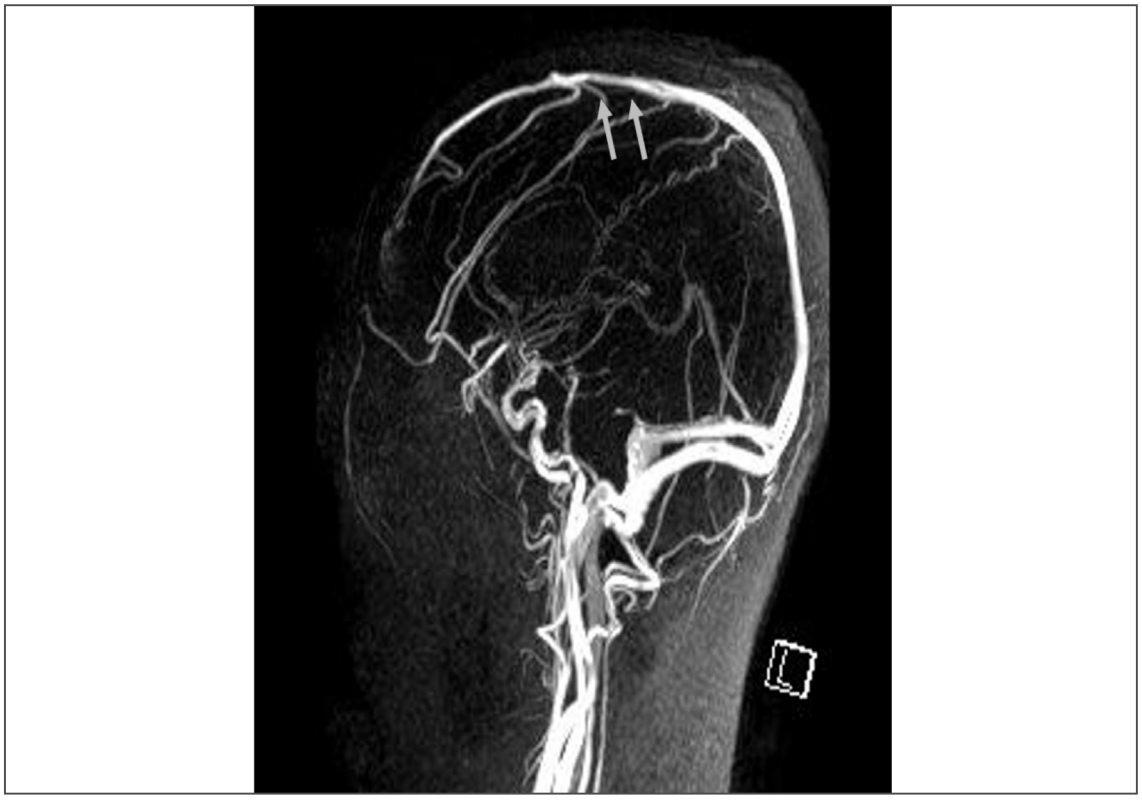
Stroke. 2011;42:1158-1192

Case

- 37 yo female
- Postpartum 0 day
- Sudden onset headache & left hemiplegia







Prognosis

Table 6. Variables Associated With Poor Prognosis in Cohort Studies

Demographic	Clinical	Neuroimaging	Risk Factors
Age >37 y[10]	Coma[10,117,277]	Intracerebral hemorrhage[10,277]	Cancer[10,177]
Male sex[10]	Neurological deficit and severity (NIHSS)[177,179]	Involvement of the straight sinus[277]	CNS infection[10]
	Encephalopathy[117]	Thrombosis of the deep venous system[10]	Underlying coagulopathy hereditary thrombophilia[66]
	Decreased level of consciousness[10]		
	Hemiparesis[10]	Venous infarction[66,179]	
	Seizures[10,179]		

NIHSS indicates National Institutes of Health Stroke Scale; CNS, central nervous system.

Stroke. 2011;42:1158-1192

Prognosis

- The main causes of death
  - hemorrhagic infarction
  - Cerebral edema → IICP and transtentorial herniation
  - Status epilepticus
  - Sepsis, pulmonary embolism