Ischemic Stroke

Last updated: August 8, 2020

PATHOPHYSIOLOGY-PATHOLOGY

Cerebrovascular PHYSIOLOGY → see p. A211 >>

Three simplified STAGES:

1. **Blood flow abnormalities**
2. **Cellular dysfunction**
3. **Structural breakdown**

CBF mL/min/100 g	**PaO_2** mmHg	**blood [glucose]** mg/dL	**Condition**	**Clinically**
> 60			Hyperemia (CBF > tissue demand)	
45-60	90	80	Normal (75-80 gray matter, 20-30 white matter)	Normal
20-30	< 40	25-30	Slowing of EEG	Stupor
16-20	< 30	20-25	Flat EEG	Coma
< 10-15	< 20	< 20	Cell death*	Brain death

* in complete absence of blood flow, neuronal death occurs within 2-3 minutes

ISCHEMIC CASCADE

- processes in stroke injury at cellular level.

- begins within seconds ÷ minutes of loss of glucose and oxygen delivery to neurons.
- failure of ATP synthesis → failure of energy-dependent membrane pumps → membranes depolarize and allow influx of Na^+ and Ca^{2+} and efflux of K^+:
  - intracellular Na^+↑ → cytotoxic edema.

- intracellular Ca^{2+}↑ → lipases and proteases activation → release of membrane-bound free fatty acids, protein denaturation.
- depolarization of presynaptic terminals → release of abnormally high concentrations of neurotransmitters → further injury (e.g. glutamate binds to NMDA receptors → further Ca^{2+} influx) – *EXCITOTOXICITY*.

  N.B. ischemia also reduces glutamate uptake into glia.

1) moderate ischemia for several seconds → reversible **cessation of electrophysiologic function** - EEG slows; if ischemia is global, patient becomes confused, lethargic, stuporous, syncope ("anoxic anesthesia").
2) if ischemia > 15-30 min → irreversible injury to few ***highly vulnerable neurons**** (**selective ischemic necrosis**) – most pronounced in survivors of global brain hypoperfusion.

   *e.g. CA1 pyramidal neurons of hippocampus, cerebellar Purkinje cells, pyramidal neurons in neocortical layers 3, 5, and 6
3) if ischemia > 1 hour → damage to all cell types (**cerebral infarction**).

Order of decreasing vulnerability to anoxia:

neurons > glia > endothelium

Hippocampus: CA1, CA4 > CA3 > granule cells
Cerebellum: Purkinje > stellate and basket > granule > Golgi cells
Striatum: small & medium-sized > large neurons
Neocortex: layers 3, 5, 6 > layers 2, 4.

- injury occurs more rapidly during hyperthermia and more slowly during hypothermia.

ISCHEMIC ZONES

Acute vascular occlusion produces heterogeneous regions of ischemia:

1. **Ischemic CORE** – region without significant flow (flow rarely reaches zero because of partial filling from collateral vessels).
   - cells die *within minutes* of stroke onset.

2. **Ischemic PENUMBRA** – region with decreased (marginal) perfusion:
   1) any **residual flow** in main arterial source
   2) **collateral supply** (e.g. VA to VA, circle of Willis, cortical anastomoses).
      - cerebral arteries act as ***end-arteries***!
      - *patient with excellent collateral blood flow from contralateral hemisphere may have minimal clinical deficits despite complete carotid occlusion; vs. patient with poor collateral flow may be hemiplegic with same lesion.*
      - *occlusion of proximal MCA proves to be inconsequential in presence of adequate collateral circulation from ACA and PCA.*
      - main causes of collateral insufficiency: atherosclerosis, congenital anomalies.
   - blood flow in penumbra is 10-18 ml/100 g/min (but as edema in core progresses, blood flow in penumbra drops further → infarction)
   - *electric silence* is present but cells remain viable *for several hours* (thanks to **anaerobic glycolysis***). *blood carries far more glucose than oxygen

Anaerobic glycolysis → lactate↑ → intracellular acidosis

N.B. hyperglycemia is associated with worse outcome!

   - penumbra is target for therapeutic interventions:
     a) revascularization (e.g. thrombolysis, thrombectomy)
     b) neuroprotective strategies - intended to extend time window for revascularization.

Neurons within **ISCHEMIC CORE** die from **energy** deprivation; vs. neurons in **ISCHEMIC PENUMBRA** die because of excessive stimulation of **glutamate** receptors.

TIME COURSE

1. Local vasodilatation and blood stasis with segmentation of red cells.

2. Edema (edema itself contributes to ischemia!):

   Cytotoxic edema (minutes ÷ hours) – due to energy-dependent membrane pumps failure;
   - predominantly in astrocytes in gray matter.
   - osmolality increases acutely from 310 to 350 mOsm.
   - water content increases from normal 79% to 81% of brain weight (insufficient to cause herniation).

   ↓

   Vasogenic edema (progressively worsens for 3-4 days after stroke) – due to BBB permeability↑ (pinocytotic transport↑ + disruption of tight junctions);
   - white matter is predominantly affected.
   - more severe than cytotoxic edema (in large strokes, ***can lead to herniation***).
   - BBB permeability tends to increase if reperfusion occurs.
   - endothelial permeability reverts to normal within 2 weeks (edema begins to regress after 2nd week).

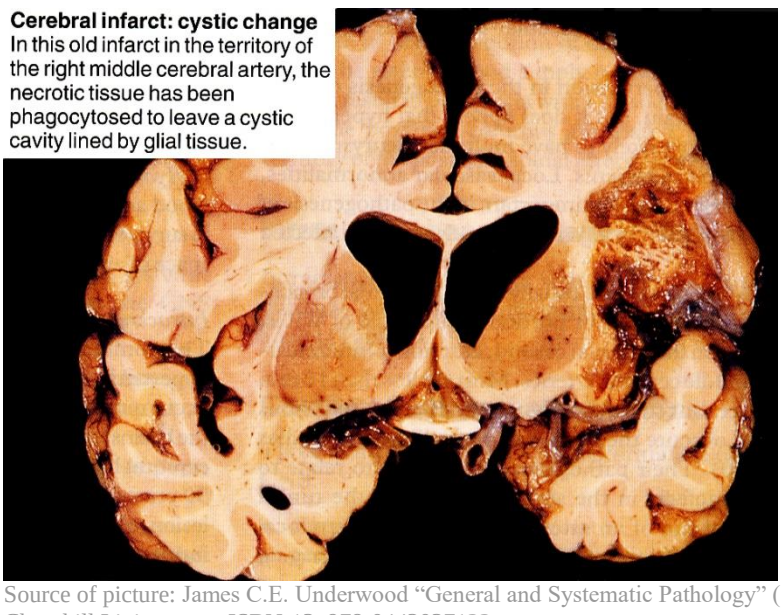
   N.B. cerebral edema & herniation cause death in 1/3 ischemic and 3/4 hemorrhagic strokes.

3. Necrosis of brain tissue (encephalomalacia) (develops simultaneously with edema): tissue **softens** → **liquefies (colliquative necrosis)** → microglia removes debris → **cavity** → astroglia attempts to fill defect (**reactive gliosis**).
   - in cerebral cortex, neuronal loss and gliosis produce uneven destruction of neocortex (preservation of some layers and involvement of others) - *PSEUDOLAMINAR NECROSIS*.

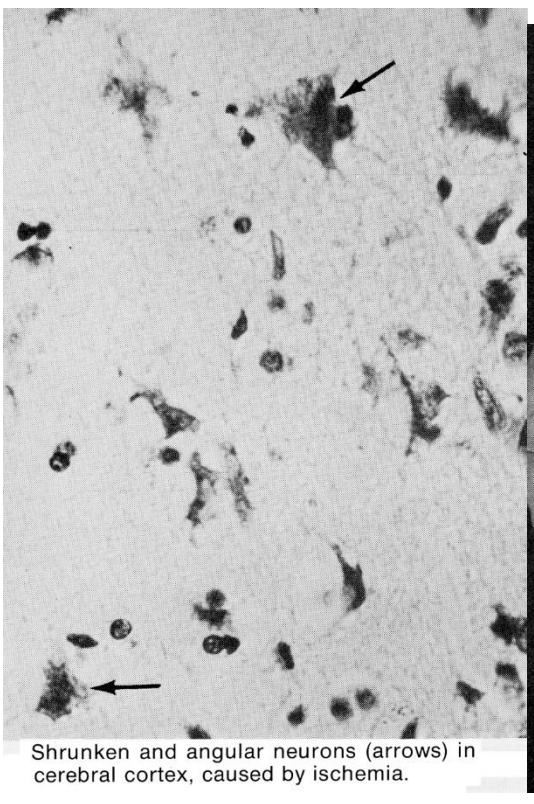
see p. S32 >>

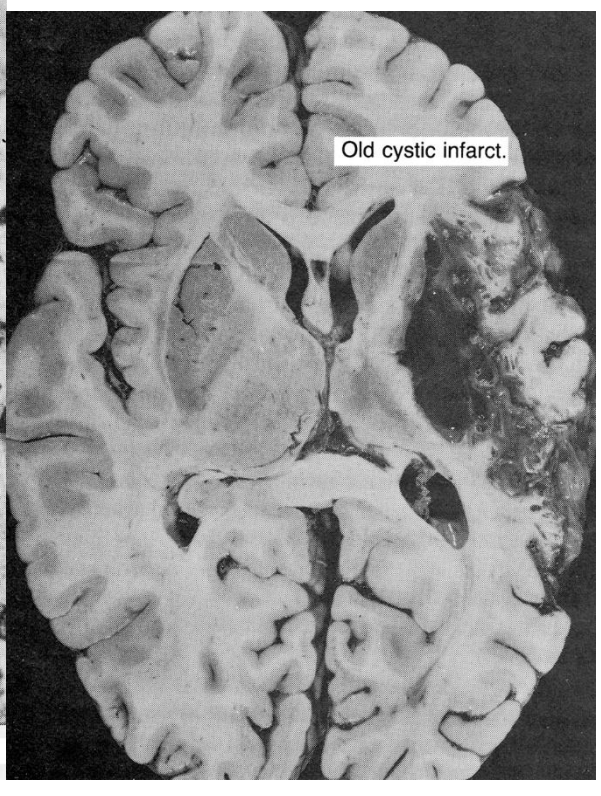
   - cavity is delimited from meninges by gliotic layer derived from molecular layer of cortex.
   - pia and arachnoid are not affected.

4. If **clot fragments** or **embolus moves** or **iatrogenic revascularization** (thrombolysis / surgery) → reperfusion occurs;
   - during ischemia, blood elements may sludge, capillary endothelium may swell, pericapillary edema may compress vessels - *blood flow may not reestablish* ("NO-REFLOW" phenomenon).
   - reperfusion generates *oxygen **FREE RADICALS*** → fatty acid peroxidation → damage to membranes.
   - ***hemorrhage*** (petechial or confluent) into necrotic tissue may occur (≈ 40%) - hemorrhagic areas lie along border zones of partially perfused tissue.

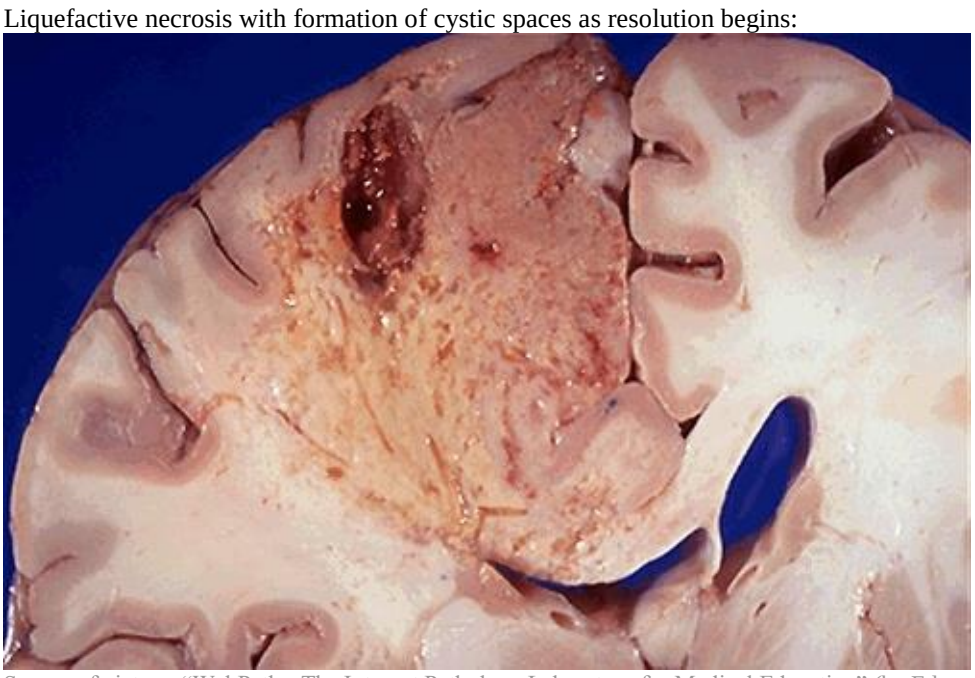


Source of picture: James C.E. Underwood "General and Systematic Pathology" (1992); Churchill Livingstone; ISBN-13: 978-0443037122 >>


Shrunken and angular neurons (arrows) in cerebral cortex, caused by ischemia.



Liquefactive necrosis with formation of cystic spaces as resolution begins:



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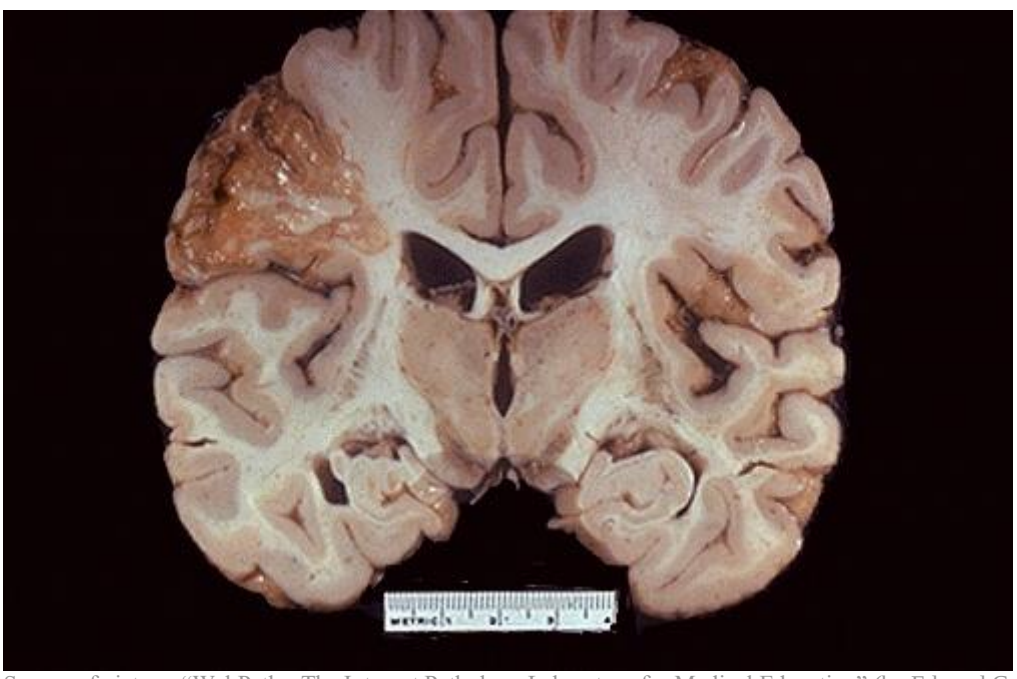

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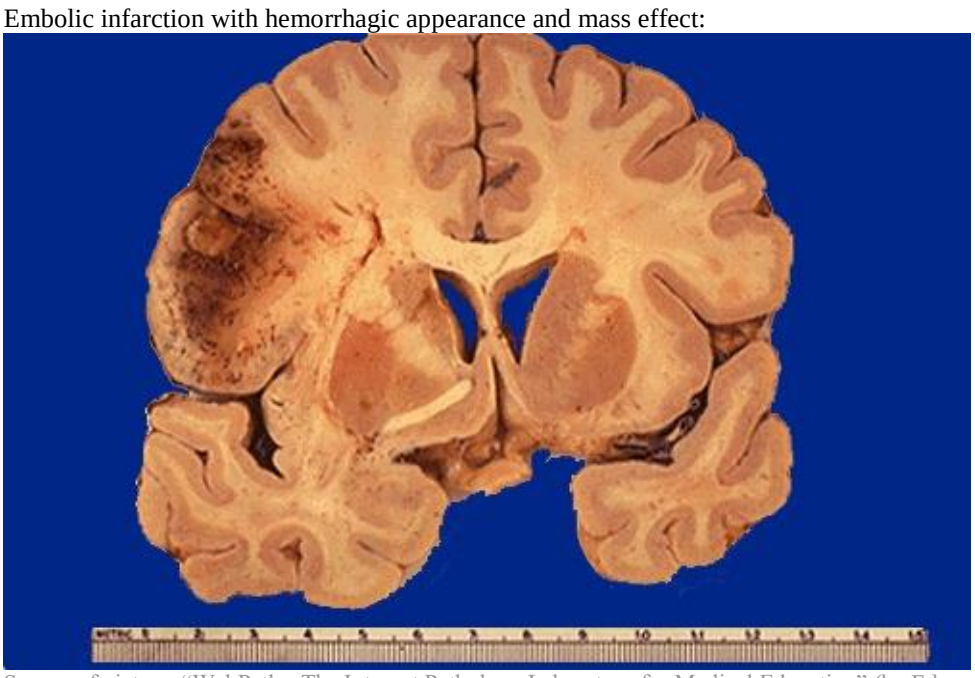
Embolic infarction with hemorrhagic appearance and mass effect:



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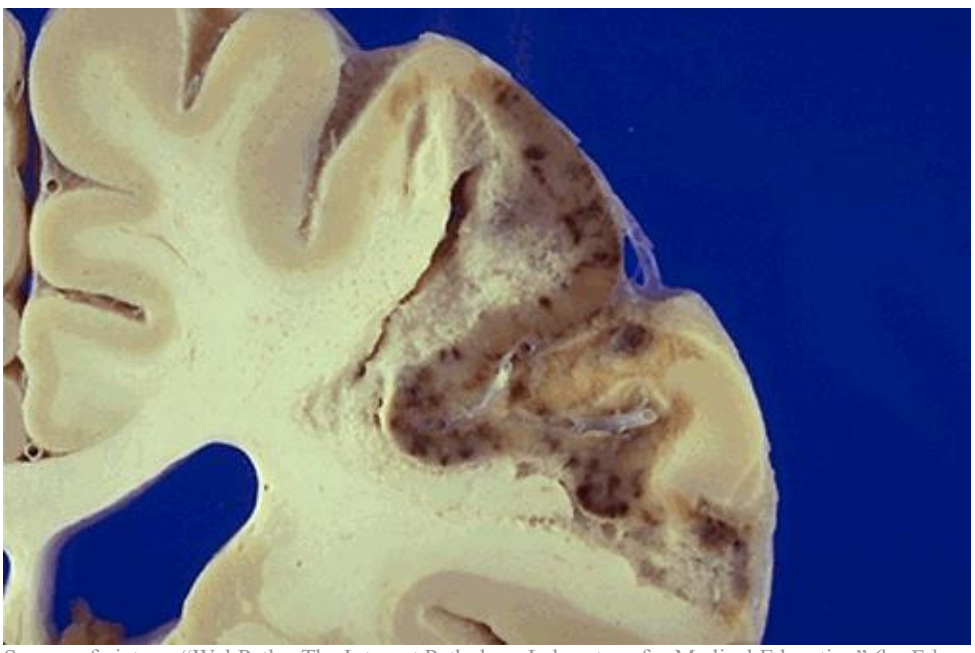
Embolic infarction with punctate hemorrhages:



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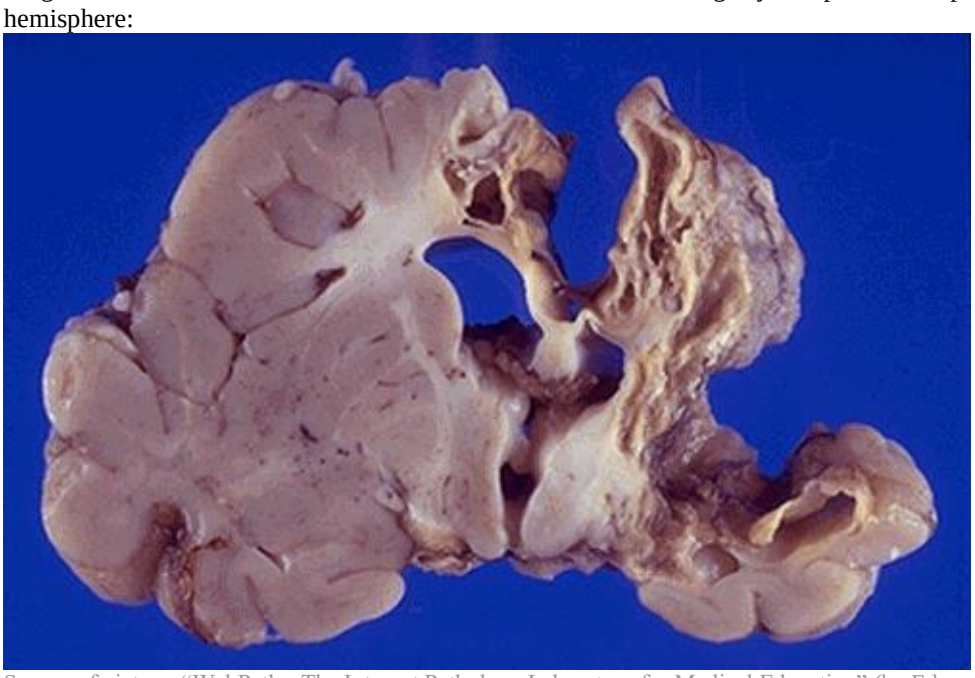
Large remote cerebral infarction in neonate - resolution has left huge cystic space encompassing much of cerebral hemisphere:



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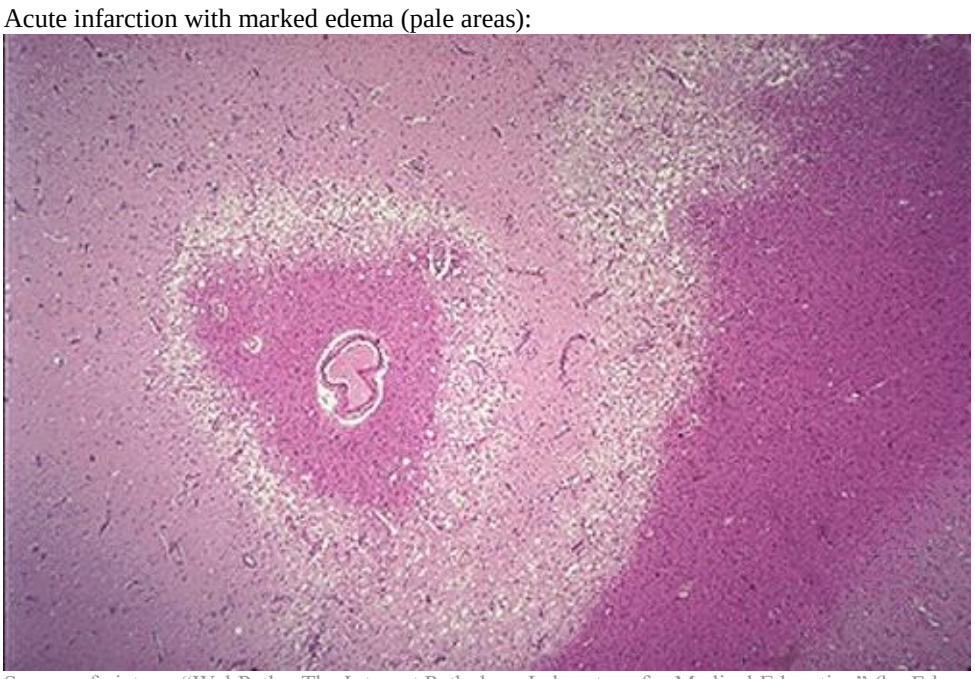
Acute infarction with marked edema (pale areas):



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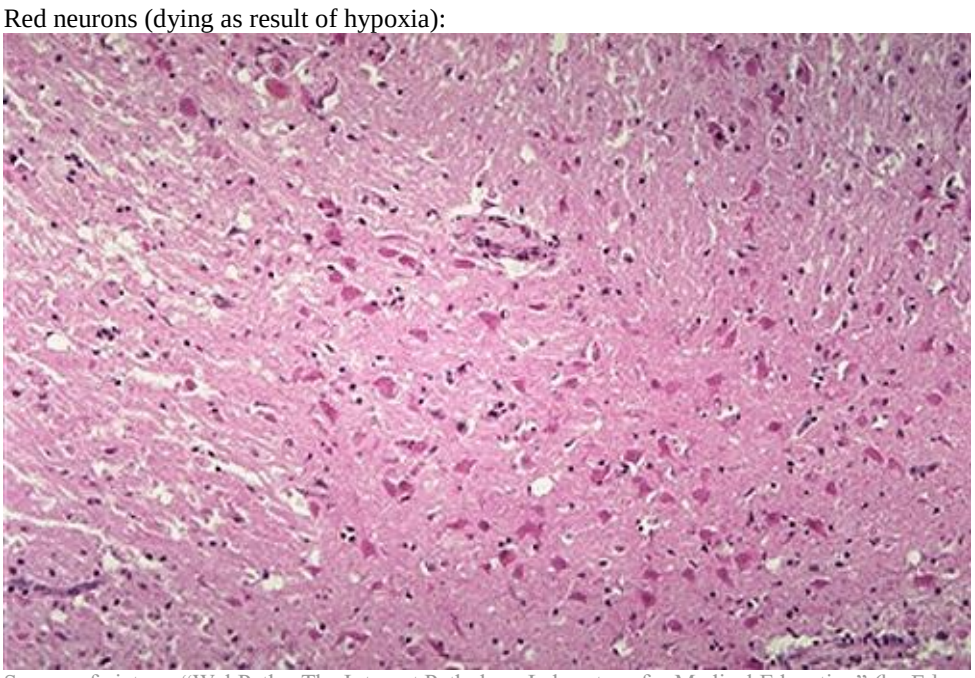
Red neurons (dying as result of hypoxia):



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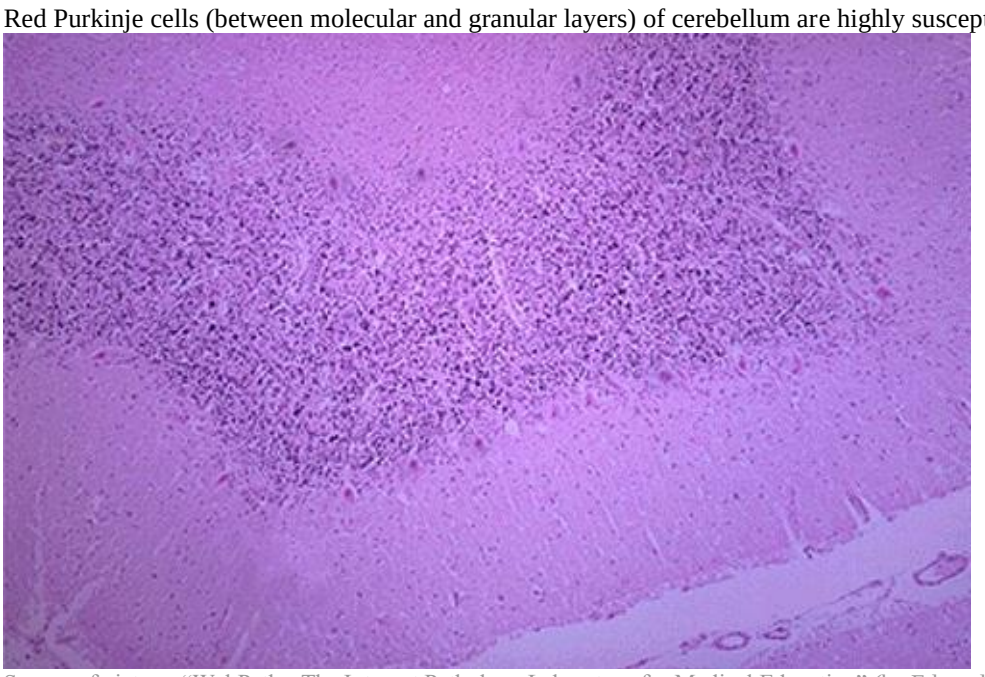
Red Purkinje cells (between molecular and granular layers) of cerebellum are highly susceptible to anoxia:



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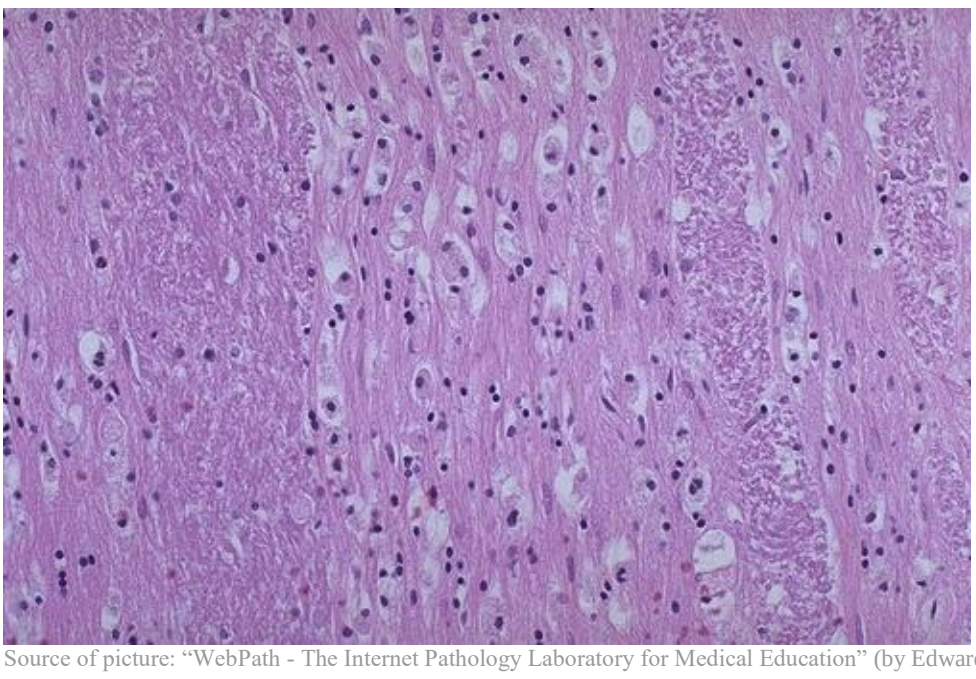
Cerebral infarctions can lead to Wallerian degeneration of descending tracts, as shown here in brainstem:



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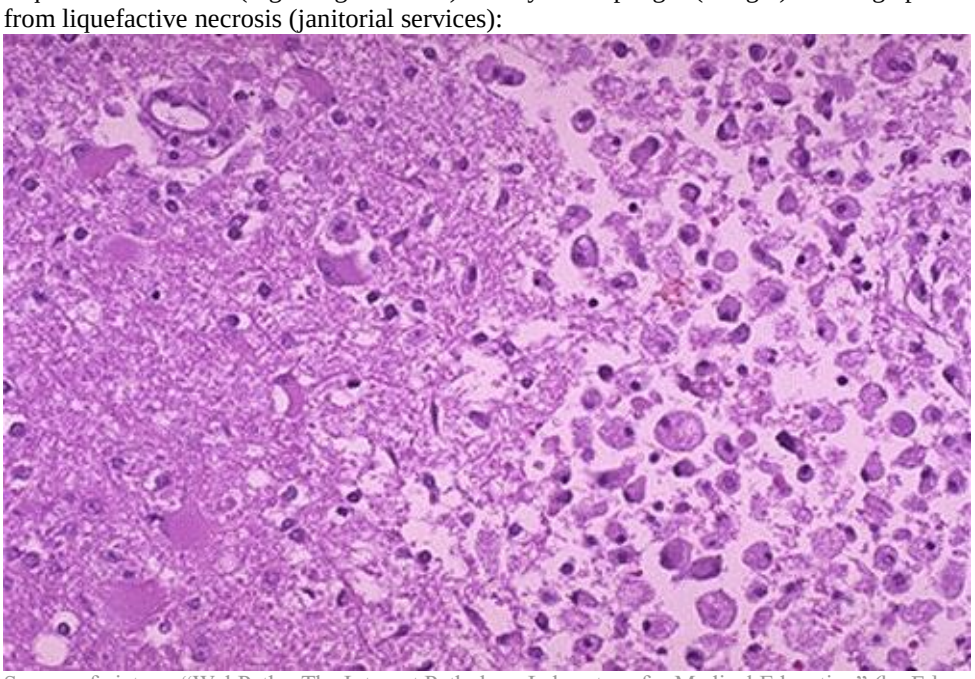
Cerebral infarction (liquefactive necrosis) - loss of neurons and glial cells, formation of clear space (at center left):

Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

Liquefactive necrosis (high magnification) - many macrophages (at right) cleaning up necrotic cellular lipid debris from liquefactive necrosis (janitorial services):



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TYPES OF ISCHEMIC INJURY

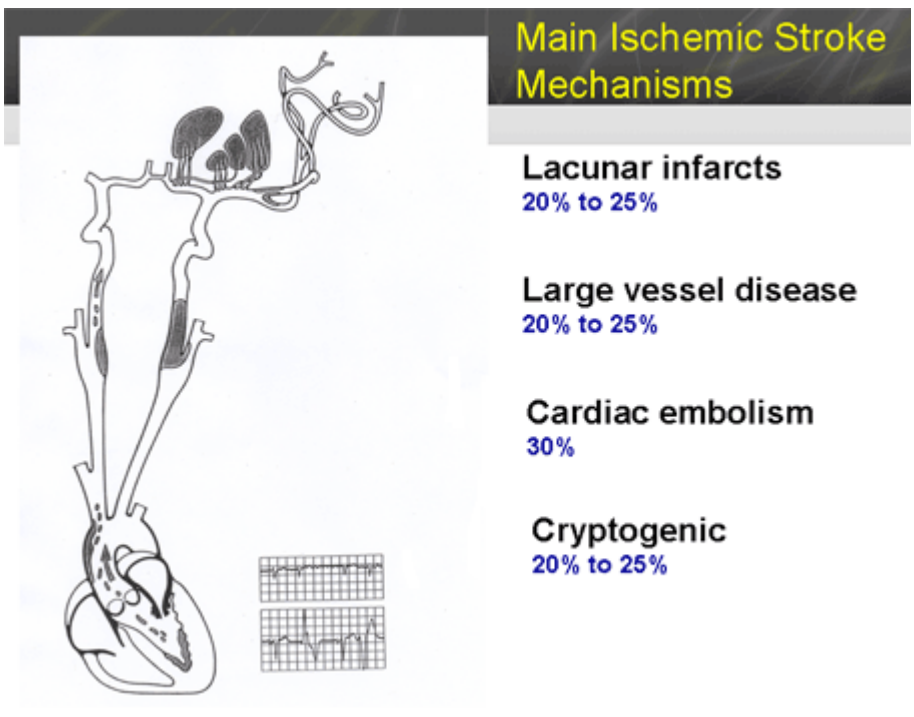
1. ***Selective ischemic necrosis* of highly vulnerable neurons** – caused by global ischemia for few minutes – *necrosis evolves slowly* (sometimes requires several days to reach full extent).

2. **Cerebral *infarction*** – necrosis of neurons, glia, and, in some areas, endothelial cells – caused by focal vascular occlusion – *necrosis evolves rapidly* (after few hours histologic stains sharply outline distinct margins between living and dying neurons and glia).

3. ***Demyelination* of central hemispheric white matter** – oligodendroglial cells die off – consequence of carbon monoxide poisoning (or other prolonged moderately severe hypoxemia or cerebral hypoperfusion).

4. **Cerebral *autolysis*** – enzymatic autodigestion – observed in brain-dead patients preserved on mechanical ventilators for several days.

ETIOPATHOPHYSIOLOGY



Exact cause of 20-30% ischemic strokes is unknown - *CRYPTOGENIC STROKES*.

1. EMBOLIC strokes

- 15-30% of all strokes (esp. in young patients).
- MCA territory is most frequently affected.
- emboli lodge where ***vessels branch*** (e.g. apex of basilar artery) or in areas of ***preexisting stenosis***.
- infarct often *becomes hemorrhagic* (anticoagulation is contraindicated in hemorrhagic infarcts!).

Types of emboli:

1. Fibrin-rich thrombi (e.g. mural thrombi due to segmental myocardial hypokinesis following MI or ventricular aneurysm)
2. Platelet-rich thrombi (e.g. non bacterial thrombotic endocarditis)
3. Calcified material (e.g. in aortic stenosis)
4. Tumor particles (e.g. atrial myxoma)
5. Fat globules
6. Air / gases

THROMBEMBOLISM

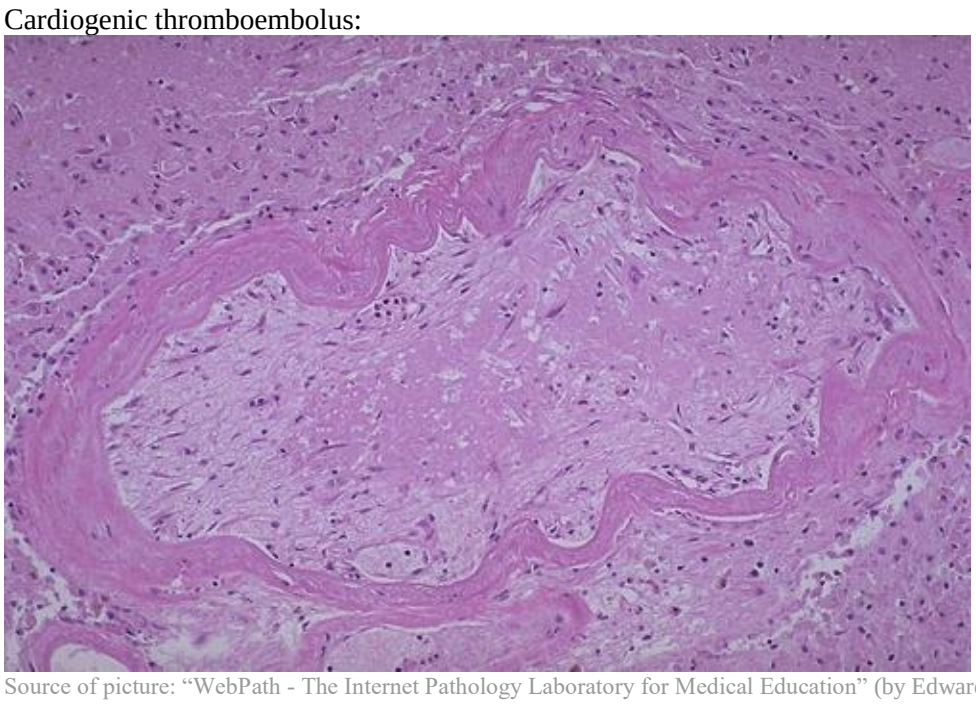
Emboli origin:

A. **CARDIAC** (mural thrombi) - most common sources (1/6 of all strokes)!
   1) **atrial fibrillation** – stroke risk is increased 5-fold (4.5-7% / year without treatment) – 75% are due to left atrial thrombi.
   2) **recent MI** (1-3% of all acute MIs within 1-2 weeks), esp. transmural, involving anteroapical wall (6%) vs. inferior wall MI (1%),
      It is not uncommon to discover underlying silent MI in patients with stroke!
   3) **prosthetic valves** (mechanical* > biologic**)
      *while on anticoagulation, stroke risk is 1.5% / year for aortic valves; 3% / year for mitral valves
      **stroke risk 2-4% / year without anticoagulation
   4) **native valvular disease** (esp. MS), **endocarditis**
   5) **dilated cardiomyopathy** (poor left ventricular function)

B. **ARTERIAL** (atherothrombotic or cholesterol emboli) - ***extracranial arteries***: arch of aorta, carotid and vertebral arteries.
   Most commonly from ulcerated plaque at carotid bifurcation!

C. **VENOUS** – via ***patent foramen ovale**** (paradoxical passage of venous emboli) – can be detected with *bubble echocardiography* (saline IV → echogenic bubbles from right-to-left shunted saline in left atrium).
   *present in 10-18% of general population (and in 56% of young adults with stroke)

Cardiogenic thromboembolus:



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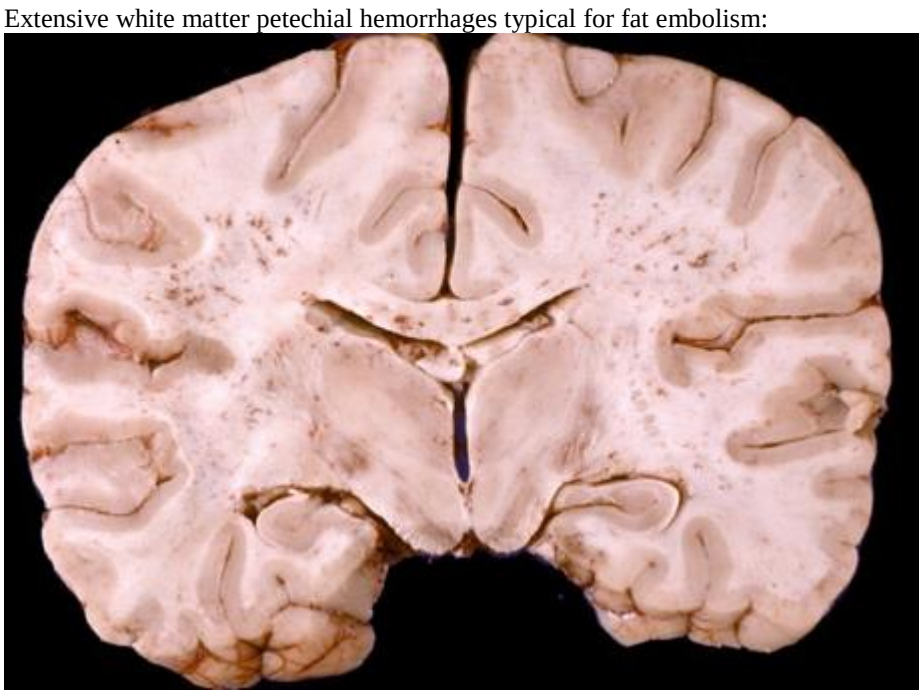
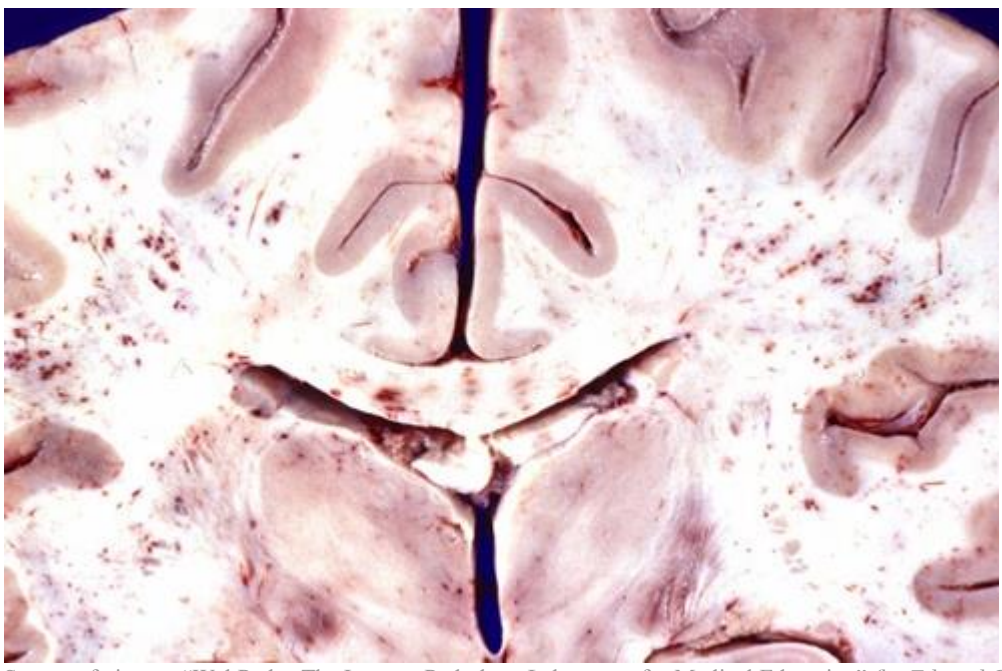
FAT EMBOLISM

- sources – ***fractures of long bones*** ("shower embolization").
- seen less often than previously (perhaps owing to better fluid replacement).
- pathologic findings – *petechiae* (mainly in white matter, due to capillary occlusion by fat globules), brain edema.
- presentation (brain injury may mask syndrome!): lucid interval of 12-48 hrs after trauma → fever with pulmonary symptoms* (dyspnea, cyanosis, blood-tinged sputum) → *generalized acute cerebral dysfunction* - disturbances of higher cortical function (up to delirium) and consciousness, seizures.
- other features: petechial rash (prominent in anterior axillary folds and supraclavicular fossae), renal failure, ARDS*.
  *cumulatively, small fat emboli have the same effect as large saddle pulmonary embolus
- diagnosis:
  1) *fat emboli* on funduscopy, retinal and conjunctival *punctate hemorrhages*
  2) *fat globules* in urine or CSF.
  3) *diffuse interstitial infiltrates* on chest X-ray (ARDS with $Pa_{O2}\downarrow$)
- treatment - large doses of **glucocorticoids**, **PEEP** (with high end-expiratory pressures); heparin or intravenous alcohol are no longer recommended.

Extensive white matter petechial hemorrhages typical for fat embolism:





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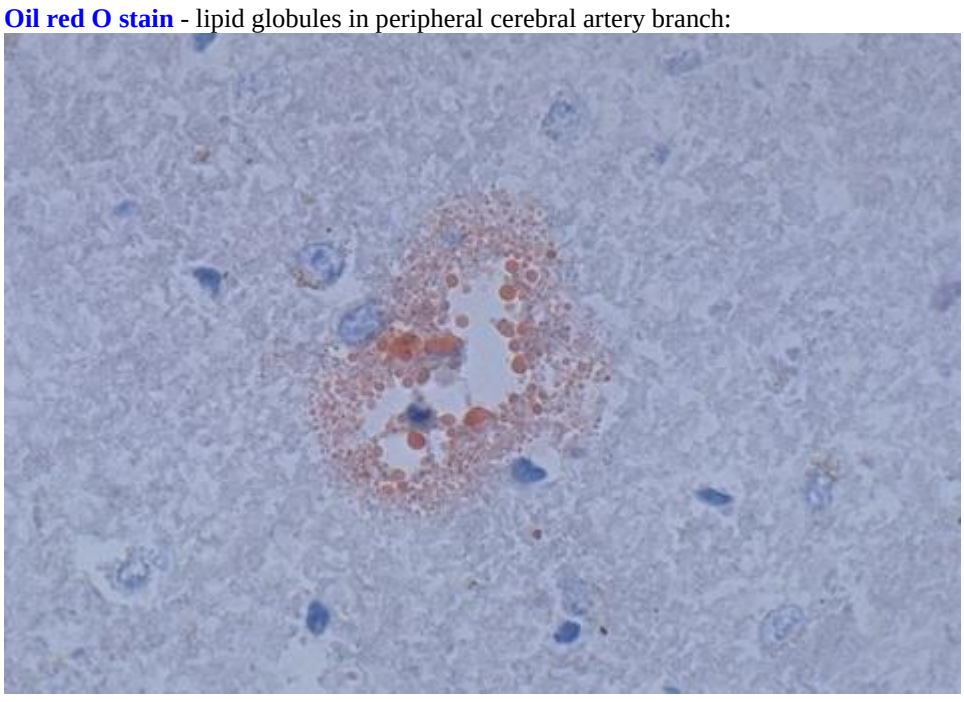
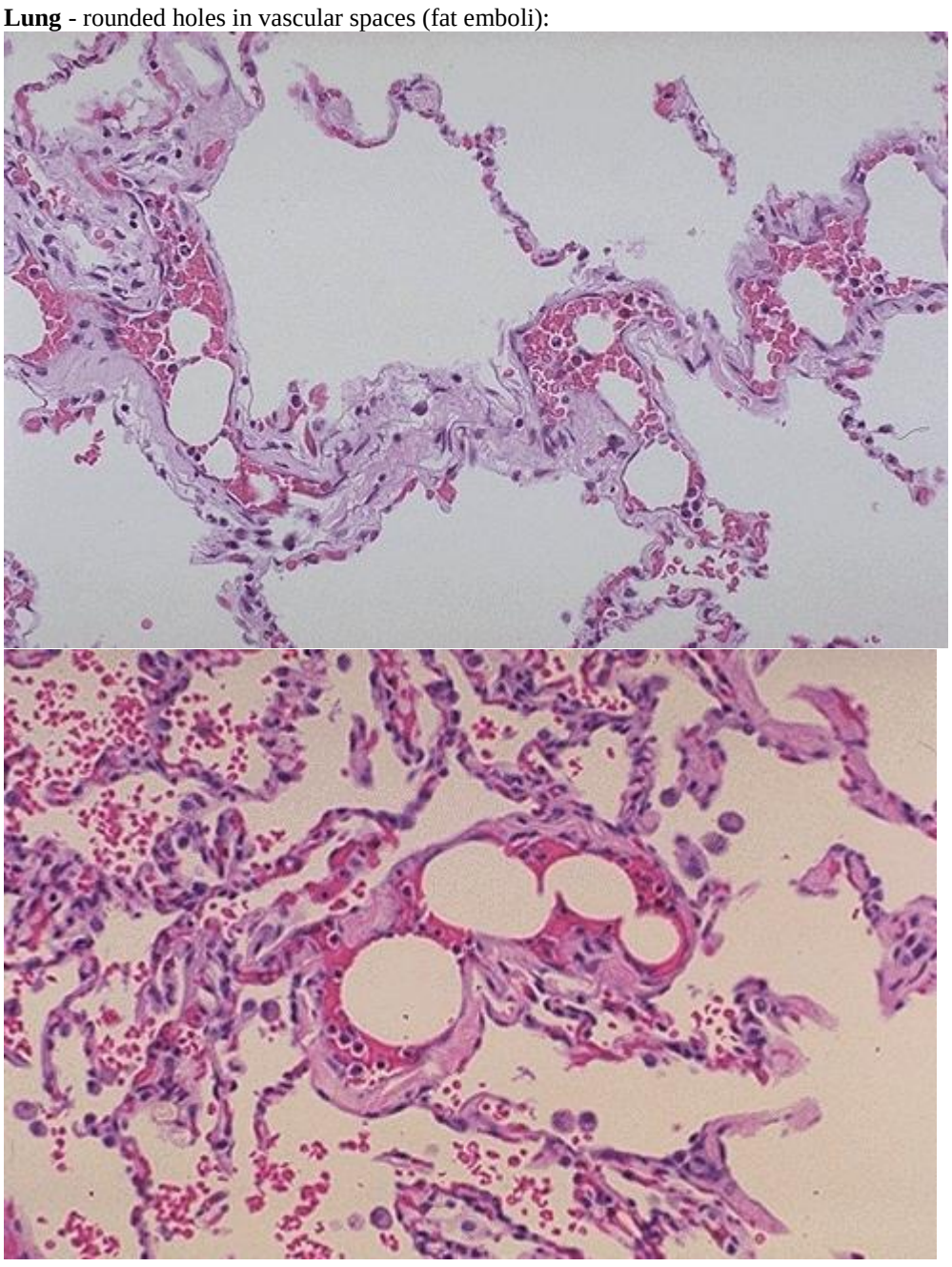
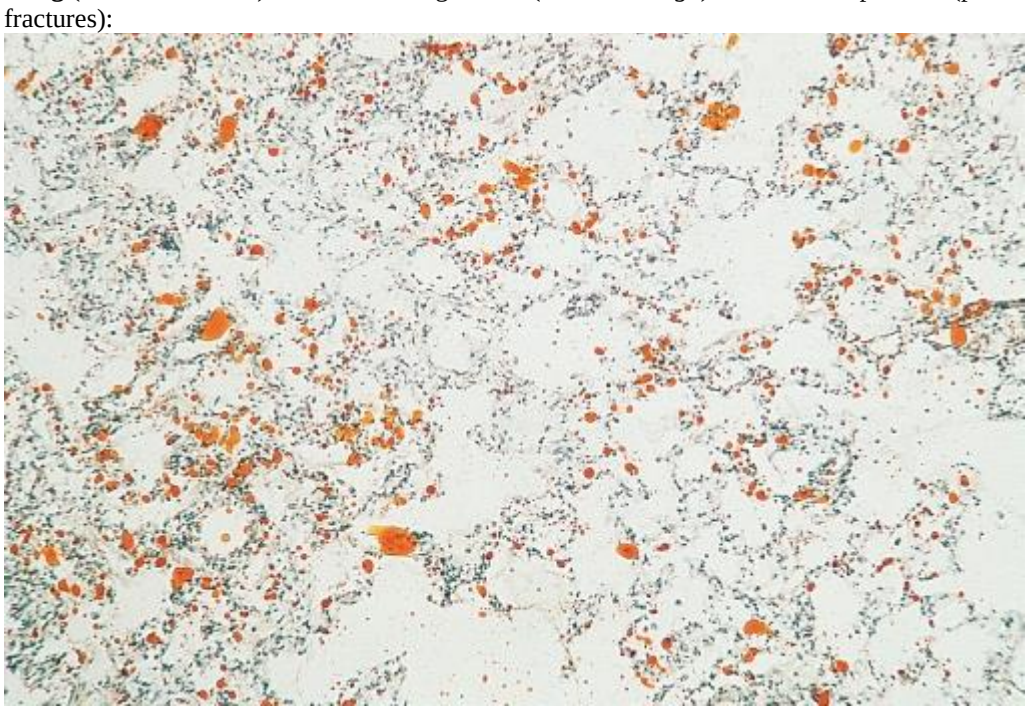
Oil red O stain - lipid globules in peripheral cerebral artery branch:

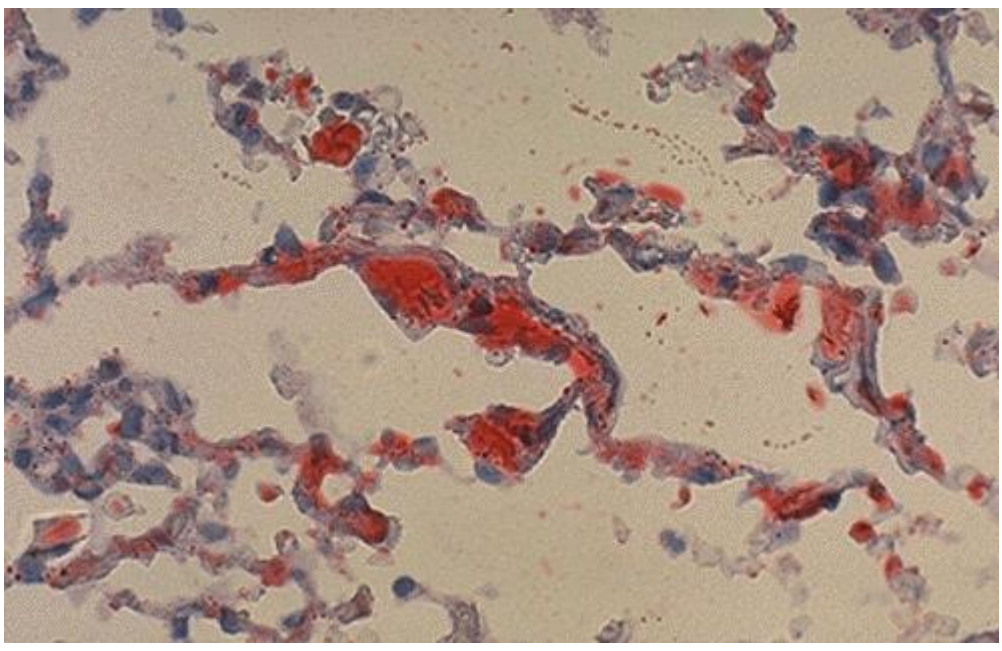


Lung - rounded holes in vascular spaces (fat emboli):

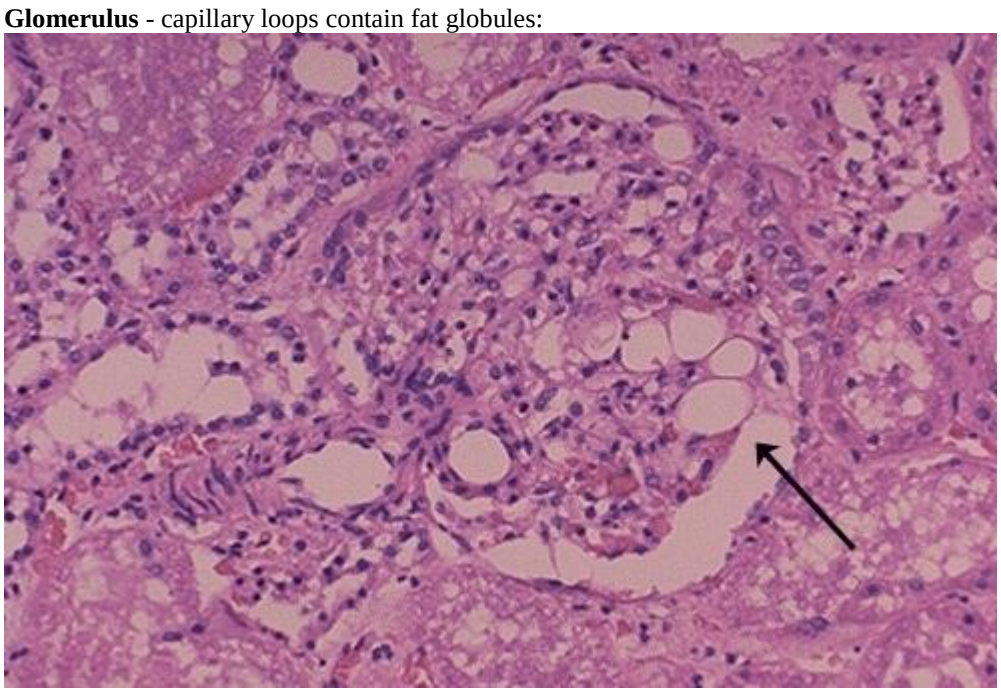


Lung (**Oil Red O stain**) - numerous fat globules (*stained orange*) in alveolar capillaries (patient with multiple bone fractures):





Glomerulus - capillary loops contain fat globules:



AIR EMBOLISM

- sources - marked ***atmospheric pressure changes*** (scuba diving, caisson disease - release of nitrogen bubbles into general circulation), ***medical procedures*** (involving lungs, dural sinuses, or jugular veins - allow air into vascular system), ***penetrating jugular vein injuries***.
- clinically - altered mental status, seizures, focal neurologic findings.

2. THROMBOTIC strokes

- in situ occlusions:

A. **LARGE-VESSEL strokes** (70%)
B. **SMALL-VESSEL (LACUNAR) STROKES** (30%); ≈ 20% of all ischemic strokes (≈ 31% in black and Hispanic people; ≈ 17% in whites).

Extracranial occlusive diseases usually affect ***white men*** and are strongly associated with coronary and peripheral vascular occlusive disease, systolic hypertension, and hyperlipidemia.

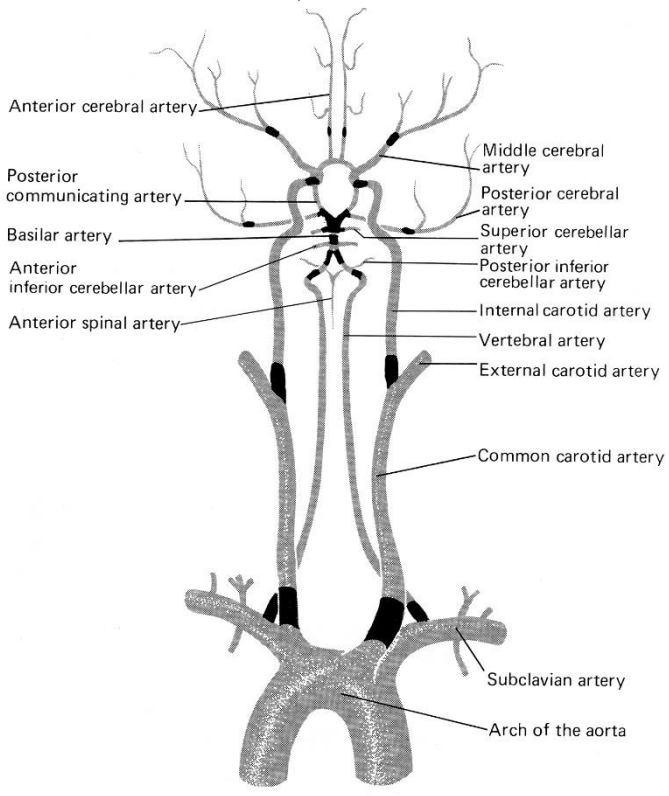
Intracranial occlusive diseases* are more severe in ***blacks***, ***Asians***, and ***women***.

*most commonly - atherosclerotic intracranial arterial stenosis

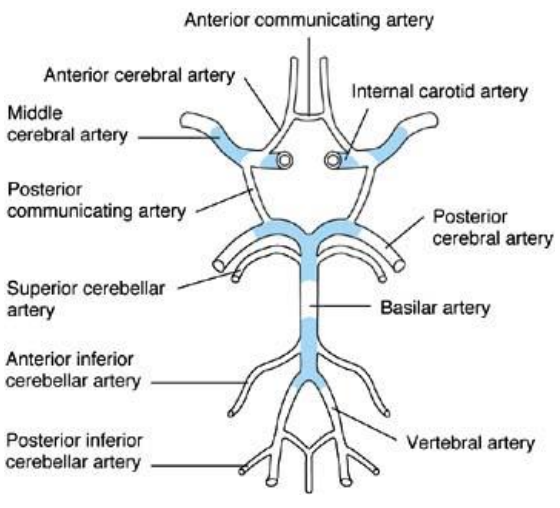
LARGE-VESSEL strokes

- characteristically on atherosclerotic lesions (i.e. ATHEROTHROMBOSIS).
- commonest sites of ATHEROSCLEROSIS (most commonly *branching points* - areas of turbulent flow):
  1) proximal CCA
  2) ICA – origin (bifurcation of CCA)*, carotid siphon
  3) proximal MCA*
  4) both ends of VA**
  5) both ends of BA**
  6) proximal PCA

*most common sites
**and origins of their branches



Dark areas: common sites of atherosclerosis and occlusion.



- **white platelet thrombi** form in fast-moving streams (irregularities along intimal surface); **fibrin-dependent red thrombi** develop in slow-moving streams (e.g. arteries with severe narrowing).
- degree of stenosis that will lead to perfusion failure (hemodynamically significant stenosis) depends on multiple factors; stenosis > 70-80% is predictive of impending hemodynamic compromise.
- infarcts are usually *nonhemorrhagic (pale, bland, anemic)*.
- prognosis depends on whether initial thrombus propagates distally or embolizes to distal arteries.

Thrombogenic factors:

A. **Injury to endothelial cells** (→ platelet activation by subendothelium):
   1) *ruptured atherosclerotic plaques* (atherothrombosis!!!)
   2) ***arterial dissections*** (e.g. traumatic) see p. Vas11 >>
   3) ***vasculitis*** (e.g. collagenoses, meningitis, syphilis) see p. Vas35 >>

B. **Activation of clotting cascade / inhibition of fibrinolysis** (e.g. antiphospholipid antibodies, protein C deficiency, protein S deficiency, DIC, carcinoma*, pregnancy & puerperium (see p. Vas1 >>), high-dose estrogen contraceptives**, homocystinuria).

*esp. mucinous adenocarcinomas
**esp. if associated with migraine (!!!), hypertension, cigarette smoking, > 35 yrs

In patients *< 40 yrs with cerebral ischemia of unknown origin*, search for hereditary thrombophilia is generally recommended!

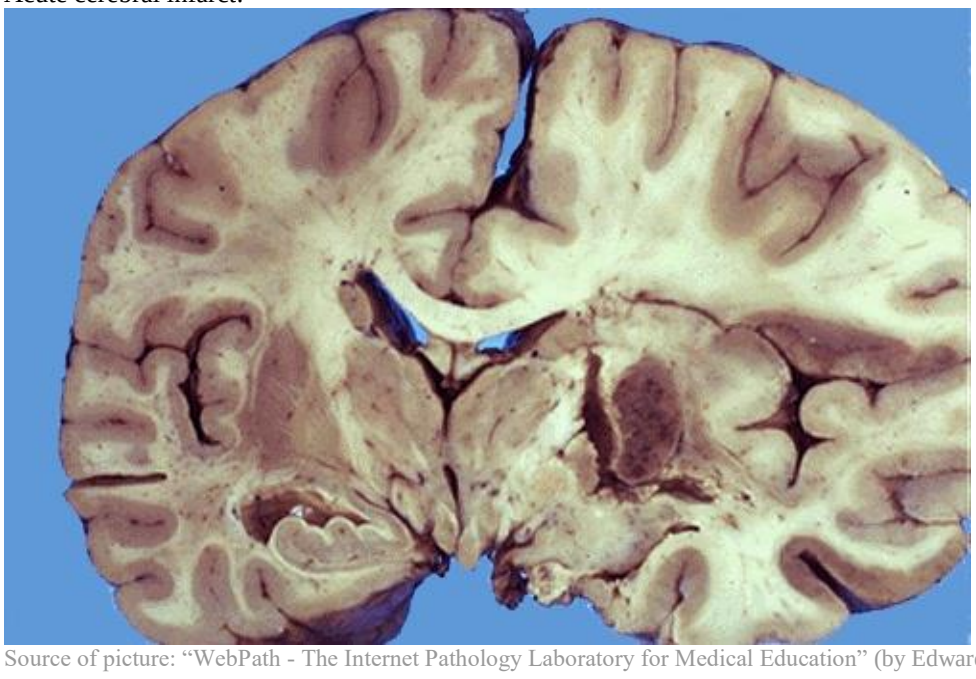
C. **Blood stasis**:

1) ***hyperviscosity syndrome*** (polycythemia, dysproteinemia, sickle cell disease*, thrombocytosis, leukemia**).
   *up to 15% patients with HbSS experience stroke (esp. children)
   **leukemia also may cause thrombocytopenia → ICH, SAH
2) ***vasospasm*** (SAH, malignant migraine, eclampsia, trauma, illicit drugs, nasal decongestants containing sympathomimetics*).
   *e.g. phenylpropanolamine (recalled from US market)
3) ***vasculopathies*** - fibromuscular dysplasia, moyamoya disease.
4) ***extrinsic compression*** of major arteries (by tumor, bony vertebral projections).
5) ***occlusion of veins*** (dehydration, pericranial infection, postpartum and postoperative states, systemic cancer).

Drug	Route	Ischemic strokes	Hemorrhage	Other Features
HEROIN	IV	+ (brain & spinal cord)	No	γ globulins↑
AMPHETAMINES	Oral, IV	No	SAH, ICH ("speed" hemorrhage)	Hypertension
COCAINE HCl	Nasal, IV	+	SAH, ICH; aneurysms and AVMs common	Hypertension
CRACK COCAINE		Very common		
MASHED PILLS*	IV	+ (microemboli)	No	Talc particles in eyes and lungs

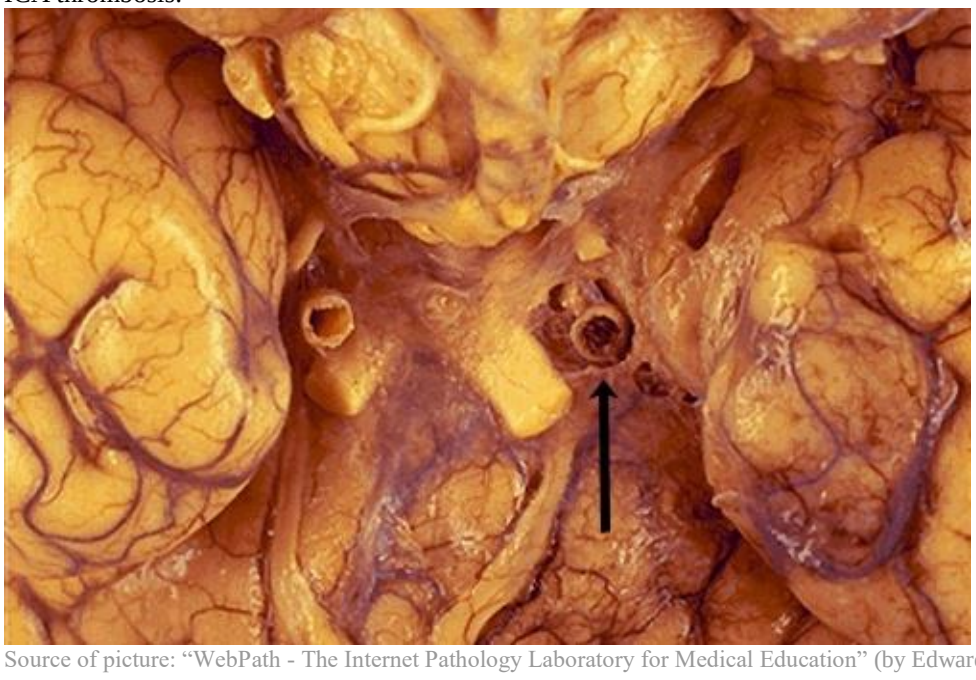
*oral medications that have been crushed and suspended in water (e.g. PENTAZOCINE, METHYLPHENIDATE); particles of talc and cellulose (ingredients in pills) are trapped by pulmonary arterioles → local arteritis → AV shunts → microemboli can reach CNS.

Acute cerebral infarct:



Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

ICA thrombosis:



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LACUNAR strokes

– occlusion of CENTRAL PENETRATING BRANCHES, esp. lenticulostriate arteries.

- ***penetrating branches*** are END ARTERIES - have no collateral flow! (vs. ***cortical branches***);
- ***penetrating branches*** arise directly from larger vessels, without gradual stepdown in size (as in distal cortical vessels) – susceptibility to damaged cerebrovascular autoregulation, which occurs with aging and higher blood pressure levels.

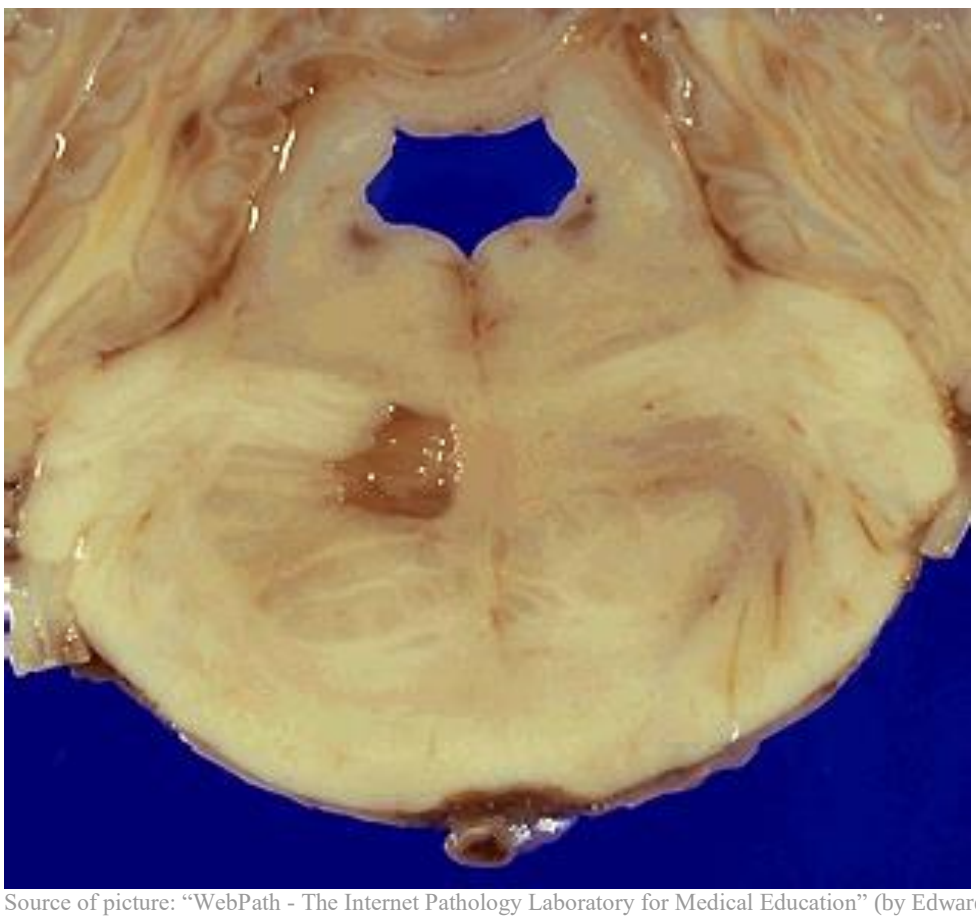
- occlusion of individual branches → small (3-15 mm) deep infarcts → necrotic tissue resorption → small circumscribed perivascular loss of brain tissue (**LACUNAE**).
  - in long standing arterial hypertension, these thin-walled central branches tend to dilate (**miliary**, s. **CHARCOT-BOUCHARD aneurysms**) → bleeding into parenchyma.
- locations of lacunes - basal ganglia (esp. putamen), internal capsule, thalamus, centrum semiovale, paramedian brainstem (esp. pons).
- **L'ETAT LACUNAIRE** - multiple lacunes - chronic progressive neuro decline. see >>

CAUSES - **small-vessel (arteriolar) disease**: [great majority are related to *hypertension*!]

1) **microatheromas** - small vessel atherosclerosis.
2) **lipohyalinosis** (secondary to hypertension): subintimal eosinophilic fibrinoid deposits in connective tissue of vessel wall; lumen is compromised not by intimal process but by thickening of vessel wall itself
3) **fibrinoid necrosis** (secondary to hypertension or vasculitis).
4) **amyloid angiopathy**.
5) *unusual etiologies* – microemboli (e.g. cholesterol), polycythemia, chronic neurosyphilis, chronic meningitis, granulomatous angiitis, SLE, neurocysticercosis, neuroborreliosis.

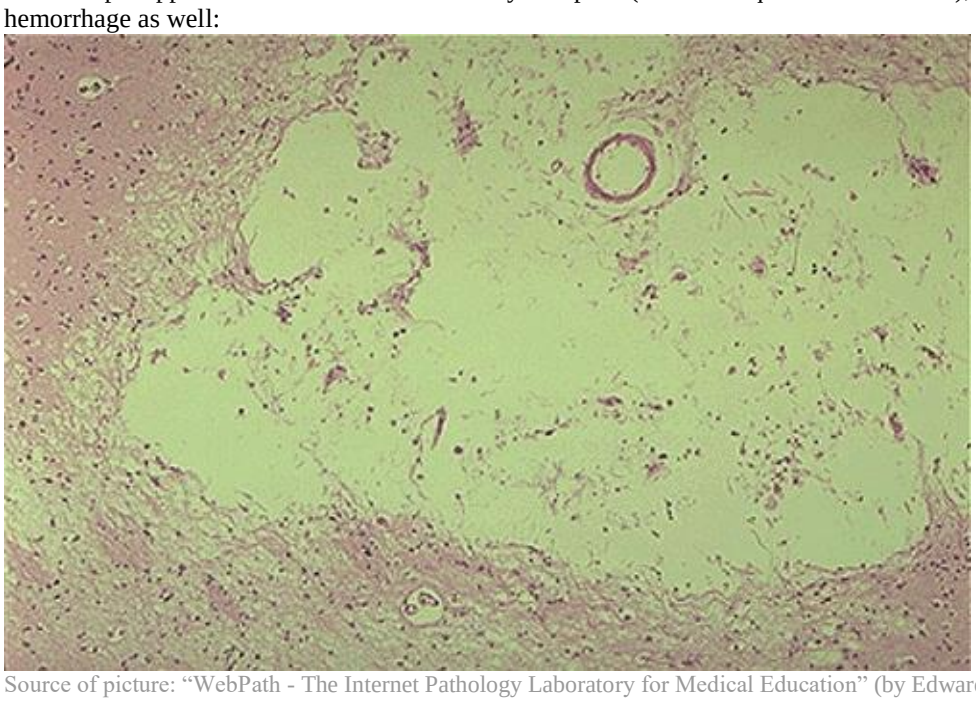
N.B. larger (> 1.5 cm) cavities ("giant lacunae") have different etiology; e.g. embolus in MCA trunk simultaneously occluding several perforating vessels.

Lacuna in pons:



Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

Microscopic appearance of a lacunar infarct - cystic space (resolved liquefactive necrosis); there can be hemosiderin from hemorrhage as well:

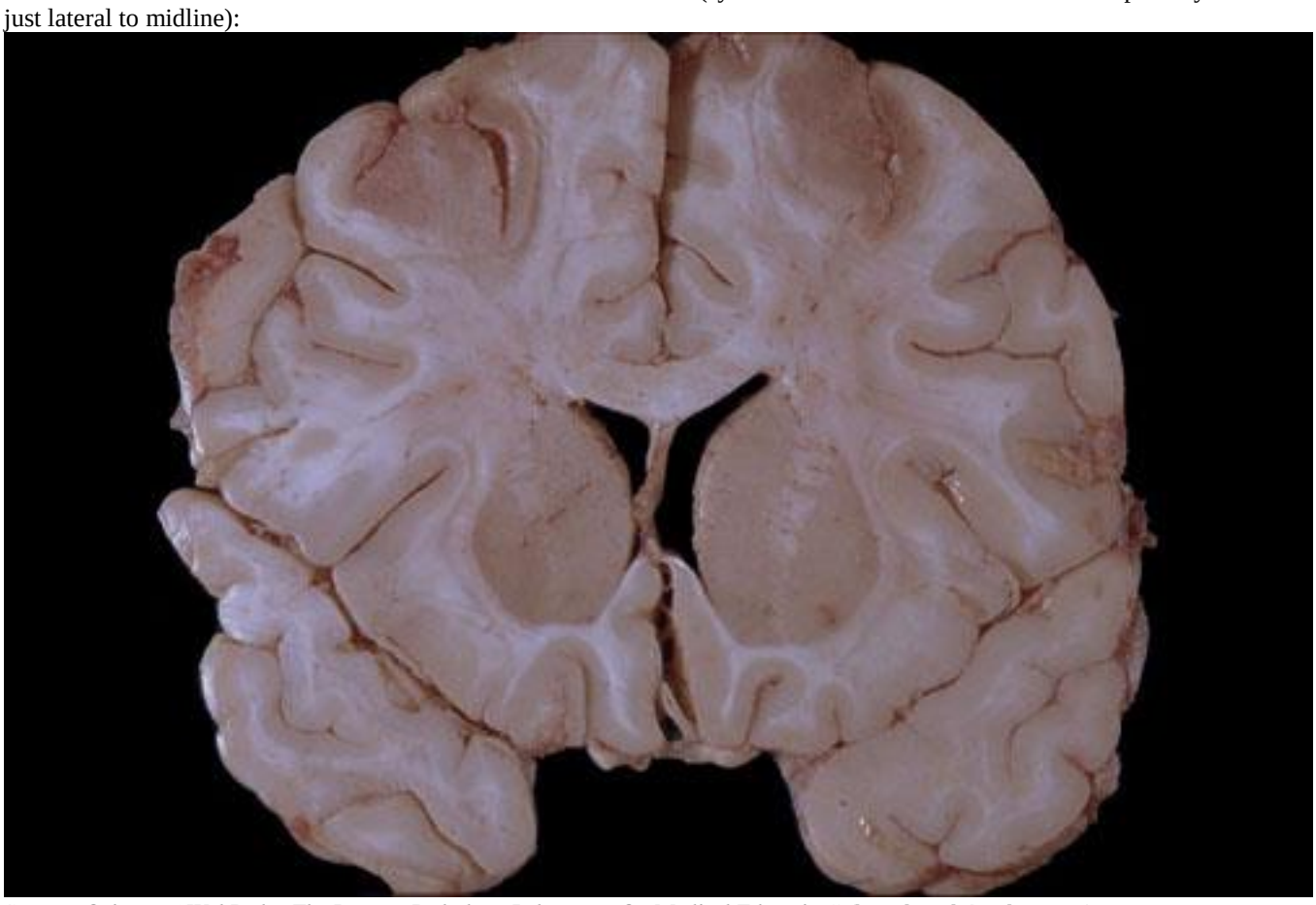


Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

3. WATERSHED (s. BORDER ZONE) infarcts

- <u>cause</u> – global hypoperfusion (most distal arterial territories suffer most):
  a) diffuse **hypoperfusion** (e.g. asystole, ventricular fibrillation, cardiac surgery, orthostatic hypotension, excessive use of antihypertensive drugs);
     – BP fall must be pronounced and sustained to compromise CBF, but if *bilateral carotid stenosis* or *hypoxemia* is present, lesser BP fall can cause infarction.
  b) **hypoxia**:
     – ***mild ÷ moderate hypoxia*** causes only cerebral dysfunction (confusion, cognitive impairment, lethargy - HYPOXIC ENCEPHALOPATHY) but not infarction* (prevented by compensatory CBF↑). *or only selective ischemic necrosis
     – ***severe hypoxia*** causes cardiac failure → hypoperfusion → coma → [a)]WATERSHED INFARCTION in sensitive regions (such as basal ganglia) / [b)]VEGETATIVE STATE / [c)]BRAIN DEATH.
- frequently associated with *surgical procedures* (e.g. cardiac surgery).
- infarctions are **wedge-shaped** and occur in ***border zones between major cerebral arteries***.

Bilateral watershed infarctions between ACA and MCA territories (symmetric dark discolored areas seen superiorly and just lateral to midline):



Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

4. ANOXIC INJURY

<u>Etiology</u>:
1. CO poisoning
2. Cardiac arrest
3. Strangulation
4. Drowning

TIA

<u>Mechanisms of TIA</u>:
A. **Tight stenosis** + BP↓ or oxygenation↓ → low-flow TIA (exaggerated by hypoxemia, hyperviscosity, etc)

B. **Thrombosis**
C. **Embolism** (carotid > vertebrobasilar)
D. **Minor bleeds**.

- collateral blood vessels may enlarge to improve blood flow to affected area, thus ending TIA.
- *risk of stroke is highest soon after TIA* (5% during first month, 20-25% within 2 years) – TIAs are emergency – treatment must be started without delay (TIA is equivalent to unstable angina)!

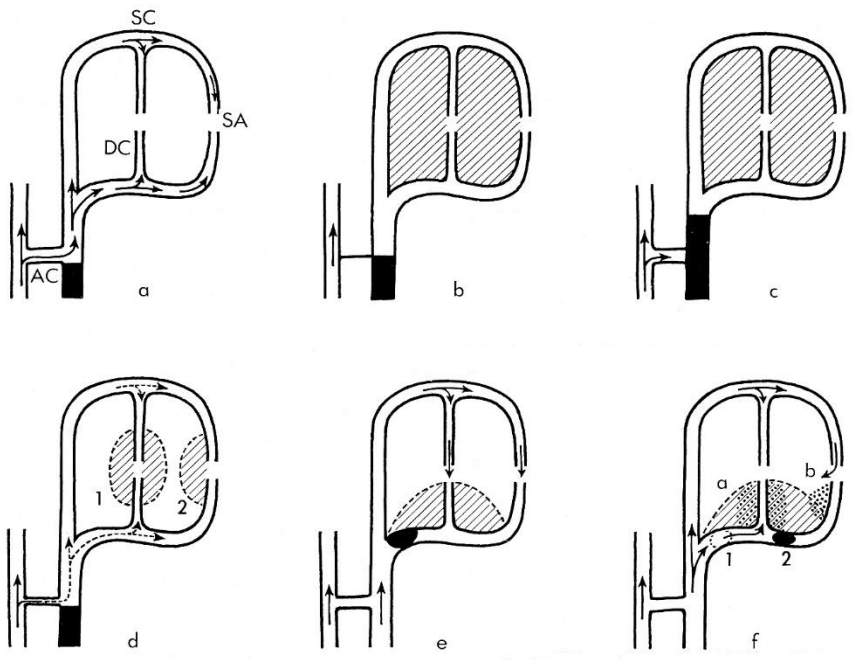


Figure 21–8. Respective roles of the anastomotic substitution pathways of circulatory supply and of the type of vascular occlusion in determining the occurrence and extent of cerebral lesions (*AC*, anastomotic vascular network; *SC*, superficial arterial circulation; *DC*, deep vascular territory; *SA*, superficial meningeal anastomoses).
a, Arterial occlusion, but with effective and adequate anastomotic substitution network of supply: no infarction.
b, Arterial occlusion without anatomically effective anastomotic network of supply *(AC)*: massive infarction of the corresponding cerebral territory.
c, Arterial occlusion extending beyond the origin of the anastomotic network of supply. No anastomotic substitution byway of vascular supply: massive infarction.
d, Occlusion proximal to the anastomotic network of supply. Insufficient anastomotic substitution byway of arterial supply. Anemic infarct of variable extent in territory (2) distal to the junction of two vascular territories (last field of irrigation or watershed infarct) and in border zone between superficial and deep vascular territories (1).
e, Proximal occlusion of one dividing branch; anastomotic substitution byway of vascular supply provided by superficial meningeal anastomosis: limited proximal infarction.
f, Embolic occlusion. Mobilization of thrombus from 1 to 2. Sudden occlusion in 1, resulting in total ischemia of both deep and superficial vascular territories and in hemorrhages in the superficial territory when border zones are undergoing reirrigation *(b)*; secondary mobilization of thrombus in 2, with hemorrhages due to secondary eruption of blood into the original ischemic deep vascular territory *(a)* (hemorrhagic infarct).

EPIDEMIOLOGY

INCIDENCE ≈ 0.5-1.0 per 1000 population (20-30 per 1000 of those over age 75 years).

- incidence for ***black men*** is 1.5 times higher than for white men; that for ***black women*** is 2.3 times higher than for white women.
- male-to-female ratio ≈ 1.35 : 1
- prevalence of SILENT CEREBRAL INFARCTS (detected by neuroimaging screening) is ≈ **10%** among apparently healthy middle-aged adults; 52% are in basal ganglia.

RISK FACTORS for ischemic stroke

- parallel those for atherosclerotic vascular disease in general:

Overall, 5 major risk factors "the big 5"

- **Hypertension**
- **Atrial fibrillation**
- **Diabetes**
- **Physical inactivity**
- **Smoking**

⇩

Account for 2/3 of all first-ever strokes

A. NONMODIFIABLE risk factors:

1) **advanced age** (75% strokes occur after age of 65) – strongest risk factor!
   - stroke can occur in patients of all ages (incl. children).
   - stroke incidence doubles with each successive decade (between ages 45 and 85).
   - in Framingham study mean age of stroke - 65.4 yrs (men) and 66.1 yrs (women).
   - as population ages, burden of stroke becomes greater.
2) **males** have slightly [≈1.3 times] higher risk than women (vs. cardiovascular ischemia – male risk is 3 times higher).
3) **black race** (because of higher prevalence, earlier onset, greater severity, and poorer control of hypertension)
   - Hispanics have lower stroke incidence than whites (but more frequent lacunar strokes and stroke at earlier age).
4) **stroke in history** - powerful predictor of recurrent stroke! (vs. asymptomatic carotid stenosis – weak risk factor)
5) heredity
6) **migraine with aura**
7) sickle cell disease (blood hyperviscosity)
8) fibromuscular dysplasia
9) AIDS - additional risk factor independent of other stroke-related risk factors. see p. 270 >>

B. MODIFIABLE risk factors:

1) **hypertension** (second strongest risk factor!) - accelerates ***atherosclerosis*** progression and predisposes to ***small-vessel disease***.
   - stroke incidence is proportional to BP level.
   - all components of blood pressure (systolic, diastolic, mean) independently correlate with incidence of stroke.
     systolic pressure is probably direct cause of stroke that is independent of secondary complications of hypertension, such as atherosclerosis
   - systolic BP↓ by 10 mmHg → stroke risk↓ by 35-40%.
2) **cardiac disease** - atrial fibrillation (stroke risk↑ 5 times – i.e. 4.5% per year; ≈ 50% embolic strokes), coronary artery disease, MI (esp. anterior wall or septum), valvular disease, mitral stenosis / prolapse, anomalies with right to left shunting (e.g. patent foramen ovale), congestive heart failure, LVH on ECG.
3) **diabetes mellitus** (particularly contributes to development of intracranial atherosclerosis).
4) **hypercholesterolemia** (more important for coronary artery disease than stroke).

5) **TIAs** (first year after TIA has greatest stroke risk); TIAs precede stroke in < 20% patients.
6) **carotid stenosis** (esp. > 75% - annual stroke risk 3.3%)
7) **obstructive sleep apnea**; for *men*, stroke risk increases with increasing OSA severity (for *women*, only severe OSA can increase stroke risk).
8) **hormone therapy (postmenopausal, oral contraceptive)** – increases stroke risk 40% (estrogen alone) or 30% (estrogen + progestin); risk↑ with higher doses.
9) **lupus anticoagulant** (40-fold increase in risk for stroke)
10) **homocystinuria** (accelerated atherosclerosis, arterial / venous thromboses; 1/3 patients have ≥ 1 strokes by age of 15 yrs), **hyperhomocysteinemia**;

    N.B. homocysteine-lowering interventions (vitamin B6, B12, folic acid) do not prevent MI or stroke!

11) **cigarette smoking** (clear dose-response relationship)
    - cigarette smoking > 1 pack per day → stroke risk↑ 11 times (risk attributed to cigarette smoking is even greater for SAH!).
    - smoking + oral contraceptive use → stroke risk↑ 22 times.
    - with smoking cessation, stroke risk declines after 2-5 years.
12) **excessive alcohol** (more important for hemorrhagic stroke)
    - J-shaped relationship: stroke risk increases with moderate to *heavy alcohol consumption** and decreases with *light drinking*.

    *combination of hemoconcentration and hypertension
13) **illicit drugs** (amphetamines, cocaine)
14) obesity & physical inactivity – questionable as independent risk factors.

MORTALITY

- stroke is 3rd most common cause of death (following cardiac diseases and cancer) in USA.
  2nd most common cause worldwide:
  highest rates - Portugal, China, Korea, most of Eastern Europe;
  lowest rates - Switzerland, Canada, United States.
- age-adjusted mortality ≈ 50-100/100,000 population/year (stroke accounts for 10% deaths).
- 23-29% patients die within 1 year following stroke (8-20% within 1 month);
  - death *within first week* is usually result of **herniation**.
  - death *after first week* is result of **infectious complications** (pneumonia, UTI) and **MI**.
- fatality:
  51% - in black males
  39.2% - in black females
  39.2% - in white females
  26.3% - in white males
  N.B. in whites, stroke incidence is higher in males, but mortality is higher in females.

MORBIDITY

- stroke is most common cause of adult disability in USA.
- stroke survivors:
  50-71% have vocational disability
  24-53% need help in taking care of themselves
  20-22% need assistance for ambulation
  16% need to be placed in institution (assisted living).
- 32% stroke survivors have **depression**, 48% have **hemiparesis**, 12-18% are **aphasic**.

CLINICAL FEATURES

	Embolus	Large Vessel Thrombosis	Lacune	Intracerebral Hemorrhage	SAH
Location	Peripheral (cortical)	Variable (depends on vessel)	Pons, internal capsule	Deep (basal ganglia thalamus, cerebellum)	Vessels at junction of circle of Willis
Onset	Sudden (maximum deficit at onset)	Sudden, gradual, stepwise, or stuttering		Smooth (deficit develops over minutes ÷ hours)	Sudden, few or no focal signs
When	Awake	Asleep or inactive		Awake and active	Asleep or inactive
Warning (TIA)	None	Usually	Variable, TIAs may occur	None	None (± "sentinel leaks")
Headache	Sometimes	Sometimes	No	**Usually**	**Always** (stiff neck)
Mental status	Normal	May be impaired*	Normal	**Usually impaired****	**Usually impaired****

*with massive or brainstem stroke
**due to ICP↑, developing hydrocephalus

TIME COURSE

Premonitory symptoms are infrequent; < 20% stroke patients have **prior TIA**.
- TIAs confer 10% risk of stroke within 30 days (≈ 50% strokes occurring after TIA, do it within 48 hours of TIA), 30% within 3 yrs, 50% within 5 yrs.
- **focal** premonitory symptoms predate ***infarction*** (rather than ***hemorrhage***).
- *TIA symptoms are similar to those produced during full stroke*, but may be so *nonspecific* that they are not recognized as signs of impending stroke.
- fleeting episodes (lasting ***only few seconds***) are not likely to be TIAs.
- attack that *does not* include either *motor defect*, *visual loss*, or *aphasia* is unusual - should be reviewed carefully before accepting TIA as diagnosis.

Sudden focal change in neurological status (hallmark of neurovascular dysfunction):

A. Most strokes reach maximal neurological deficit ***within few hours*** (vs. TIAs - reach maximum almost immediately*); involved body parts are ***affected simultaneously***;
   Historical term for stroke stable for ≥ 72 hrs – "COMPLETED STROKE"

   *no symptoms → maximal symptoms in < 5 minutes

B. In some strokes, neurological deficit occurs in ***stepwise (stuttering) progressive pattern***;
   Historical term - STROKE IN EVOLUTION (s. PROGRESSIVE STROKE, UNSTABLE STROKE).

   Treatment to limit brain damage may be possible!

   Deciding **stroke stability / completeness** may be difficult, since in theory *all strokes require some period to reach stable maximum* (as practical matter, distinction is based on severity of functional loss, e.g. hemiplegia versus hemiparesis)

  - in carotid distribution, there is usually little likelihood of progression after 24 hours.
  - in vertebrobasilar distribution, progression may continue for up to 72 hours.
  - causes of "progression" of ischemic event (one or combination):
    1) cerebral edema / herniation (only in large strokes)
    2) thrombus propagation (s. thrombus-in-evolution) - progressively obliterating collateral branches
    3) occlusion of stenotic artery due to thrombus
    4) recurrent embolism
    5) hemorrhagic transformation
    6) hypoperfusion due to systemic hypotension (e.g. myocardial ischemia, cardiac arrhythmias, congestive heart failure)
    7) hypoxia (e.g. pneumonia, pulmonary embolus)
    8) seizures
    9) medication effects
    10) other medical conditions (e.g. electrolyte disturbances, dehydration, sepsis)

Establishing TIME OF ONSET is especially critical when *THROMBOLYTIC THERAPY* is option.
- if patient **awakens with symptoms**, time of onset is defined as time patient was last seen without symptoms.
- *help of family members* / *bystanders* is required in right hemispheric strokes (with neglect) or left hemispheric strokes (with aphasia).

FURTHER COURSE
- function commonly improves within first few days (unless infarct is extensive); further improvement occurs gradually for up to 1 yr.

EMBOLIC strokes

a) ***no warning***
b) ***history of infarctions in other vascular territories*** (incl. systemic emboli to limbs or other organs).

- abrupt onset (most often *during waking hours*) with maximum deficit at onset.
- emboli tend to move peripherally, giving **cortical deficits** ± **headache** and/or **focal seizures**.
- deficit usually improves within 1-2 days (sometimes within hours).
- *thoroughly examine heart* - most common source of emboli!
- ***hemorrhagic transformation*** typically occurs 12-36 h after embolization and is often asymptomatic (frank hemorrhage always causes clinical worsening).

THROMBOTIC strokes

- often occur *during sleep (inactivity)* - present upon arising in morning.
- deficit usually progresses in stepwise fashion - may take hours ÷ days to reach maximum.

TIA warning is common in thrombotic strokes.

  - TIA symptoms frequently vary.
  - TIAs in anterior circulation more frequently herald presence of ICA disease than of intracranial atherosclerosis.
  - TIA symptoms precede stroke by days ÷ months.

LACUNAR strokes

- occur abruptly or in stuttering fashion over hours ÷ days.
- there may be **stereotyped TIA warning** over hours to days.
- ***hypertension*** is usually present; headache is rare.

VITAL SIGNS

In ED, start with PHYSICAL EXAMINATION of ***all major organ systems***, starting with **ABCs & vital signs**.
  - ischemic strokes (unless very large or involving brainstem) do not cause immediate ABC problems (vs. intracerebral hemorrhage / SAH - frequent problems with airway protection, ventilation, cardiac rhythm).
  - *constant reassessment is critical* - patients can deteriorate quickly (esp. with hemorrhagic stroke).
- with suspected ischemic stroke, examination should be directed to cardiovascular disease - heart rate & rhythm, cardiac murmurs, BP (incl. differences between two arms or orthostatic changes);
  - ***ARTERIAL HYPERTENSION is common*** (esp. in hemorrhagic stroke); BP decreases spontaneously over few days - medical intervention is not proven to be beneficial (unless malignant hypertension, AMI, CHF, or aortic dissection).
- ***HYPERTHERMIA*** in early phase (usually indication of systemic infection) may be direct consequence of stroke (esp. brain stem or SAH).
- ***HYPERHIDROSIS*** (sometimes unilateral) may follow brain stem hemorrhage or large hemispheric stroke.

NEUROLOGIC EXAMINATION

NEUROVASCULAR EXAMINATION → see p. D1 >>

Neurologic signs & symptoms usually cannot be used to definitively differentiate type of stroke (ischemic vs. hemorrhagic).

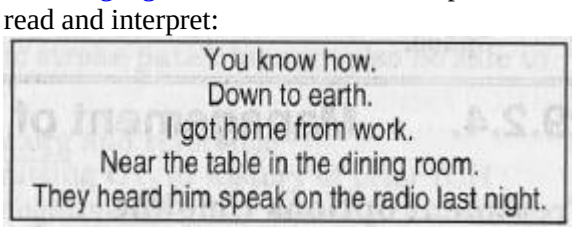
Exceptions - features more likely in hemorrhage than infarction:
1) **catastrophically acute onset**
2) **headache**; but *onset headaches* are present in 17% ischemic strokes (esp. **large-vessel**, **embolic**).
3) **vomiting**; but *vomiting* is common in **cerebellar** / **brainstem** strokes.
4) **seizures**; but occur acutely at onset of 5-10% ischemic strokes (esp. **embolic**).
    - acute (early) seizures are result of local metabolic alterations – such seizures are transient (self-limited).
    - seizures markedly increase O_2 demand → accelerated infarction of ischemic tissue.
5) **coma**; *ALERTNESS* is generally preserved in acute strokes, *unless lesion involves RAS* ***directly*** (**basilar artery embolism** → diencephalic or rostral brain stem damage → initial loss of consciousness) or ***indirectly*** (by **mass effect** → progressive loss of consciousness).
    - in patients who are not fully alert, *metabolic derangement* must be excluded (esp. hypoglycemia - may cause focal signs that mimic stroke!).

- "**silent stroke**" may occur:
    a) patient & family are unaware of minor symptoms
    b) silent area of brain.
- ***hemorrhagic transformation*** (bland → hemorrhagic infarct) is usually clinically silent.
- multiple strokes may cause **multiinfarct (s. vascular) dementia**.

NATIONAL INSTITUTES OF HEALTH STROKE SCALE (NIHSS)

≥ **10** is significant stroke!
8-19 is moderate to severe stroke
≥ 20 is the most severe stroke

- useful tool in measuring neurological impairment.
- reliable and valid - used by most stroke teams and stroke neurologists.
- higher NIHSS scores correlate with *more proximal vascular lesions* (larger vessel occlusion → more widespread deficit); NIHSS score ***strongly correlates with outcome***.
- administer in order shown.
- record initial performance only (do not go back).

	Category	Score and Description	Score
1a	Level of consciousness (LOC)	0. **Alert** (keenly responsive) 1. **Drowsy** (arousable by minor stimulation to obey, answer or respond) 2. **Stuporous** (requires repeated stimulation to attend, or requires strong painful stimulation to make movements (not stereotyped)) 3. **Coma** (responds only with reflex motor posturing or autonomic effects, or totally unresponsive, flaccid and areflexic)	
1b	LOC questions – ask: month age	0. Answers **both** correctly (no credit for being close) 1. **Answers 1 correctly** or cannot answer because of problem **not secondary to aphasia** (ET tube, orotracheal trauma, severe dysarthria, language barrier) 2. **Incorrect on both** or is aphasic, stuporous, or does not comprehend questions	
1c	LOC commands – ask: open-close eyes grip and release nonparetic hand	0. Obeys both correctly 1. Obeys 1 correctly 2. Incorrect on both Substitute another 1-step command if both hands cannot be used. Credit is given for unequivocal attempt even if it cannot be completed due to weakness. If there is no response to commands, demonstrate (pantomime) task. Record only first attempt.	
2	Best horizontal gaze (follow finger*) *use motion to attract attention of aphasic patients	0. Normal 1. Partial gaze palsy or isolated CN III, IV or VI paresis 2. **Forced deviation** or **total gaze paresis** not overcome by oculocephalic (Doll's eyes) maneuver (do not do caloric testing)	
3	Best visual (visual fields) - test upper and lower quadrants by confrontation (may be scored as normal if patient looks at side of finger movement); use ocular threat where consciousness or comprehension limits testing. - then test with double sided simultaneous stimulation (DSSS).	0. No visual loss 1. Partial hemianopia or extinction to DSSS 2. Complete hemianopia 3. Bilateral hemianopia (i.e. blind, including cortical blindness)	
4	Facial palsy – ask (or pantomime) to show teeth, raise brows, squeeze eyes shut; use painful stimulus and grade grimace response in poorly responsive or non-comprehending patients	0. Normal 1. Minor 2. Partial (total or near total paralysis oflower face) 3. Complete of one or both sides (absent facial movement in upper and lower face)	
5a = left 5b = right	Motor arm left / right (raise 90° if sitting or 45° if supine, hold 10 seconds) may cue patient by actively lifting arms into position while verbally instructing patient to maintain position	For each limb: 0. No drift 1. Drift (but does not hit bed) 2. Cannot resist gravity (hits bed) 3. No effort against gravity (falls immediately) 4. No movement 9. Amputation, joint fusion	
6a = left 6b = right	Motor leg left / right (raise 30° in supine, hold 5 seconds)		
7	Limb ataxia (finger-nose, heel-shin) - looking for unilateral cerebellar lesion. Ataxia is scored only if clearly out of proportion to weakness. Ataxia is absent in patient who cannot; comprehend or is paralyzed.	0. Absent 1. Present in 1 limb 2. Present in 2 limbs 9. Amputation, joint fusion	
8	Sensory (pinprick to face, arm, leg) When consciousness or comprehension impaired, score sensation normal unless deficit clearly recognized (e.g. clear-cut asymmetry of grimace or withdrawal).	0. Normal 1. Partial loss (patient aware of being touched) 2. Severe loss (patient unaware of being touched in face, arm and leg) N.B. Only hemisensory losses attributed to stroke are counted as abnormal.	
9	Best language - name items, describe pictures, read and interpret: 	0. No aphasia 1. **Mild to moderate aphasia** (some loss of fluency, word finding errors, naming errors, paraphasias and/or impairment of communication by either comprehension or expression disability) 2. **Severe aphasia** (great need for inference, questioning and guessing by listener; limited range of information can be exchanged) 3. **Mute** or **global aphasia** or **coma** intubated patient should be asked to write	
10	Dysarthria (test if patient was normal on previous tests) - ask patient to read "mama, tip-top, fifty-fifty, thanks, huckleberry, baseball player, caterpillar"	0. Normal articulation 1. Mild to moderate dysarthria (slurs some words, can be understood with some difficulty) 2. Near to unintelligible or worse (unintelligible slurred speech in the absence of, or out of proportion to any dysphasia, or is mute/anarthric) 9. Intubated or other physical barrier	

11	Extinction and inattention (formerly neglect) (double simultaneous testing)	0. Normal, no sensory loss 1. Visual, tactile, auditory, spatial or personal inattention or extinction to DSSS in one of sensory modalities 2. Profound hemi-inattention or hemi-inattention to more than one modality. Does not recognize own hand or orients to only one side of space. If patient has severe visual loss preventing visual DSSS, but cutaneous stimuli are normal, score is normal	
		Total: 0-42	0- 42
12	Change from previous exam	Same Better Worse	S B W
13	Change from baseline	Same Better Worse	S B W

VASCULAR TERRITORIES

Vascular territories are constant → constant clinical features.

- if occlusion is **proximal in arterial tree**, ischemia may involve *more than one vascular territory*.
- **intracranial proximal occlusions** may result in both *penetrant artery* and *surface branch* territory infarction.
- significance of circle of Willis aberrations:
  – if both ACAs arise from common trunk (azygos ACA), ICA occlusion may cause bilateral leg weakness;
  – if one or both PCAs arise from ICA, occlusion of BA is less likely to cause visual symptoms.
- 25% of ischemic strokes occur in vertebrobasilar circulation.

ANTERIOR CEREBRAL ARTERY (ACA) DISTRIBUTION

1. Hemispheric ACA branches irrigate medial hemispheric wall:
   1) "leg area" → **contralateral leg* plegia & sensory loss** (discriminative and proprioceptive). *esp. distal
      – if damage includes recurrent artery of Heubner, face and arm are also weak.
      see below >>
   2) "genital area" (s. cortical micturition center in paracentral lobule) → **urinary incontinence**.

2. Corpus callosum (anterior part) → **ideomotor apraxia and tactile anomia of left limbs** (*ANTERIOR DISCONNECTION SYNDROME* - disconnection of left language-dominant hemisphere from right motor or sensory cortex).

3. *Bilateral ACA* (e.g. if both A_2 segments arise from single A_1 stem): orbitofrontal cortex, supplementary motor cortex, cingulate gyrus, deep limbic structures → **akinetic mutism** (apathy, abulia, motor inertia, or total unresponsiveness with open eyes), **paratonia** (gegenhalten), **suck and grasp reflexes**, **speech disturbances** (considered aphasic by some physicians and kind of motor inertia by others), impaired judgment and insight.
   – does not typically cause spastic paraparesis (more common with spinal cord disease or, rarely, occlusion of superior sagittal sinus).

- ACA infarctions are uncommon* (excluding vasospasm after SAH – commonest cause of ACA infarctions) ≈ 3% infarctions.
- A_1 stem occlusion is usually well tolerated because of collateral flow via AComA.

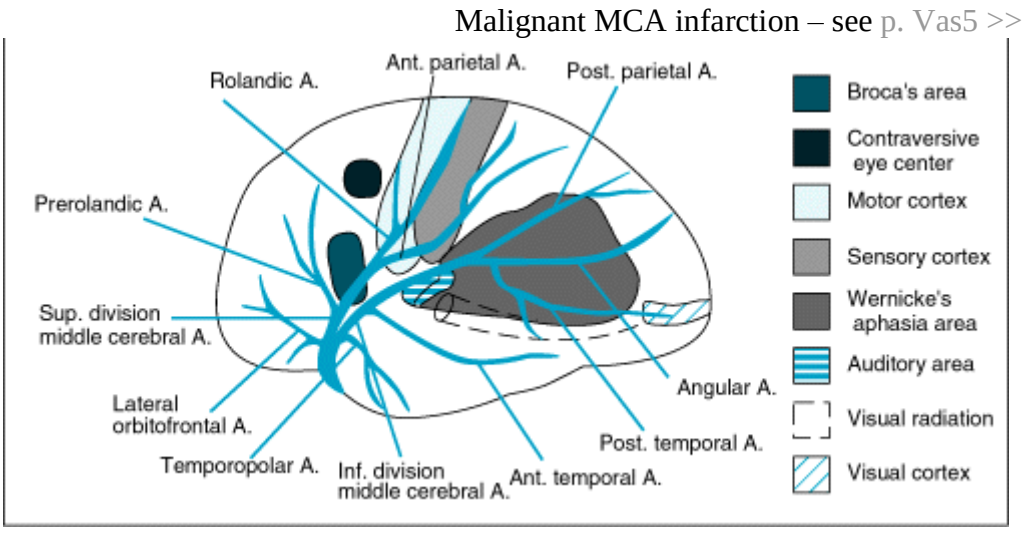
*embolism is not very likely + excellent collateral flow

MIDDLE CEREBRAL ARTERY (MCA) DISTRIBUTION

Malignant MCA infarction – see p. Vas5 >>

- most commonly affected distribution in carotid system (most commonly due to **embolism** or **ICA occlusion** in neck)

- ***cortical collaterals*** and differing arterial configurations may cause partial MCA syndromes.



	complete (M1 occlusion)	superior division	inferior division
(CL) weakness of UE > LE	X	X	
(CL) weakness of lower face	X	X	
(CL) hemisensory loss (UE & LE)	X	X	
(CL) hemisensory loss face (all modalities)	X	X	
(CL) neglect†	X	X	
(IL) gaze preference	X		
(CL) homonymous hemianopsia	X		X‡
receptive aphasia§ (Wernicke's area)	X		X
expressive aphasia§ (Broca's area)	X	X	
Gerstmann syndrome: with dominant parietal lobe infarct			

CL – contralateral
IL – ipsilateral
† with involvement of nondominant hemisphere
‡ plus CL upper quadrantanopsia
§ with involvement of dominant hemisphere

1. *Superior branch of MCA* → **contralateral hemianesthesia** (esp. discriminative modalities and proprioception*) greatest in face and arm.

   *may be severely disturbed → limb ataxia, pseudoathetosis

2. *Superior branch of MCA* → **contralateral hemiplegia** greatest in lower face & distal arm!!!

   vs. *central penetrating branches of MCA* → **pure motor hemiparesis** (face, arm, and leg equally affected) unaccompanied by visual, language, or sensory disturbances.

- motor loss is accompanied topographically by sensory loss.
- **BRACHIAL syndrome** - arm and hand weakness alone (embolic occlusion of single branch).
- ***clumsiness*** (slowness of movement) – resembles parkinsonian bradykinesia or cerebellar lesion.
- less often affected:
  1) leg – *ACA territory*
  2) proximal limbs, trunk, upper face, pharynx, jaw – represented *bihemispherically*.

3. **Contralateral conjugate gaze palsy** ("eyes look to stroke side") – lasts only 1-2 d. – frontal eye field.
   N.B. full-range oculocephalic / oculovestibular reflexes remain!

4. Geniculocalcarine tract → **contralateral homonymous hemianopia**
   - hemianopia more likely reflects **visual inattention** than true blindness, since deeply penetrating MCA branches supply only dorsal, parietal half of optic radiations!
   - in some cases, just **quadrantanopia**:
     superior branch of MCA (parietal lobe) → inferior quadrantanopia;
     inferior branch of MCA (temporal lobe) → superior quadrantanopia.

5. Side specific symptoms:

   Left MCA – **global aphasia**, **alexia & agraphia** (left angular gyrus), **Gerstmann's syndrome** (supramarginal gyrus);
   superior branch of left MCA → Broca aphasia
   FRONTAL OPERCULAR syndrome - facial weakness with Broca aphasia ± arm weakness.
   inferior branch of left MCA → Wernicke aphasia (without hemiparesis!)

   Right MCA – **spatial perception disturbance**, **left hemineglect**, **anosognosia** (parietal lobe), acute confusional state.

POSTERIOR CEREBRAL ARTERY (PCA) DISTRIBUTION

Postcommunal (≥ P_2) syndromes (peripheral or cortical territory)

Contralateral homonymous hemianopia (striate cortex, optic radiations, lateral geniculate body)
- macular (central) vision tends to be spared (*TUNNEL VISION*) – occipital pole is partially supplied by MCA!
- cortical lesions have feature of preserved opticokinetic nystagmus (vs. lesions of optic radiations), pupillary response.
- *bilateral PCA* → **cortical blindness**;
  ANTON syndrome (affected parietal cortices adjacent to calcarine cortex) – lack of awareness of being blind.
- *bilateral* occipitoparietal (superior occipitotemporal) lesions → **BALINT syndrome**.
  see p. Eye62 >>
- possible additional features (in blind field):
  - *callosal branches of left PCA* (left area 17, splenium of corpus callosum) → **pure alexia** without agraphia ± anomia for colors, acalculia.
  - *right PCA* → **left visual field neglect**.
  - partial preservation of vision, visual perseveration (palinopsia), visual hallucinations ("release hallucinations"), visual agnosias (achromatopsia, prosopagnosia, simultanagnosia), poor eye-hand coordination, difficulty coordinating gaze, metamorphopsia.

Bilateral mesiotemporal infarctions → severe and lasting **amnesia** (resembling Korsakoff syndrome) ± **agitated delirium**.
- TIAs that affect these areas may account for **TRANSIENT GLOBAL AMNESIA**. see p. S6 >>

Proximal precommunal (P_1) syndromes (central territory)

- midbrain, subthalamus, and thalamus

Penetrating PCA branches to DIENCEPHALON
1. *Thalamogeniculate branch* (posterior thalamic nuclei) → contralateral severe loss of all sensory modalities → after few weeks ÷ months → **thalamic pain (s. central post-stroke, Déjérine-Roussy) syndrome**. see p. S20 >>
2. Nucl. subthalamicus → **contralateral hemiballism**.

Penetrating PCA branches to MIDBRAIN
1. Supranuclear fibers to CN3, MLF, interstitial nucleus of Cajal, nucleus of Darkschewitsch, posterior commissure → **eye signs**: CN3 palsy, internuclear ophthalmoplegia, **PARINAUD syndrome**, corectopia (eccentrically positioned pupil).
2. Cerebral peduncle → **contralateral hemiplegia**, incl. **supranuclear CN7 palsy**.
   Ventral midbrain (WEBER) syndrome (cerebral peduncle and CN3) - contralateral hemiplegia with ipsilateral CN3 palsy. see p. A59 >>, p. Eye64 >>
3. Superior cerebellar outflow above its decussation → **contralateral ataxia**.
   CLAUDE syndrome (red nucleus or dentato-rubro-thalamic tract and issuing CN3) - contralateral cerebellar ataxia with ipsilateral CN3 palsy. see p. Eye64 >>
   BENEDIKT syndrome (red nucleus, superior cerebellar peduncle and issuing CN3) - contralateral hemichorea, hemiataxia, hemiathetosis. see p. Eye64 >>
   NOTHNAGEL syndrome see p. Eye64 >>
4. Pars reticulata of substantia nigra (or thalamus) → **peduncular hallucinosis** (formed vivid hallucinations of brightly colored scenes and objects).
5. Damage to RAS → **altered consciousness**.

Bilateral proximal PCA occlusion → extensive infarction in midbrain and subthalamus: coma, bilateral pyramidal signs, decerebrate rigidity.

INTERNAL CAROTID ARTERY (ICA) DISTRIBUTION

MCA (!) ± ACA ± **ipsilateral amaurosis fugax** details → see p. Vas7 >>
- complete ICA occlusion is found in 10-15%
- complete ophthalmic occlusion – only 10-15% chance of blindness (collateral blood supply from ethmoidal arteries); % much higher if more distal – central retinal artery (has no anastomoses).

VERTEBRAL ARTERY (VA), BASILAR ARTERY (BA) DISTRIBUTIONS

CIRCUMFERENTIAL (LATERAL) VESSELS perfuse *lateral brain stem & cerebellum* → standard *LATERAL SYNDROMES* - affect cerebellum*, sensation, and lateral cranial nerves. see p. A59 >>

*large cerebellar infarctions → edema, ICP↑ in posterior fossa → altered consciousness, hydrocephalus, herniation.

PERFORANT (PARAMEDIAN) VESSELS perfuse *midline brain stem structures* → great variability of *MIDLINE SYNDROMES* - affect pyramidal system, consciousness, and midline cranial nerves (extraocular muscles). see p. A59 >>

N.B. brain stem infarction is more often result of occlusion of VA or BA than of their paramedian or lateral branches.

- many different syndromes; in real life, combinations of syndromes are seen (vs. isolated classic syndromes) → varied, poorly defined and vague manifestations, often making diagnosis difficult.
- involvement of posterior fossa structures is suggested by:
  1) bilateral long tract signs (motor / sensory) (e.g. drop attacks, locked-in state)
  2) crossed motor / sensory signs (e.g. left face - right limb) – lesions in pons or lower.
     N.B. anterior circulation symptoms are limited to one side of body + hemiparesis and hemisensory loss parallel each other in individual limb!
  3) dissociated hemisensory loss (medial lemniscus vs. tr. spinothalamicus)
  4) cerebellar signs (e.g. ataxia)
  5) alterations in consciousness (!)
     N.B. posterior fossa strokes can swell → rapid unpredictable deterioration – check patient frequently!!! (H: EVD, posterior fossa decompression ± debridement)
  6) disconjugate eye movements (diplopia), nystagmus, vertigo
  7) Horner syndrome
  8) cranial nerve lesions not usually affected by single hemispheric infarcts (e.g. unilateral deafness, pharyngeal weakness)
- other suggestive symptoms: perioral numbness, tinnitus, dysarthria*, homonymous hemianopsia.

  *may also occur with carotid ischemia
- number of medical conditions may mimic vertebrobasilar ischemia: inappropriate use of antihypertensive medications, cardiac arrhythmias, anemia, brain tumors, inner ear pathology (incl. cerebellar-pontine angle tumors), benign vertiginous states, basilar artery migraine, post-SAH vasospasm.

Posterior Inferior Cerebellar Artery (PICA) syndrome

- lateral MEDULLARY (**Wallenberg**) syndrome (CN9, CN10, nucl. tractus solitarii of CN7 + lateral structures*). see p. A59 >>

Anterior Inferior Cerebellar Artery (AICA) syndrome

- lateral INFERIOR PONTINE syndrome (CN7, CN8, pontine gaze center + lateral structures*). see p. A59 >>

Superior Cerebellar Artery (SCA) syndrome

- lateral SUPERIOR PONTINE syndrome (lateral lemniscus + lateral structures*). see p. A59 >>

*nucl. sensorii of CN5, tr. spinothalamicus, tr. reticulospinalis, vestibular connections, inf. cerebellar peduncle.

Vertebral Artery (VA) syndrome

- **ends** (V_1 and V_4 segments) tend to be affected by atherosclerosis; **middle segments** (V_{2-3}) are subject to dissection, fibromuscular dysplasia, encroachment by osteophytic spurs.
- V_4 segment occlusion → combination of lateral and medial MEDULLARY syndromes see p. A59 >>

Basilar Artery (BA) syndrome

- bilateral signs:
  1) long tract dysfunction (sensory and motor), incl. locked-in state
  2) cranial nerve dysfunction
  3) cerebellar dysfunction
  4) stupor
- in complete occlusion of basilar artery, ***death*** often results (therapeutic goal is to recognize *impending** basilar occlusion before devastating infarction occurs!).

  *series of TIAs or slowly progressive, fluctuating stroke

Basilar Artery Apex (s. Top of Basilar, mesencephalo-thalamic) syndrome – infarction of midbrain, thalamus (paramedian thalamo-peduncular infarction), and portions of temporal and occipital lobes.

- usually caused by ***emboli*** – sudden onset.

Bilateral symptoms (various combinations):

1) initial reduction in arousal (up to coma)
2) amnesia, agitated delirium
3) abnormalities of vertical gaze and pupillary reactivity, Collier's sign
4) blindness, peduncular hallucinosis (visual hallucinations), Balint syndrome
5) long tract motor and sensory deficits, cerebellar ataxia

CENTRAL PENETRATING BRANCHES (LACUNAR STROKES)

Most lacunae are ***asymptomatic***.
Lacunae in critical zones → 5 characteristic syndromes: (Fisher listed > 70 syndromes in 1991)

N.B. no signs of cortical dysfunction (aphasia, seizures, etc)!

I. Pure hemiparesis (57%) - **tr. pyramidalis** in:

a) corona radiata
b) internal capsule (genu and posterior limb) - *central penetrating branches of M_1* (anterolateral central s. lenticulostriate arteries)
c) mid-cerebral peduncle
d) basis pontis
e) medullary pyramid

N.B. reliable localization based on clinical findings cannot be made!

Clinical features - paralysis of arm & leg on one side (monoparesis almost never occurs secondary to lacunar infarct!); possible additional features:

1) paralysis of face on the same side
2) transient numbness / subjective heaviness of affected limbs at onset of motor deficit.

- clinical course is often stuttering (symptoms develop in stepwise fashion over several hours).
- TIAs ("capsular warning") precede (within 48 h) pure hemiparesis in 30% patients.
- clinical course is more benign than that of other types of hemiplegia.

II. Pure hemisensory stroke (6-7%) - **nucl. ventralis posterior thalami** (rarely, parietal cortex, corona radiata, posterior limb of internal capsule, centrum semiovale/thalamocortical pathway).

Clinical features - persistent (or transient) paresthesias* and mild sensory loss over one side of body (incl. face, arm, trunk, and leg)

*affected parts are numb, hot, asleep, heavy, tight, itching, or "dead"

- sensory loss extends over entire side of body, splitting it almost exactly in midline (characteristic of thalamic / thalamocortical pathway lesions).
- symptoms are mainly paresthetic!

- bothersome dysesthetic symptoms (as in classic thalamic pain syndrome) have also been reported - may start at onset of symptoms or appear hours to months later.
- clinical course is usually benign (symptoms subside within few days ÷ weeks); sometimes after few weeks ÷ months → **thalamic pain (s. central post-stroke, Déjérine-Roussy) syndrome**.
- CT detection is poor

III. **Sensorimotor stroke** (20%) - **posteroventral thalamus** with **posterior limb of adjacent internal capsule** – this is unusual, because vascular supply of thalamus (PCA) is separate from one for internal capsule (MCA)!

IV. **Ataxic hemiparesis** (10%) - **tr. pyramidalis** + adjoining **frontopontocerebellar system** (i.e. lacunae in basis pontis at junctian of upper third and lower two thirds)

Clinical features - any combination of weakness and incoordination, out of proportion to weakness, on same side of body

e.g. homolateral ataxia and crural paresis, - i.e. leg weakness (esp. ankle and toes) and Babinski sign, associated with striking dysmetria of arm & leg on same side; dysarthria, nystagmus and unidirectional toppling possible

- face involvement is uncommon, no dysarthria?
- improvement occurs within days ÷ weeks.

V. **Clumsy hand - dysarthria** (6%) - ***upper paramedian basis pontis*** or ***genu of internal capsule***.

Clinical features:

1) supranuclear facial weakness, severe dysarthria, dysphagia, numb lips
2) mild hand weakness and clumsiness (± some weakness of arm / leg)

- prognosis is favorable.

If bilateral and multiple (**ÉTAT LACUNAIRE**, s. **ÉTAT CRIBLÉ**): [*Fr.* état – state]

1) **vascular dementia** (**BINSWANGER disease**) see p. S12 >>
2) **pseudobulbar palsy**
3) **imbalance, shuffling short-step gait** (**marche a petits pas**)
1) **incontinence**.

ANTERIOR CHOROIDAL artery (last branch of ICA before bifurcation into ACA and MCA): triple **H**

see p. A205 >>

Difficult to distinguish from MCA ischemia!

1) posterior limb of internal capsule → contralateral **Hemiparesis** (involving face, arm, and leg)
2) posterolateral nucleus of thalamus or thalamocortical fibers → contralateral **Hemisensory loss**
3) lateral geniculate body or early geniculocalcarine tract → contralateral **homonymous Hemianopsia** (with striking beak-like sparing of horizontal meridian).

- AChA territory is also supplied by penetrating vessels of MCA, PComA, PCA - patients frequently recover substantially.

MEDIAL STRIATE (s. **RECURRENT OF HEUBNER**) **artery** (branch of A_2) → portions of anterior limb of internal capsule → mild **weakness of face & arm** (proximal muscles weaker than distal) without sensory loss;

± unpredictable combinations of dysarthria, abulia, agitation, contralateral neglect, and language disturbance (caudate nucleus and, variably, head of putamen).

WATERSHED INFARCTS

- in junction zones between arterial territories.

- possible at onset of hypotension episode: *syncope*, *focal seizures*.
- **MCA territory borders** ("basket handle" arc):
  1) **transcortical aphasia**
  2) **bibrachial palsy and sensory loss** ("arm area" is in interface between ACA and MCA).
  3) **BALINT syndrome** (border zone between MCA and PCA). see p. Eye62 >
  4) defects in *higher cortical function* (dyslexia, dysgraphia, dyscalculia, etc).

  N.B. bilateral symptoms!
- also may be affected: vision (lower altitudinal visual field defects; saccade/pursuit defects), memory, basal nuclei, cerebellum (border zones between PICA, AICA, and SCA → gait and limb ataxia)
- also may be affected: midthoracic spinal cord (watershed area).
- if patients do not regain consciousness within 2-3 days, prognosis for return of independent function becomes poor.

ANOXIC INJURY

- basal ganglia injury is anatomical substrate that accounts for various **adventitious movements** frequently seen in survivors of cardiac arrest and other severe hypoxic-ischemic events.

DIFFERENTIAL DIAGNOSIS

1. Acute focal neurologic dysfunction (hallmark of TIA / stroke) – focal seizures (H: involuntary motor activity, positive sensory phenomena, march of symptoms, seizures occur before focal signs are evident).

   N.B. Todd's postictal paralysis following (unobserved) seizures is likely to imitate ischemic deficit! - rapid differentiation may be difficult!

2. Acute diffuse neurologic dysfunction ***without focal features*** – diffuse cerebral hypoperfusion (presyncope / syncope).

   N.B. diffuse cerebral hypoperfusion may cause ***focal neurologic symptoms*** if cerebral circulation has stenoses.

3. Gradual onset of symptoms with accumulation of deficits over time (as in stroke in evolution) – space-occupying lesion (e.g. neoplasm, abscess) - evolve in days ÷ weeks (longer than stroke).

4. Positive neurological phenomena* (distinctly unusual for neurovascular dysfunction!) – migraine.

   *e.g. visual hallucinations, scintillating visual symptoms

   N.B. migraine pathophysiology involves both *ischemic* and *non-ischemic* ("cortical spreading depression") mechanisms!

5. Transient (may persist for several days) paresis or aphasia associated with altered consciousness – hypoglycemia.

6. Coma + total paralysis of ocular motility + flaccid paralysis of limbs + preserved pupillary reactions (rare combination in stroke) – barbiturate intoxication.

Symptoms not to be considered as ischemic: isolated vertigo, isolated diplopia, isolated dysarthria, isolated unconsciousness, isolated confusion, isolated amnesia, drop attacks alone.

DIAGNOSIS – SEARCH FOR CAUSE

GENERAL MEDICAL EXAMINATION – clues to *etiopathogenesis*.
NEUROLOGIC EXAMINATION – clues to *lesion site*.

Evaluation must proceed especially rapidly in **TIAs** (high risk of subsequent ischemic stroke)!

BLOOD TESTS

1. **Electrolyte disorders**, **hyperglycemia** / **hypoglycemia**, **uremia** - may cause mental and physical deficits!
   - *transient mild hyperglycemia (glycosuria)* often follows stroke but does not approach elevations seen in diabetic coma.
   - **hyperglycemia** increases lactic acidosis in regions of ischemia, aggravating edema.
2. **CBC** with differential, platelet count, ESR.
   - ↑risk for stroke - sickle cell disease, polycythemia, thrombocytosis, subacute bacterial endocarditis, severe anemia, giant cell arteritis.
3. **Coagulation studies**
   - **PT**, **aPTT** - elevated INR may preclude thrombolysis!
   - younger patients who lack obvious causes for stroke → protein C, protein S, platelet function, tests for collagen vascular diseases, lupus anticoagulant & anticardiolipin antibodies.

     N.B. factor V Leiden gene, prothrombin gene mutations are associated with ***venous*** (but not arterial) thromboses!
4. Lipid analysis
5. Luetic serology (serum VDRL)

CARDIAC EXAMINATION

Cardiac monitoring (incl. BP) is recommended for first 24-48 hours (high frequency of cardiac dysfunction, e.g. due to increased circulating levels of catecholamines)

ECG - cardiac arrhythmias, acute ischemia / MI.

Chest X-ray

Echocardiography (esp. young patients, or otherwise unexplained ischemic stroke): ***transthoracic*** (TTE) or ***transesophageal*** (TEE) - intracardiac thrombi, valve vegetations, valvular stenosis / insufficiency, right-to-left shunting.

– TEE is more sensitive!!!

DOPPLER ULTRASONOGRAPHY

- can assess location and degree of occlusions in extracranial and large intracranial vessels.

- ***carotid duplex scanning*** is routinely performed early in evaluation (!!!), not only to [1]define cause of **stroke** but also to [2]stratify **TIA** patients for either medical management or carotid endarterectomy (symptomatic critical stenoses require anticoagulation before endarterectomy is performed).
- ***TCD*** can be used to detect flow restoration after thrombolytic therapy.

LUMBAR PUNCTURE

There is almost no indication for LP in suspected ischemic stroke or intracerebral hemorrhage!

- CSF is usually normal;
  – may show transient mild ÷ moderate *pleocytosis* (up to 500).
  – 50-500 *RBCs* is suggestive of embolus (hemorrhagic transformation → RBCs further↑).
  – *protein* may increase to 80 mg/dL, glucose may decrease slightly.
- rare indication - to rule out meningitis or SAH when ***CT is negative*** but clinical suspicion remains high.

  N.B. LP precludes thrombolysis* + risk of brain herniation (in large strokes)!

  *anticoagulation begun within 6 hours after LP risks causing spinal epidural hematoma

OPHTHALMOSCOPY

1) papilledema
2) retinal cholesterol / platelet-fibrin emboli (Hollenhorst plaques)
3) retinal hypertensive changes
4) diabetic retinopathy

VASCULAR IMAGING

- see below

DIAGNOSIS – SEARCH FOR STROKE

Three simplified stages:

1. **Blood flow abnormalities** - can be detected immediately after onset of stroke:
   1) ***macrovascular level*** - angiography, MRA, CTA.
   2) ***microvascular level*** - perfusion studies (CT or MR perfusion imaging, Xenon-CT, SPECT, PET).
2. **Cellular dysfunction** - electrical activity↓ (EEG), cytotoxic edema (MR diffusion imaging, CT).
3. **Structural breakdown**:

   SUBACUTE phase - vasogenic edema: CT (hypodensity), MRI (T1-hypodensity, T2-hyperintensity)
   - vasogenic edema involves both grey and white matter (extensive white matter edema without cortical involvement suggests alternative diagnoses – tumour, infection, etc).
   - vasogenic edema starts to regress after 2nd week.

   CHRONIC phase - encephalomalacia with focal atrophy (enlargement of adjacent sulci and ventricles).

Contrast enhancement reflects **BBB disruption** (vasogenic edema, initially) → **neovascularity** (associated with repair, can persist for 8–12 months after stroke).

- in most instances, use of IV contrast is not required for diagnosis of infarction.
- contrast agents:
  1) risk of *neurotoxicity* to ischemic tissue
  2) may *normalize density* of otherwise hypodense infarct, making infarct less visible!

EEG

- polymorphic delta waves over stroke region (esp. anterior-circulation large-vessel disease).

- EEG may be abnormal in ***early hours after stroke*** (when CT remains normal).
- focal EEG abnormalities accompany half of hemispheric TIAs.
- EEG *gradually improves with time* (vs. focal slowing in **neoplasms** - remains same or worsens).
- normal EEG (in patient with neurologic deficit) strongly suggests LACUNAR infarction (subcortical, brainstem).

N.B. EEG is usually normal in POSTERIOR-CIRCULATION or LACUNAR strokes

STRUCTURAL imaging

Two main purposes:
1. Traditional purpose - ***differential diagnosis*** (may be indication for contrast-enhanced imaging*).
2. Modern purpose - ***identification of early ischemic change*** (important for thrombolytic treatment).

*e.g. tumors, abscesses usually demonstrate enhancing mass (vs. stroke)

Most sensitive and specific imaging is DWI-MRI !!!

TIA – negative imaging (analogy with concussion in TBI)

CT

- performed urgently (as first baseline test) to exclude hemorrhage (noncontrast CT is very sensitive and inexpensive!) or alternative causes of patient's symptoms (e.g. tumor).

Recanalization strategies require absence of intracranial hemorrhage on CT

CT cannot always detect cerebral infarction - size, location, and age of lesion affect lesion's visibility:

I. Size of lesion - infarcts < 5 mm in diameter often escape CT detection.

II. Location of lesion - infarcts in posterior fossa can be obscured by bone artefacts (H: MRI).

III. Age of lesion - stroke visibility by CT:
5% - within first 12 hours;
50% - within 24-48 hours;
90% - by end of 1st week.

- CT is not very sensitive for early ischemia - CT is often negative in first few days (ISODENSE zone), contrast enhancement may or may not occur.

Normal CT within first several hours is consistent with ischemic stroke!

Subtle signs of early ischemia:
1) **dense MCA sign** (low sensitivity, but if present it is very specific and earliest detectable change on CT) - suggests *fresh thrombus in horizontal segment of MCA* (risk for significant hemispheric stroke) → aggressive thrombolytic therapy.
   – heavily calcified MCAs can occasionally mimic this sign, but are usually bilateral.
2) focal low attenuation within gray matte,.
3) loss of gray-white matter interface, obscuration of basal nuclei
4) loss of insular ribbon (hypodensity involving insular region)
5) loss (effacement) of sulci

2)-4) reflect cytotoxic edema (grey matter decreases its Hounsfield number - no longer distinguishable from adjacent white matter)

N.B. EARLY (within 24 hours) ***mass effect with hypodensity*** (edema) suggest *irreversible injury with collateral supply* (higher risk of hemorrhage if given thrombolytics);
   – significant hypodensity (on baseline scan) should prompt physician to question time of onset.
   – hypodensity in area > 1/3 of MCA distribution is contraindication for thrombolytics and indication for hemicraniectomy.

- standard CT techniques do not distinguish ischemia from infarction - physician may be frustrated in determining how much tissue is viable / permanently damaged (stable Xe-CT was used in the past; now - pCT).

After 24 h, infarct is usually visible as HYPODENSITY (vasogenic edema peaks between 3 and 5 days) with increasingly well-demarcated margins and decreasing mass effect (as edema decreases after 2nd week) in ***single vascular distribution***.
   – it is highly unusual for infarct to have significant mass effect after 2nd week.
   – infarct margins should be clearly defined within 3 weeks.

- **temporary contrast-enhancement** (usually seen within 1 week and may persist for 2 weeks ÷ 2 months) often assumes gyral pattern (aka "ribbon" enhancement)

N.B. not associated with significant mass effect (vs. brain tumors)!

rule of thumb: there should not be enhancement at the same time there is mass effect

rule of 2's: 2% enhance at 2 days, 2% enhance at 2 mos

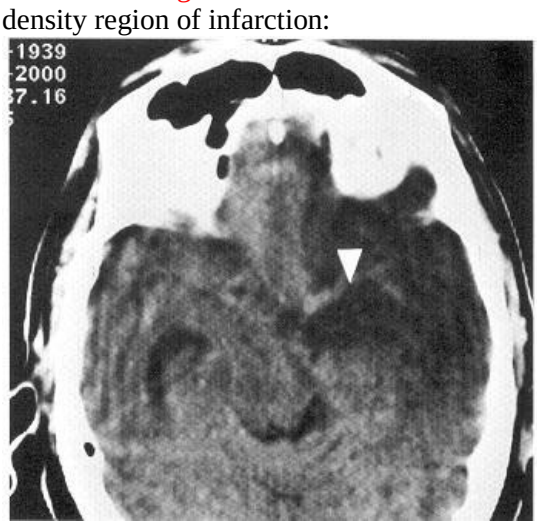
- in 5-10% there may be short window (at around day 7-10) where stroke becomes isodense - "fogging effect"; IV contrast will usually demonstrate these.

Late (> 2-5 weeks) – ***focal demarcated atrophy*** ("negative mass effect") without contrast enhancement, area approaches CSF density.

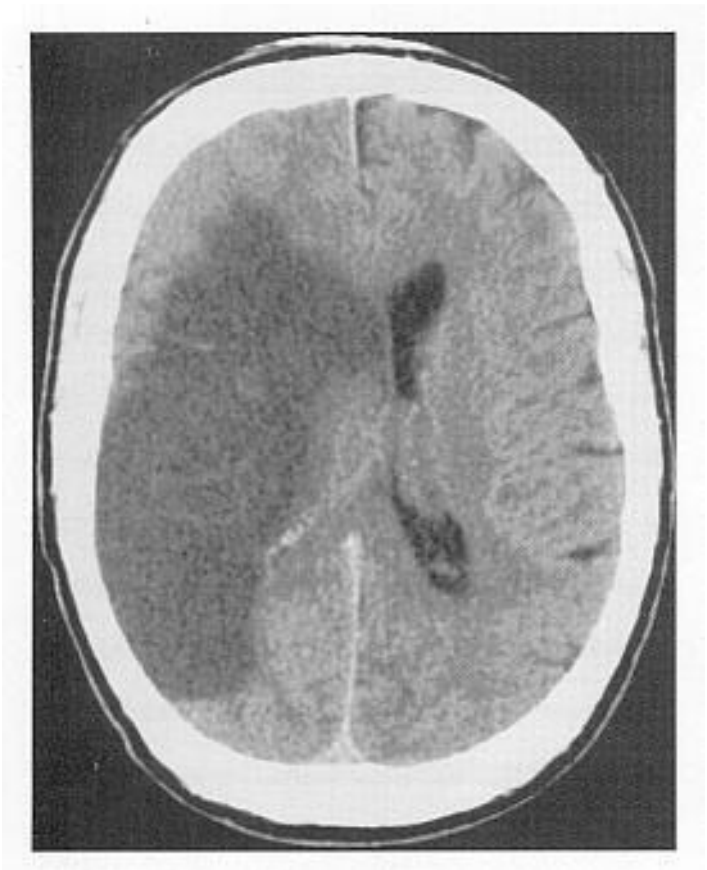
- only 1-2% of strokes calcify (in kids; none in adults*)

*in adult, calcifications almost rule-out stroke (consider AVM, low grade tumor ...).

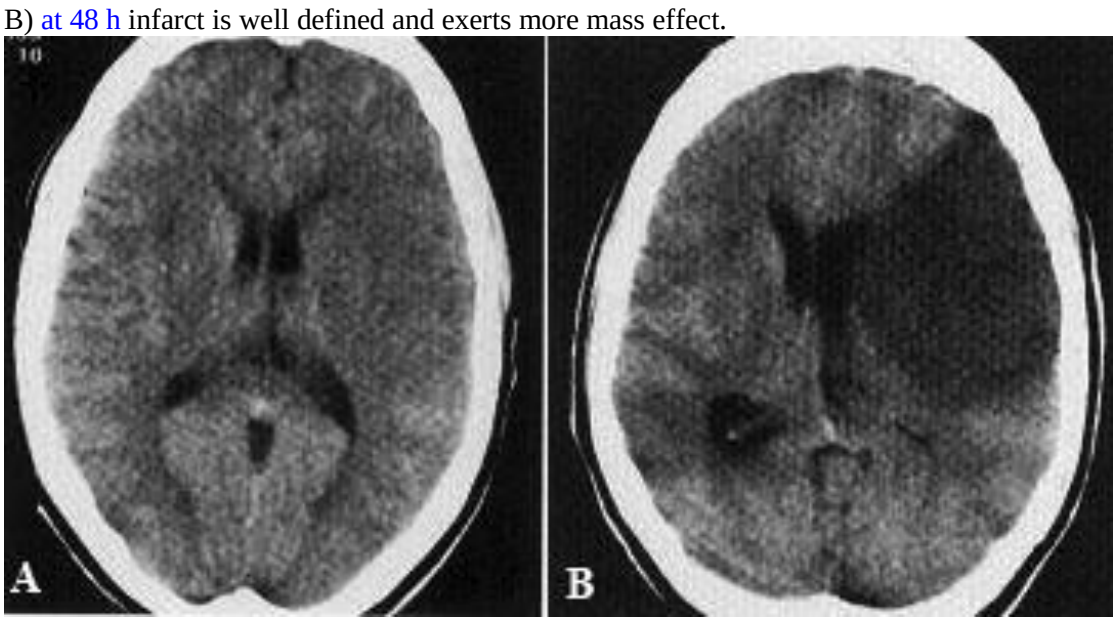
Dense MCA sign - acute thrombus in left MCA (*arrow*) appears dense and is easily seen in surrounding low-density region of infarction:



Infarction of right MCA (including lateral lenticulostriate perforators to caudate and putamen) - sharp boundaries, loss of gray-white differentiation, edema causing midline shift:



Acute ischemic infarct in left MCA territory:
A) CT < 24 h from stroke onset - loss of grey-white-matter differentiation in left frontal region and obscuration of caudate and lentiform nuclei; effacement of left frontal sulci.
B) at 48 h infarct is well defined and exerts more mass effect.

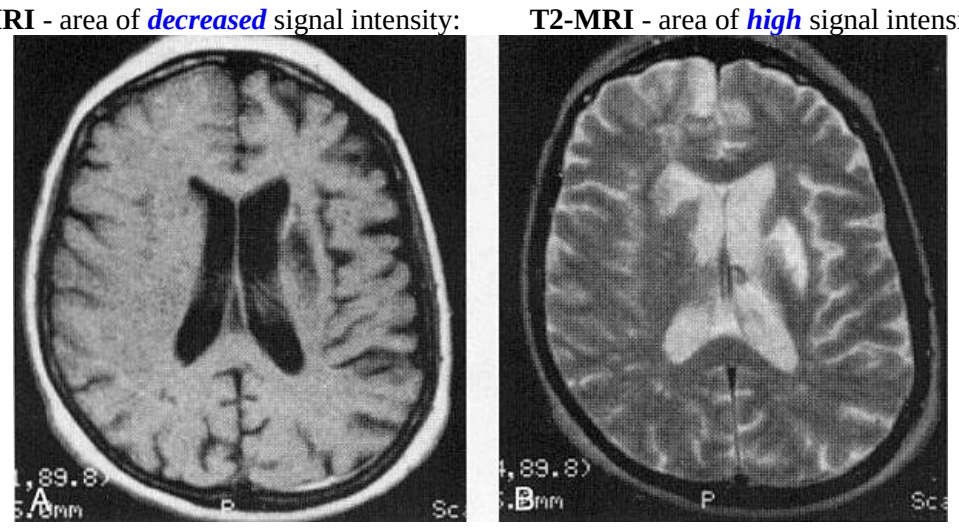


MRI

- superior to CT (esp. early lesions, lesions in posterior fossa, small lacunar lesions).
- MRI is not used acutely (difficult patient monitoring in MRI unit).

Acute infarct in right basal ganglia (seen only as vague mass effect) + old infarct in left basal ganglia (no mass effect, but with signal changes):

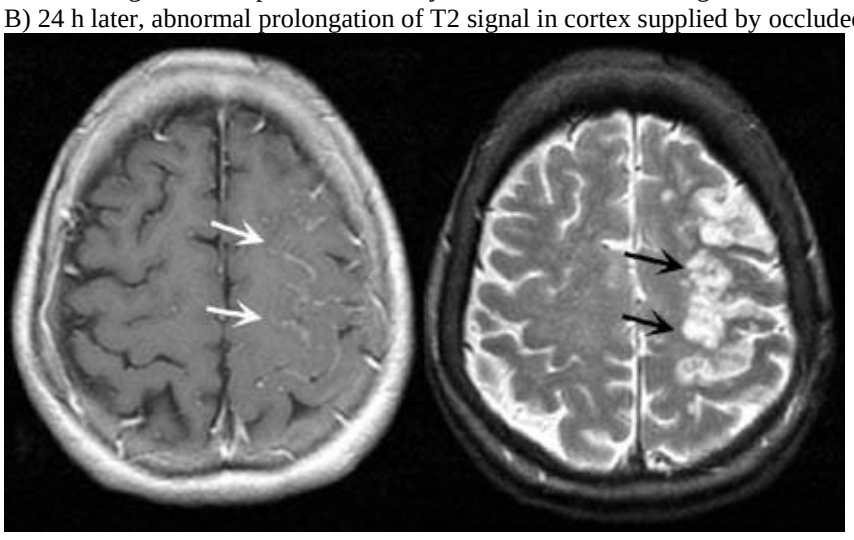
T1-MRI - area of ***decreased*** signal intensity: **T2-MRI** - area of ***high*** signal intensity:



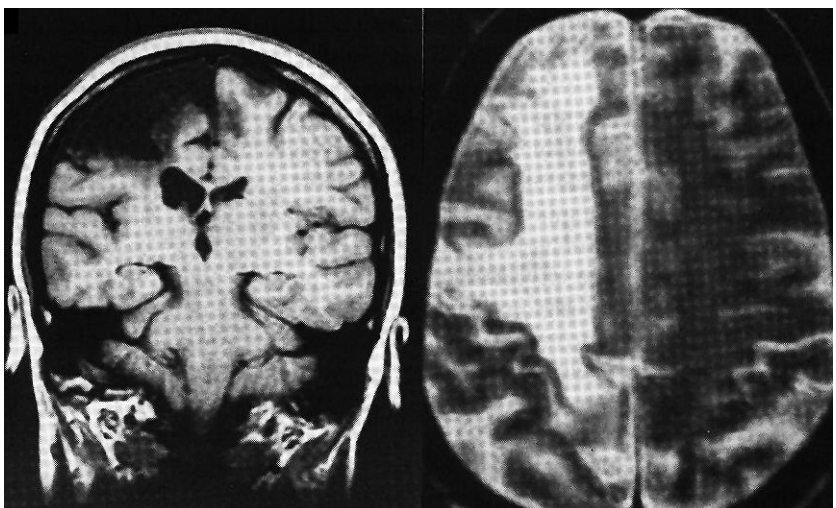
- **lack of flow void** (occlusion of major intracerebral vessel) represents MRI equivalent of "dense MCA sign" on CT.
- ***hemorrhagic transformation*** (can occur during first 2 weeks) - detected easily on MRI (hyperintense area on T1-weighted / hypointense area on T2-weighted images).
- ***Wallerian degeneration*** - evanescent high-T2-signal change in corticospinal tract and brain stem atrophy.
- **transitional enhancement** (usually IV contrast is not used for stroke)
    1) ***intravascular enhancement***: occurs in 75% of 1-3 day-old cortical infarcts, and is due to sluggish flow and vasodilatation (thus, it is not seen with complete occlusion).
    2) ***meningeal enhancement*** (especially dura): occurs in 35% of 1-3 day-old cortical infarcts (not seen in deep cerebral or brainstem strokes).
    3) ***parenchymal enhancement***: classically as cortical / subcortical gyral ribbon enhancement; not be apparent for first 1-2 days, and gradually approaches 100% by 1 week; may eliminate "fogging effect" (as on CT) which may obscure some strokes.

        N.B. by the time stroke starts to enhance, edema is subsided (no mass effect – differential from tumors)

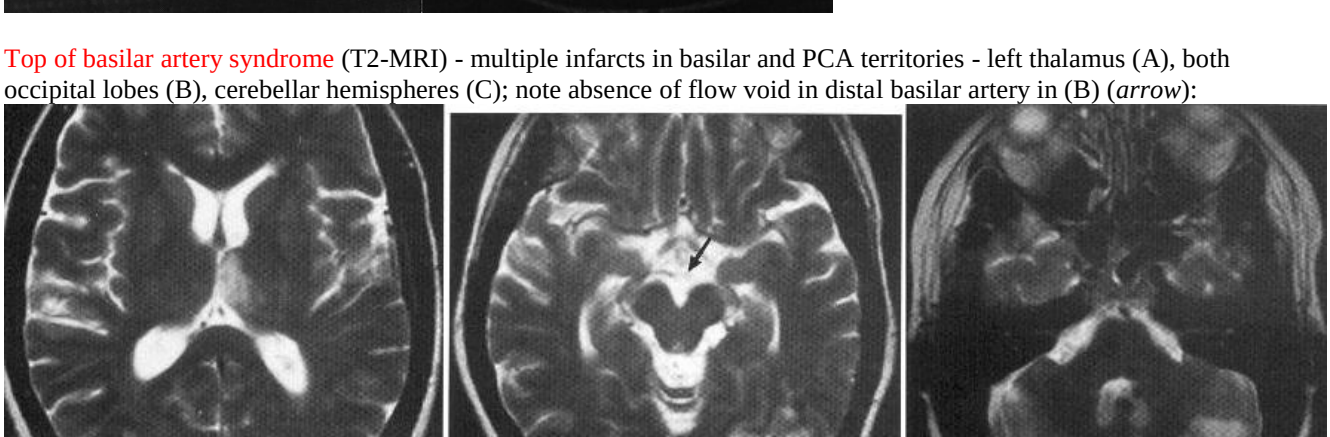
Left MCA infarction:
A) postcontrast T1-MRI: contrast enhancement within vascular bed (*white arrows*) distal to high-grade stenosis or occlusion - gadolinium percolates slowly into these vessels through collaterals.
B) 24 h later, abnormal prolongation of T2 signal in cortex supplied by occluded MCA (*black arrows*).



Right ICA infarction - A) T1-MRI B) T2-MRI:

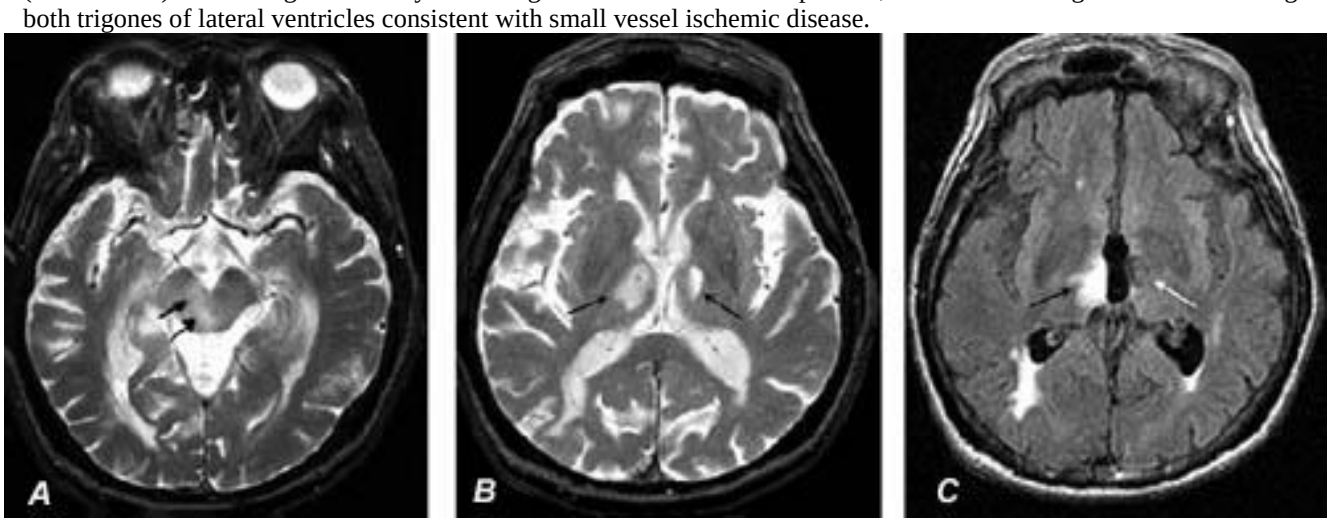


Top of basilar artery syndrome (T2-MRI) - multiple infarcts in basilar and PCA territories - left thalamus (A), both occipital lobes (B), cerebellar hemispheres (C); note absence of flow void in distal basilar artery in (B) (*arrow*):

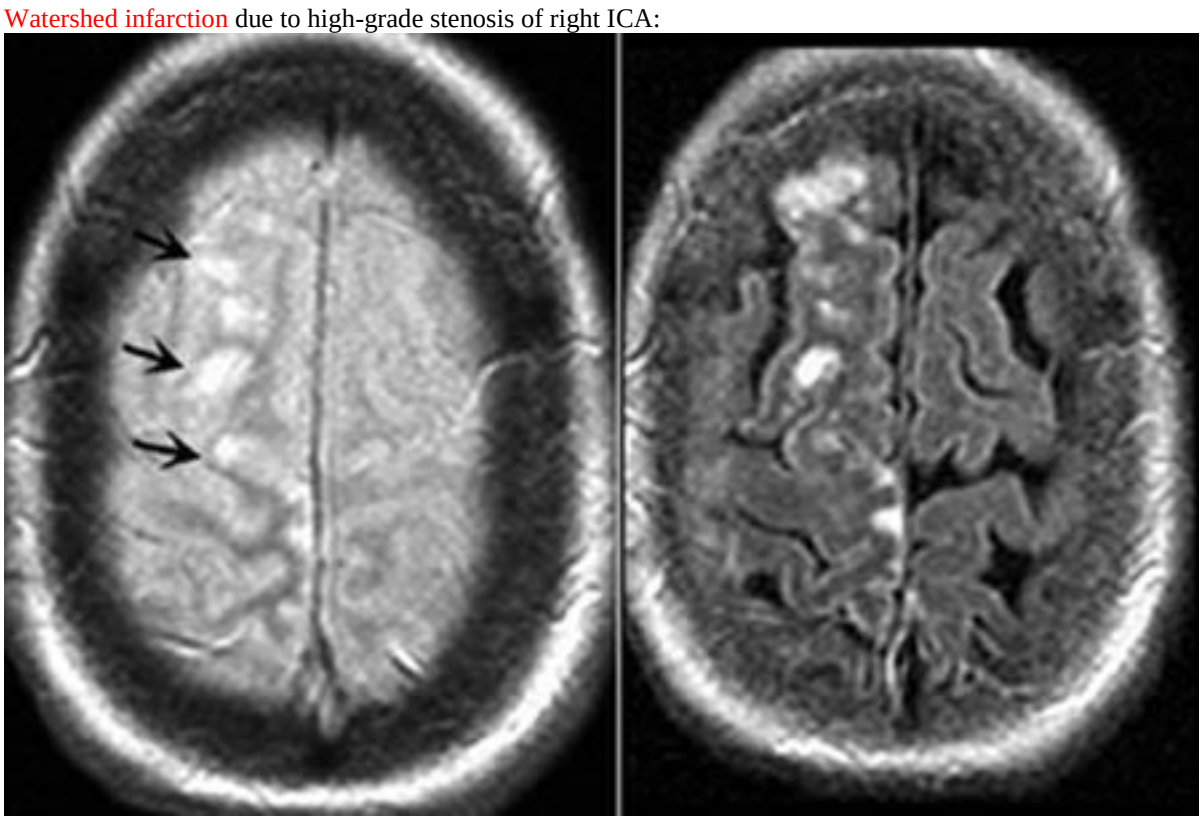


Top of basilar artery syndrome (T2-MRI):

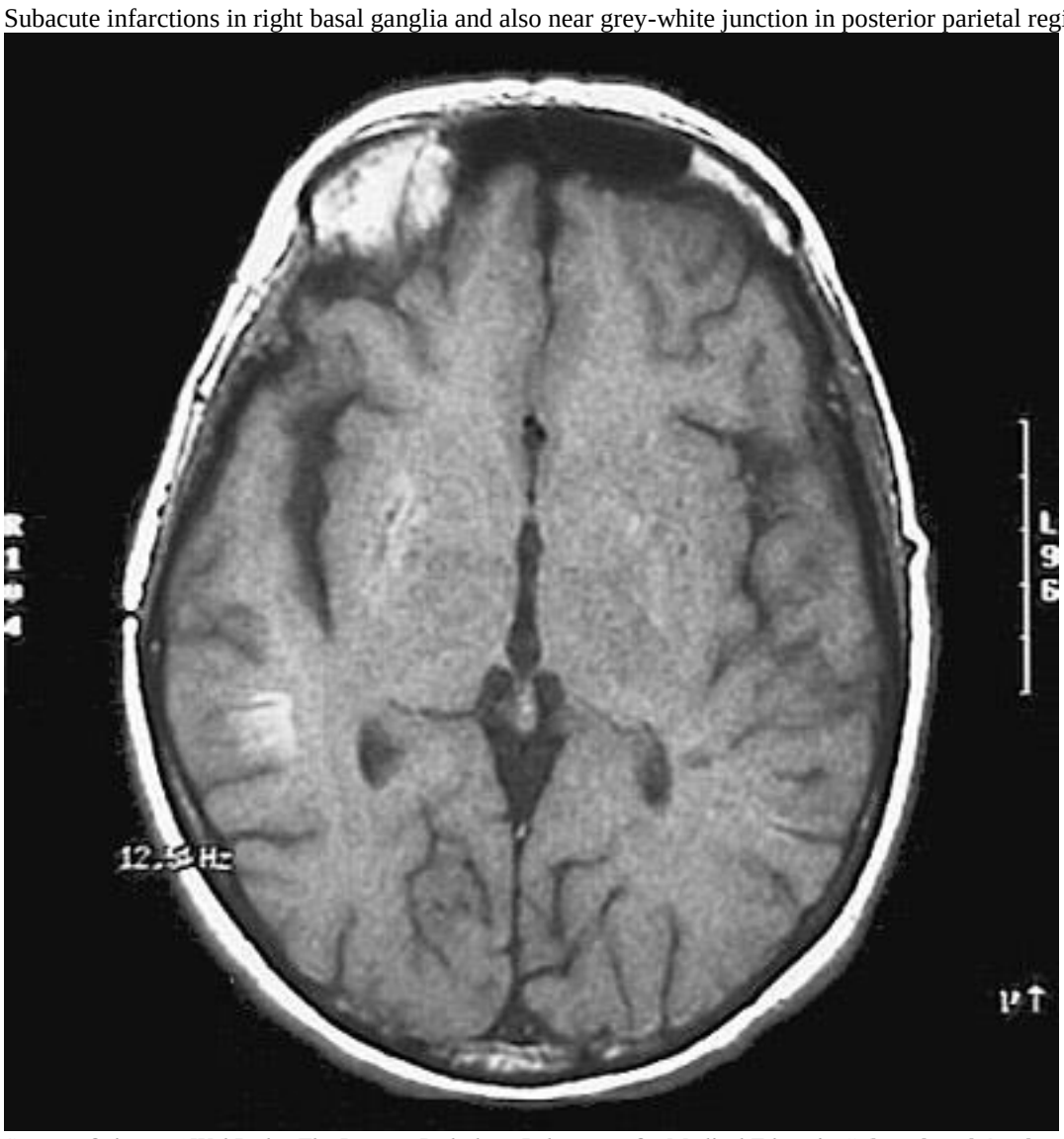
A. Wedge-shaped abnormal signal intensity - midbrain infarction extending from aqueduct ventrally along CN3 course (*arrows*).
B. Bilateral thalamic infarctions (*arrows*).
C. T2 with FLAIR: right thalamic infarction (*black arrow*) has abnormal high signal intensity while left thalamic infarction (*white arrow*) has low signal intensity indicating more chronic cavitated process; note abnormal signal intensities along both trigones of lateral ventricles consistent with small vessel ischemic disease.



Watershed infarction due to high-grade stenosis of right ICA:



Subacute infarctions in right basal ganglia and also near grey-white junction in posterior parietal region:



Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

CIRCULATION / VASCULAR / METABOLIC imaging

Main purposes:

1. ***Secondary prevention*** of TIAs / strokes - primarily concerns EXTRACRANIAL VESSELS - obtain carotid ultrasonogram within 12 hours of admission to look for treatable stenosis.
2. ***Demonstration of acute vascular occlusion*** + ***tissue at risk (ischemic penumbra)*** - for reperfusion treatment:
   intra-arterial thrombolysis - use catheter angiography as part of procedure.
   IV thrombolysis - noninvasive visualization is desirable (CTA or MRA).

- combined use of ***noninvasive tests*** (Doppler, MRA, CTA) is usually adequate for evaluation of most stroke patients.

MRA

- most useful in evaluation of ***extracranial*** (carotid, vertebral) arteries.

DIFFUSION-WEIGHTED MRI (DW-MRI)

- detects changes in *water molecule mobility* (i.e. changes in random Brownian motion of water molecules) - highest sensitivity (among available neuroimaging modalities) for early ischemia detection! (able to detect ischemic changes within minutes of onset - within therapeutic window for thrombolysis!) – better sensitivity than CT!

N.B. 30% TIAs also leave DW-MRI abnormalities – should we call these stroke (vs. TIA)?

- often performed as Echo Planar Imaging (EPI) - fastest imaging technique available – eliminates motion artefacts but lower quality images.
- also include Gradient Echo (highly sensitive to hemorrhage).
- water diffusion is restricted* in ischemic areas - appear bright ("**light bulb sign**").
  *possible mechanism - *shrinkage of extracellular space* (due to cellular swelling - redistribution of extracellular water into intracellular compartment - cytotoxic edema)

Acute infarct is **very bright** on DWI

- DWI becomes positive immediately, vs. FLAIR image (showing edema) takes 3-4 hours to become visible.

DWI-positive and FLAIR-negative (DPFN) findings mean stroke very fresh = in tPA window.

- abnormalities begin to normalize between 7 and 14 days (pseudonormalization); after this period there is increased water mobility* in gliotic tissue (stroke zone appears dark) - can distinguish between old and acute lesions.
  * loss of cell wall integrity causes diffusion to increase

APPARENT DIFFUSION COEFFICIENT (ADC) MAPS – reduced diffusivity shows up as zone of lower intensity

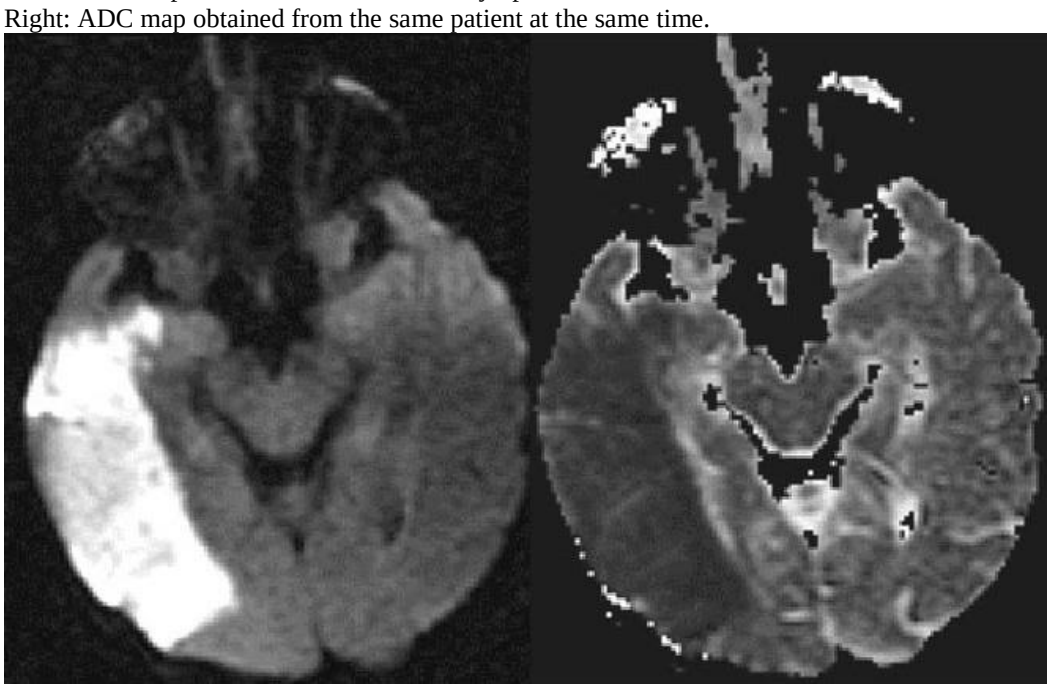
Acute infarct appears **black** on ADC

N.B. ADC helps to differentiate from old infarct (increased water content) - appears as area of DW-MRI brightness ("**T2 shine-through**") but is also bright on ADC.

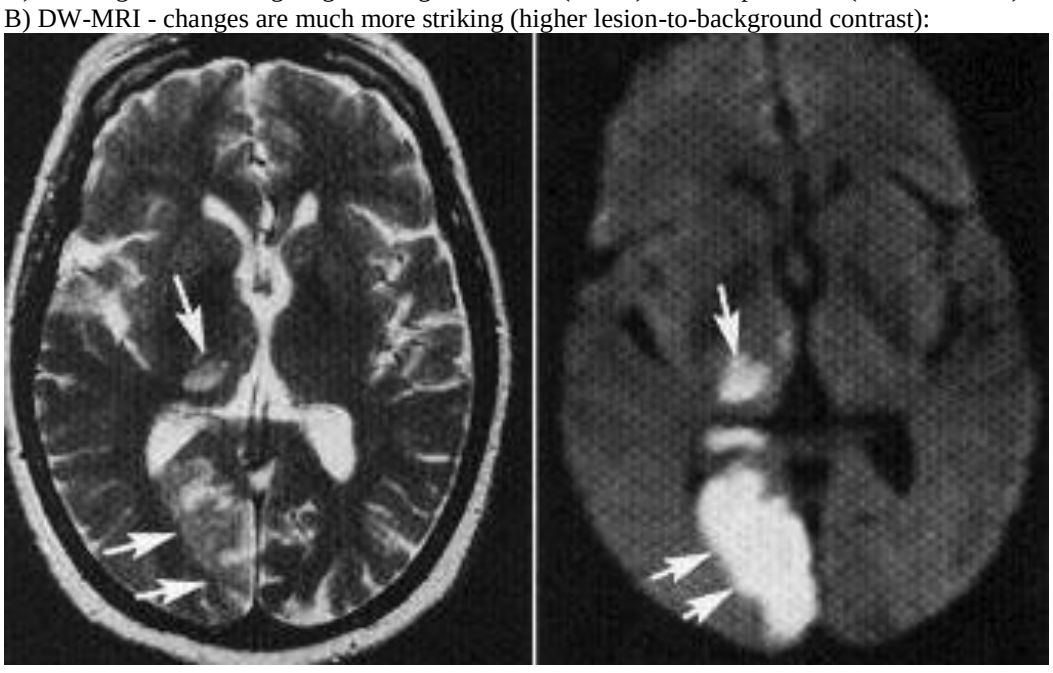
- both acute and chronic infarction will be high intensity on standard T2-weighted or FLAIR images.

Fluid appear **bright** on ADC – T2 shine-through

Left: DW MRI performed 35 minutes after symptom onset.
Right: ADC map obtained from the same patient at the same time.



Acute right PCA infarct:
A) T2-weighted FSE - high signal in right thalamus (*arrow*) and occipital lobe (*double arrows*).
B) DW-MRI - changes are much more striking (higher lesion-to-background contrast):



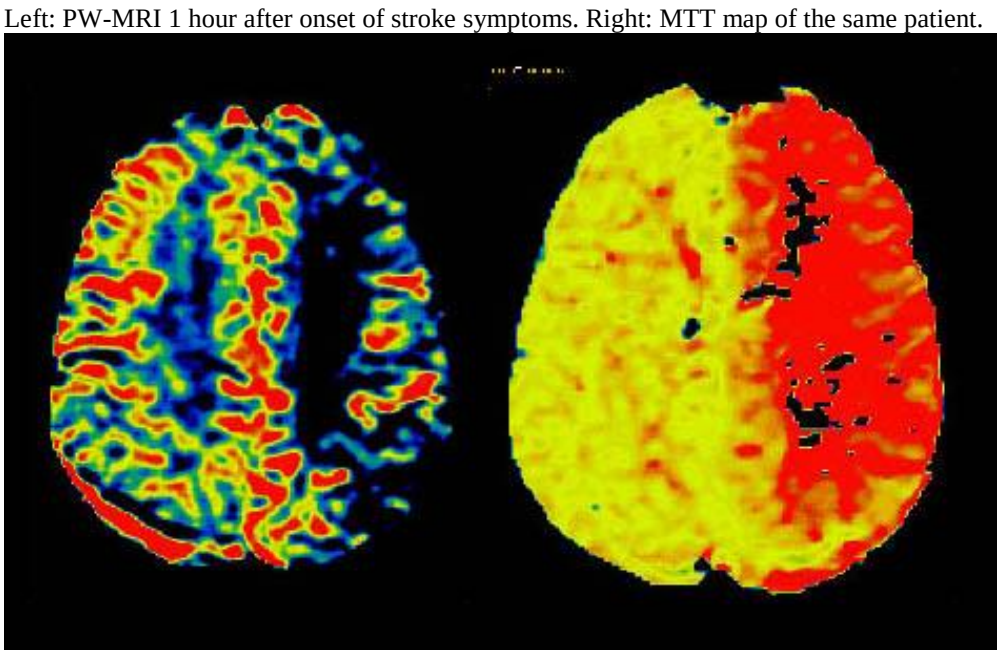
PERFUSION-WEIGHTED MRI (PW-MRI)

- demonstrates areas of decreased perfusion (i.e. vascularization at capillary microcirculation level):
  SUBACUTE STAGE - rCBV increase in infarcted region (recanalization of occluded vessel).
  CHRONIC STAGE - rCBV decrease.

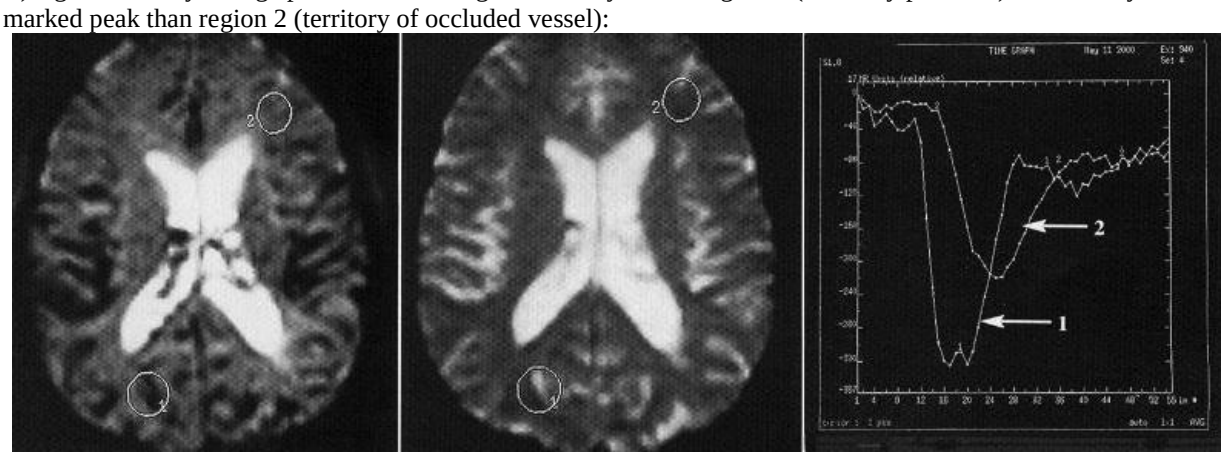
- uses injected *exogenous contrast material (gadolinium)* or *magnetic labeling (spin tagging) of arterial water* – PW-MRI exploits magnetic susceptibility effects within brain tissue during first pass of contrast agent.
- higher spatial resolution and minimal invasiveness (in comparison to angiography, PET, SPECT).

- quantitative maps of cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), time to peak (TTP), and various other hemodynamic parameters can be obtained.

Left: PW-MRI 1 hour after onset of stroke symptoms. Right: MTT map of the same patient.



Left ICA occlusion (PW-MRI):
A) T2-weighted baseline image
B) T2-weighted image acquired during gadolinium bolus passage - dramatic decrease of signal intensity of cerebral blood vessels and brain parenchyma in (B) compared to (A).
C) signal intensity change plotted as time–signal intensity curve: region 1 (normally perfused) shows early and more marked peak than region 2 (territory of occluded vessel):



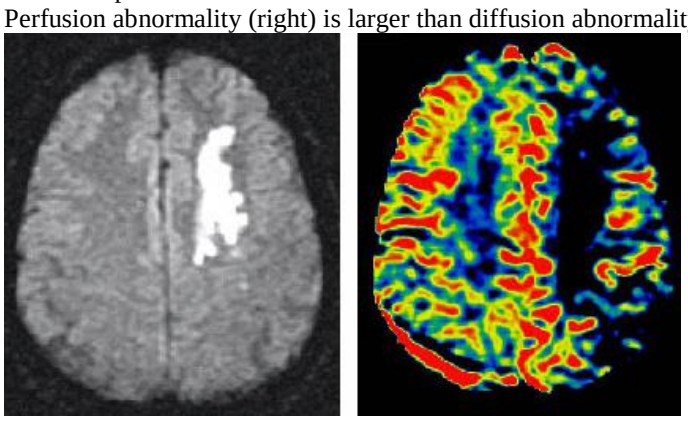
DIFFUSION-PERFUSION mismatch

- combination of PW-MRI with DW-MRI yields areas of DW imaging/PW imaging mismatch, theoretically identifying potentially salvageable tissues (i.e. in hyperacute stage, abnormalities are more extensive on perfusion-weighted than on diffusion-weighted images - this **diffusion-perfusion mismatch** represents *ISCHEMIC PENUMBRA*).

PWI abnormalities mismatched with normal DWI = PENUMBRA

- this assumes that abnormalities on DW images are irreversible and represent core of infarct, whereas area of perfusion/diffusion mismatch (surrounding core) indicates potentially salvageable tissue.
  i.e. larger difference between perfusion and diffusional abnormalities, greater need for acute intervention with thrombolytic agents; if there is no perfusion abnormality (or it is equal to diffusional lesion) = infarction has occurred (thrombolysis will not be effective and potentially harmful due to risk of hemorrhagic transformation).

Diffusion-perfusion mismatch in acute ischemic stroke.
Perfusion abnormality (right) is larger than diffusion abnormality (left), indicating ischemic penumbra:



PERFUSION CT (PCT)

Three parameters are typically used:

1. Mean transit time (MTT) or time to peak of the deconvolved tissue residue function s. delay in contrast arrival time (Tmax)
2. Cerebral blood flow (CBF)
3. Cerebral blood volume (CBV)

Normal perfusion parameters:

	gray matter	white matter
MTT (seconds)	4	4.8
CBF (ml/100 g/min)	60	25
CBV (ml/100 g)	4	2

Tmax > 6.0 sec, CBF < 30%, CBV < 2.0, MTT > 145% are considered significantly abnormal

Stroke

Decreased CBF and prolonged MTT (Tmax) match decreased CBV

Ischemic penumbra (salvageable tissues)

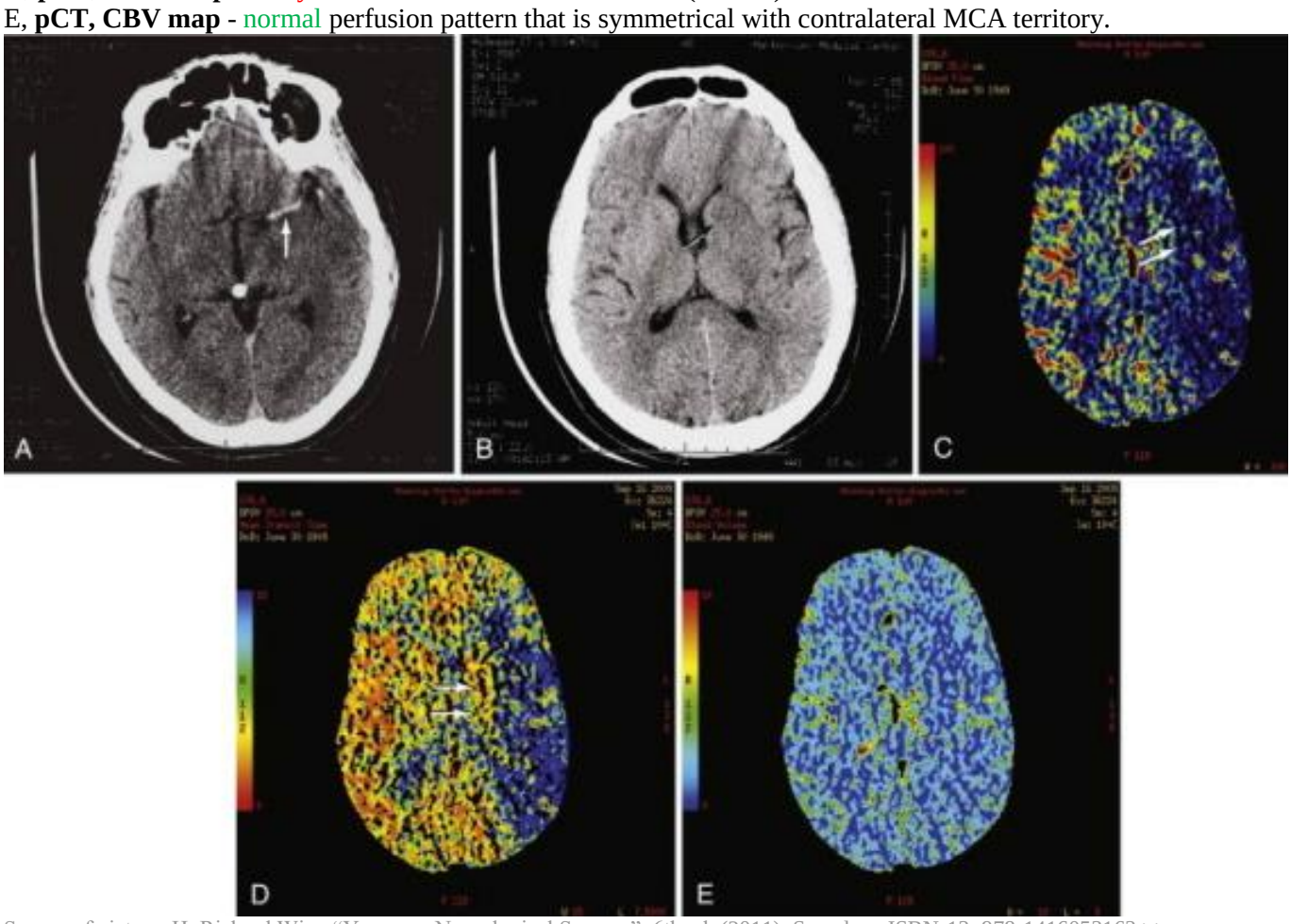
CBF and MTT perfusion defects mismatched with normal or even increased CBV (brain autoregulatory vasodilation) = PENUMBRA

N.B. **CBV is used to 'eye-ball' pCT scan** (if one uses CBF alone to visually assess core size, it is easy to overestimate infarct core, as the penumbra often has reduced CBF also).
N.B.B. in cases of seizures, **the ictal region shows hyperperfusion**, which may lead to an interpretation of hypoperfusion in the contralateral hemisphere mimicking infarct.

- it has recently been demonstrated that **CBF < 30% against Tmax > 6** mismatch is more reliable than **CBV < 2.0 against MTT > 145%** mismatch in identifying infarct core and ischemic penumbra at admission - as a consequence, the new CTP mismatch model Tmax/CBF is used to evaluate acute ischemic stroke patients for endovascular treatment.

  Interpretation: both in infarct and in penumbra contrast arrives late (Tmax↑); in infarct, due to decreased blood volume, the flow is more decreased compared to penumbra (where blood volume is increased and compensates for sluggish flow).

Ischemic penumbra within left MCA territory:
A, **Plain CT** - "dense MCA sign"
B, **Plain CT** - early ischemic changes - hypodensity within left lenticular nuclei (*arrow*).
C, **pCT, CBF map** - perfusion defect in left MCA distribution on (*arrows*)
D, **pCT, MTT map** - delayed MTT in left MCA distribution (*arrows*).
E, **pCT, CBV map** - normal perfusion pattern that is symmetrical with contralateral MCA territory.

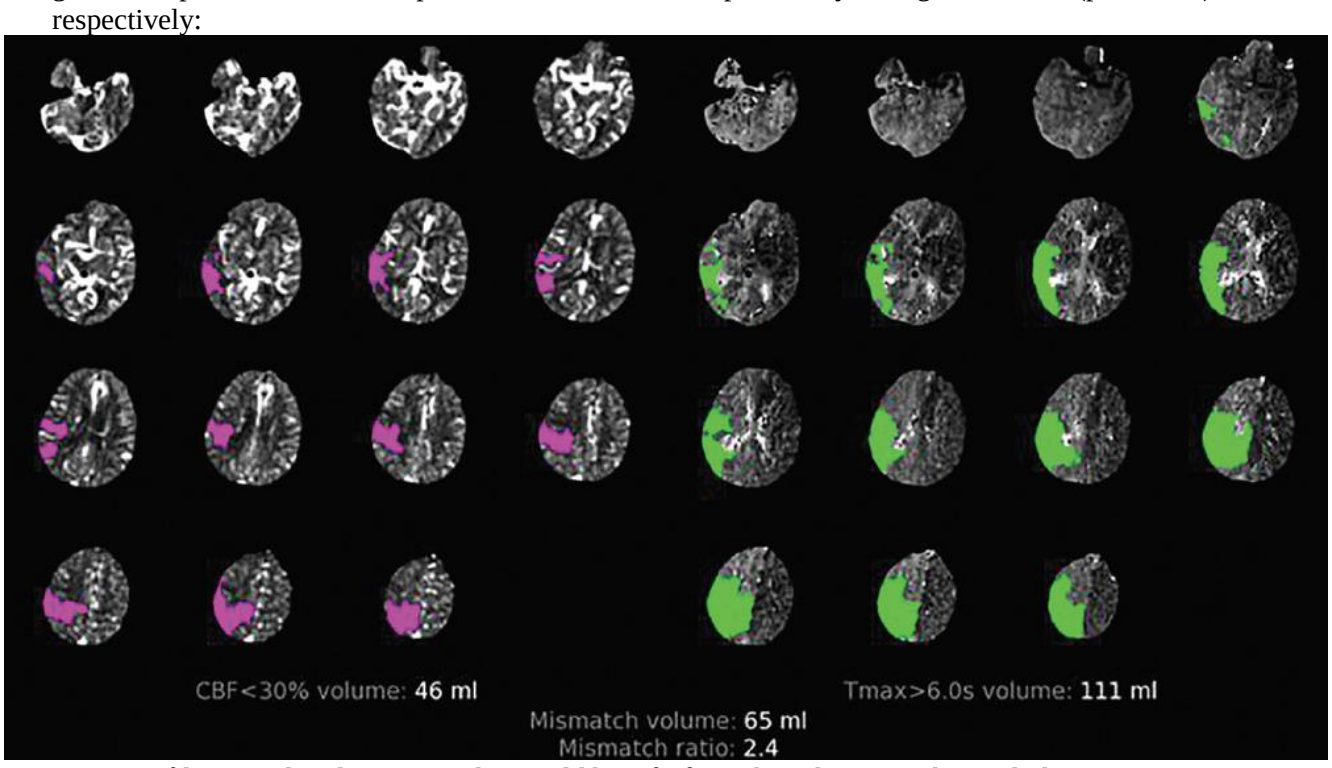


Source of picture: H. Richard Winn "Youmans Neurological Surgery", 6th ed. (2011); Saunders; ISBN-13: 978-1416053163 >>

Implication: reperfusing (thrombolytics / interventional treatment) **stroked area** (vs. **penumbra**) increases morbidity and mortality without clinical benefit.

RAPID automated CTP (iSchemaView)
- to quantify core infarct (irreversibly damaged) vs penumbra (potentially salvageable).

- automated perfusion maps display less than 30% of maximum CBF in pink and Tmax of > 6 seconds in green as representations of the predicted core infarct and potentially salvageable tissue (penumbra), respectively:



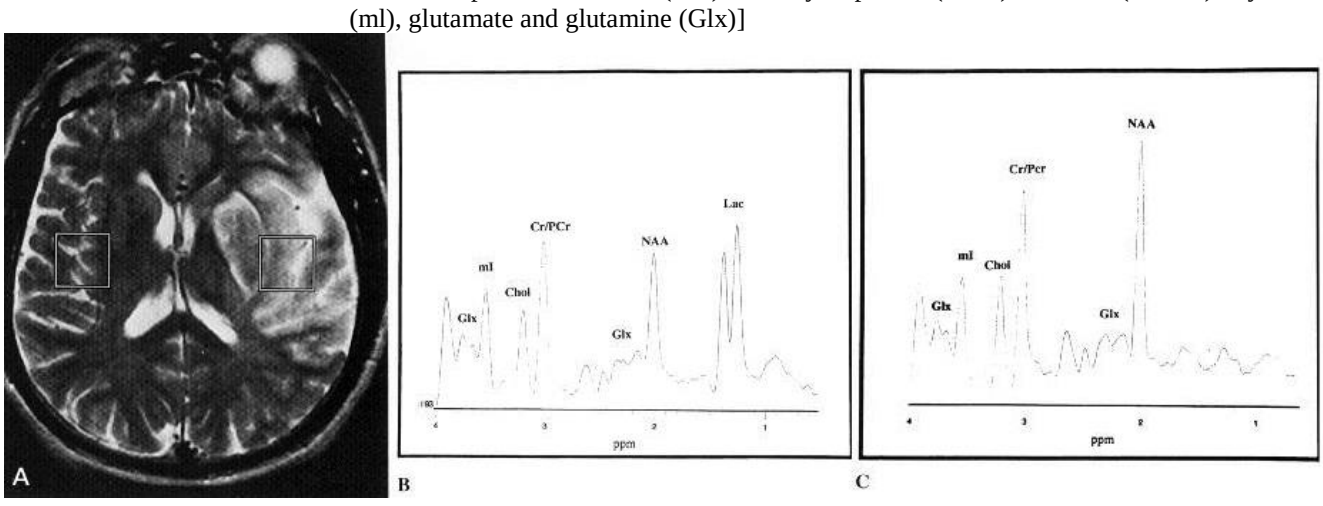
- target profile is used to determine who would benefit from thrombectomy that includes:
  1) ratio of hypoperfused tissue to ischemic core > 1.8,
  2) ischemic core volume (CBF > 6 seconds) < 70 mL, and
  3) severely delayed volume (Tmax > 10 seconds) less than 100 mL.

- if these criteria are met in a technically satisfactory study in the proper clinical context, a benefit of thrombectomy is likely

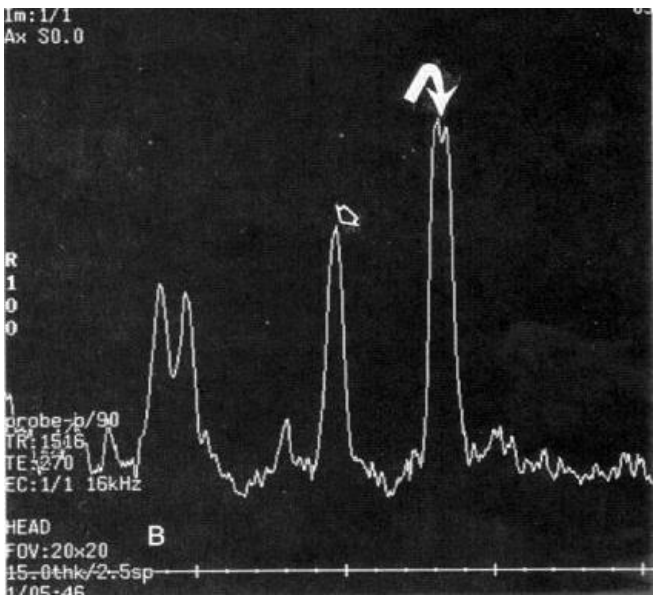
MR SPECTROSCOPY (MRS)

Within infarction region:
lactate appears
N-acetylaspartate (NAA)↓ - neuronal marker (so decreases in conditions with neuron loss)
creatine↓
choline↓

Acute left MCA stroke (MRS):
A) T2-fast spin-echo image.
B) total creatine (3.03 ppm) and choline (3.22 ppm are reduced, NAA peak (2.01 ppm) is almost absent, large lactate doublet at 1.33 ppm compared to (C) contralateral hemisphere.
[resonance peaks are Lactate (Lac), N-acetyl aspartate (NAA), Creatine (Cr/PCr), myoinositol (ml), glutamate and glutamine (Glx)]



Acute stroke (MRS) - decreased amount of N-acetyl aspartate (*arrow*) and markedly increased amount of lactate (*curved arrow*), indicating change of infarction:



PET

- unlikely to have major role in acute stroke diagnosis - limited availability and time delay in radiopharmaceutical preparation.

- PET is able to measure changes in CBF, CBV and OEF (oxygen extraction fraction) using ^{15}O.
- as CBF falls, CBV and OEF increase to maximal levels.

SPECT

- shows perfusion defect as soon as vascular occlusion occurs; still relatively experimental.

- will not exclude intracranial hemorrhage.
- may miss small infarcts (below resolution of nuclear examination).
- *ACETAZOLAMIDE challenge* can differentiate subclasses of cerebral ischemic syndromes.
- *crossed cerebellar diaschisis* - hypoperfusion of contralateral cerebellum in patients with cortical strokes (secondary to disruption of corticopontine tracts).

ANGIOGRAPHY

Indications:

1) possible *candidate for surgery* (e.g. carotid endarterectomy). see p. Vas7 >>
2) *uncertain diagnoses - suspected treatable diseases* - aneurysm, AVM, vasculitis, moyamoya disease, fibromuscular dysplasia.
3) stroke in *young*.

N.B. angiography in acute setting (esp. if unstable or severe disabling neuro deficit) increases morbidity!

Indications for EMERGENCY angiography:

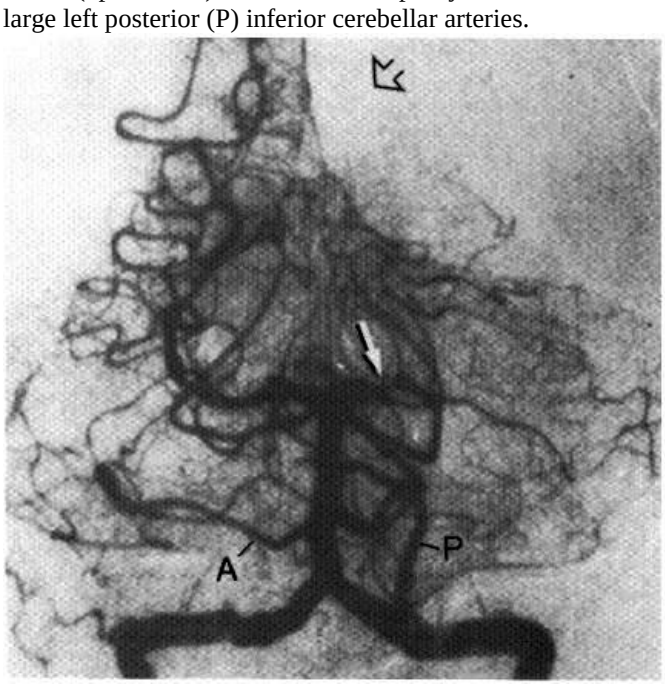
1. Early stroke in carotid distribution + history of amaurosis fugax or bruit or retinal emboli, etc. (suggesting increasing carotid stenosis, thrombogenic ulcerated plaque, or carotid dissection)
2. If diagnosis still questionable (e.g. aneurysm, vasculitis)
3. Rapid recovery, suggesting carotid TIA in face of increasing stenosis

Findings:

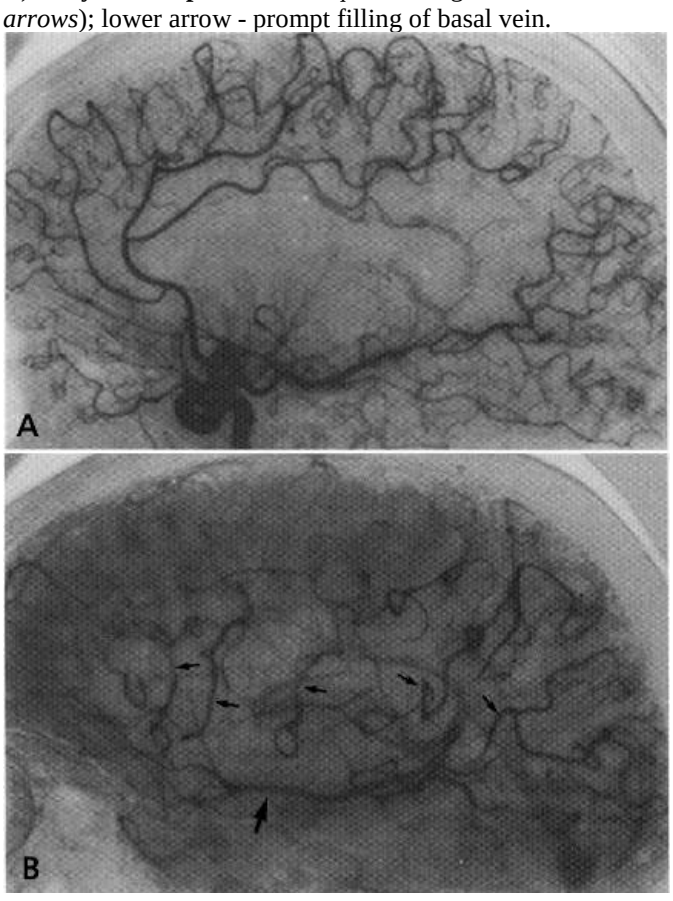
1. **Cutoff sign**: vessel *ends abruptly* at point of obstruction
2. **String sign**: narrow *strand of contrast* in vessel with high grade stenosis
3. **"Luxury perfusion"**: reactive hyperemia* - *accelerated circulation* adjacent to infarct with blush and early venous drainage

*blood flow in excess of demand - response of cerebral tissue to injury (trauma, infarction, epileptogenic focus ...)

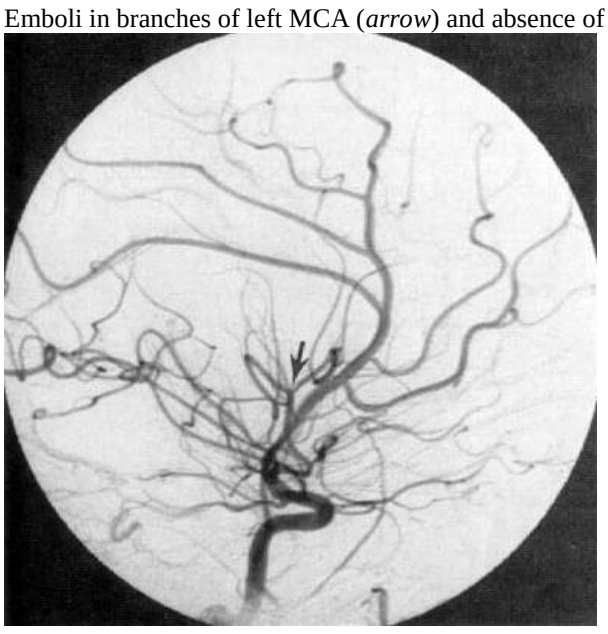
Occlusion of main trunk of left PCA (*arrow*) (vertebral angiogram, AP projection): absent vessels in region of left occipital cortex (open arrow). Note normal disparity in size of vertebral arteries, left being larger; also large right anterior (A) and large left posterior (P) inferior cerebellar arteries.



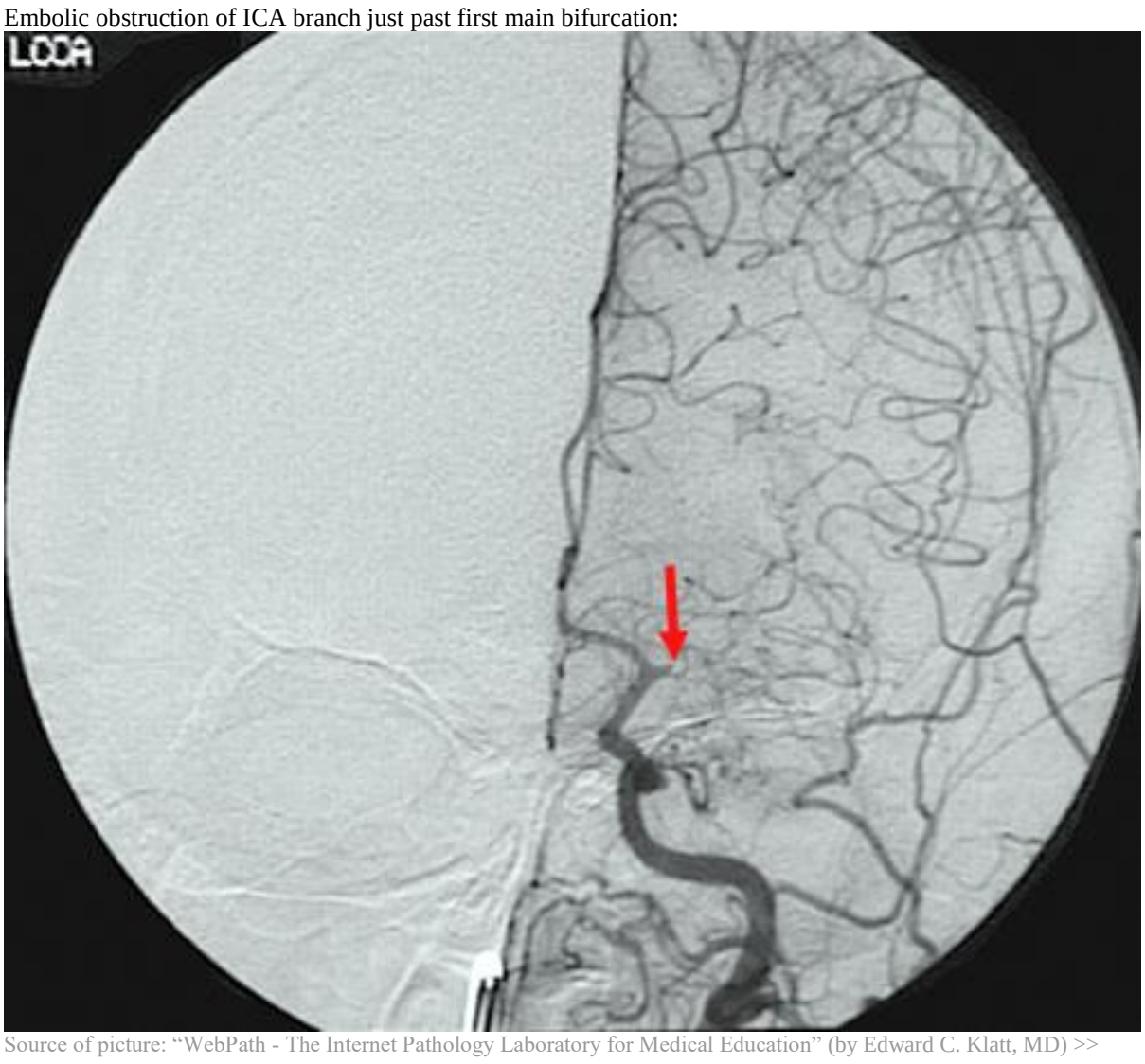
MCA occlusion (common carotid injection, lateral projection):
A) **arterial phase** - cortical branches of MCA are not seen.
B) **early venous phase** - subsequent filling of cortical MCA branches via retrograde flow mainly from ACA (*small arrows*); lower arrow - prompt filling of basal vein.



Emboli in branches of left MCA (*arrow*) and absence of branch called precentral sulcus artery:



Embolic obstruction of ICA branch just past first main bifurcation:



Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

IMAGING FEATURES IN TIME LINE

Time	MRI finding	Etiology
2-3 min	DWI - Reduced ADC	Decreased motion of protons
	PWI - Reduced CBF, CBV, MTT	Decreased CBF
0-2 h	T2-WI - Absent flow void signal	Slow flow or occlusion
	T1-WI - Arterial enhancement	Slow flow
2-4 h	T1-WI - Subtle sulcal effacement	Cytotoxic edema
	T1-WI - Parenchymal enhancement	Incomplete infarction
8 h	T2-WI - Hyperintense signal	Vasogenic and cytotoxic edema
16-24 h	T1-WI - Hypointense signal	Vasogenic and cytotoxic edema
5-7 d	Parenchymal enhancement (cortical in gyriform pattern; subcortical homogenous central pattern) - disappears by 3-4 months	Complete infarction
> 21 d	T1 hypointensity and T2 hyperintensity persist; ex-vacuo hydrocephalus	

DIAGNOSTIC FEATURES OF DIFFERENT ETIOLOGIES

EMBOLIC strokes

- **neuroimaging** - cerebral surface infarction + (previous) infarcts in *several vascular territories*.
- **transesophageal echocardiography** - detecting cardiac mural thrombi.
- **ophthalmoscopy** - retinal emboli, Roth spots of bacterial endocarditis.
- **CSF** may have RBCs (esp. after hemorrhagic transformation).
- **angiography** in first 12 hours shows emboli, but after 48 hours most emboli are no longer detectable (persistence of embolic occlusion is *exception rather than rule*).

Differential diagnosis:

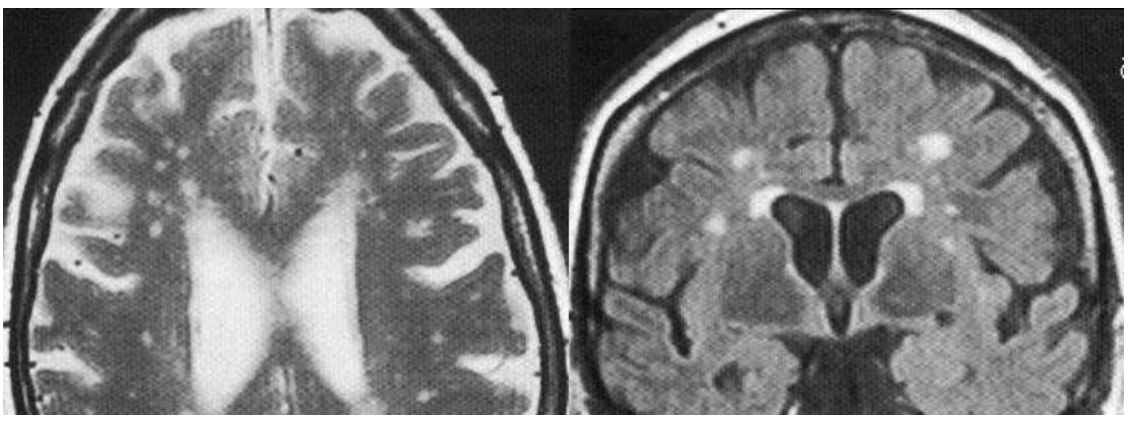
1) vasculitis
2) intracranial atherosclerosis (focal plaques, more common in Asian populations that consume Western diets)
3) intravascular lymphomatosis

LACUNAR strokes

- **neuroimaging** (MRI is most sensitive) - strategically placed* small (< 1.5-2 cm), deep infarcts.
  *territory of small penetrating arteries

T2: small area of high signal is seen in thalamus (*arrow*):

T2 and FLAIR: multiple high signal foci in white matter; periventricular lesions are better shown on FLAIR:



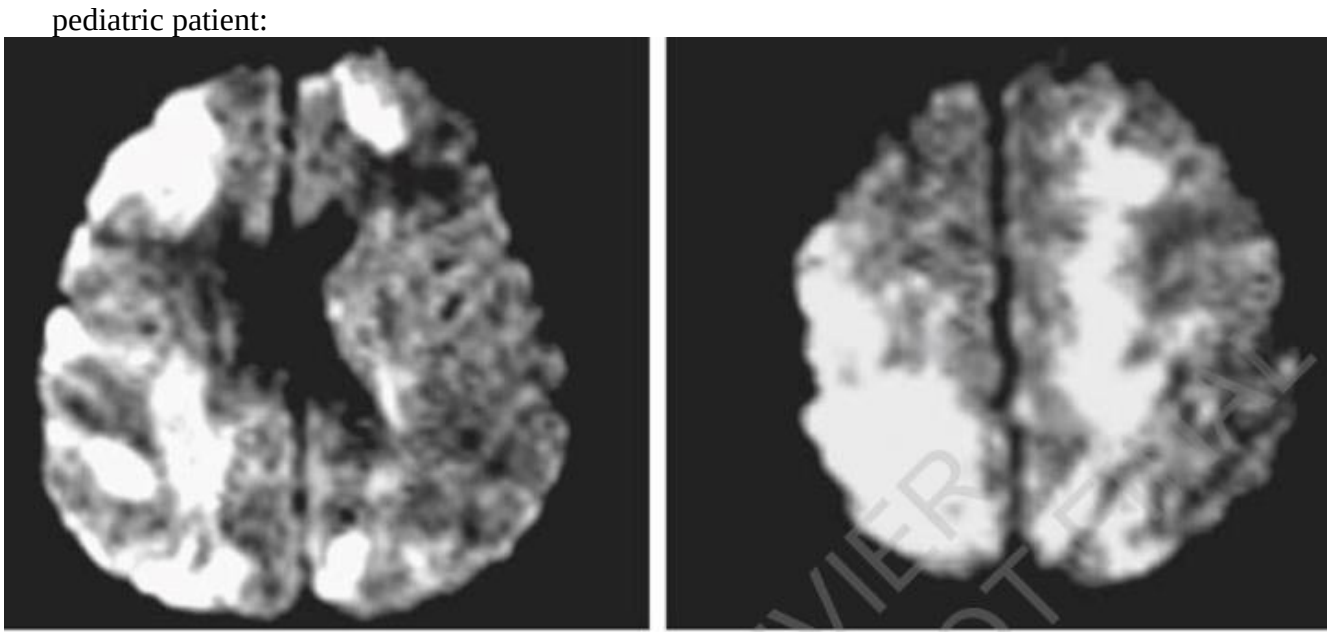
N.B. multifocal or diffuse white matter changes are common in "normal" ageing population!

- **angiography** - normal (responsible vessels are only 200-400 μ in diameter); incidental large-vessel disease may be found.
- **EEG** – normal.

WATERSHED strokes

- **neuroimaging** - uni- or bilateral linear or wedge-shaped infarcts in watershed areas.
- **EEG** - diffuse slowing (correlates with ↓level of consciousness).

Restricted diffusion in internal and external watershed distributions 4 days after cardiac arrest in pediatric patient:

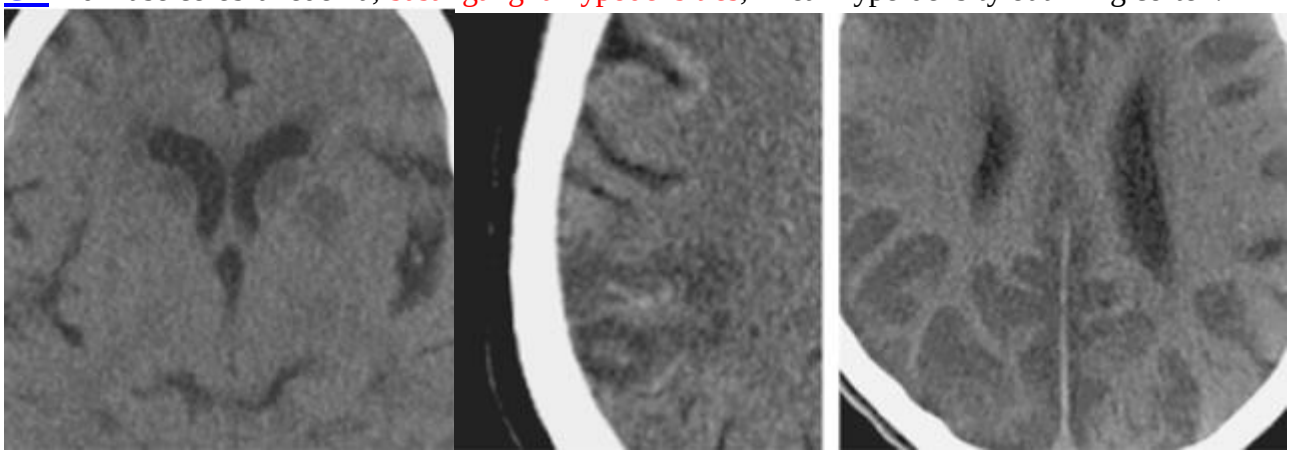


ANOXIC injury

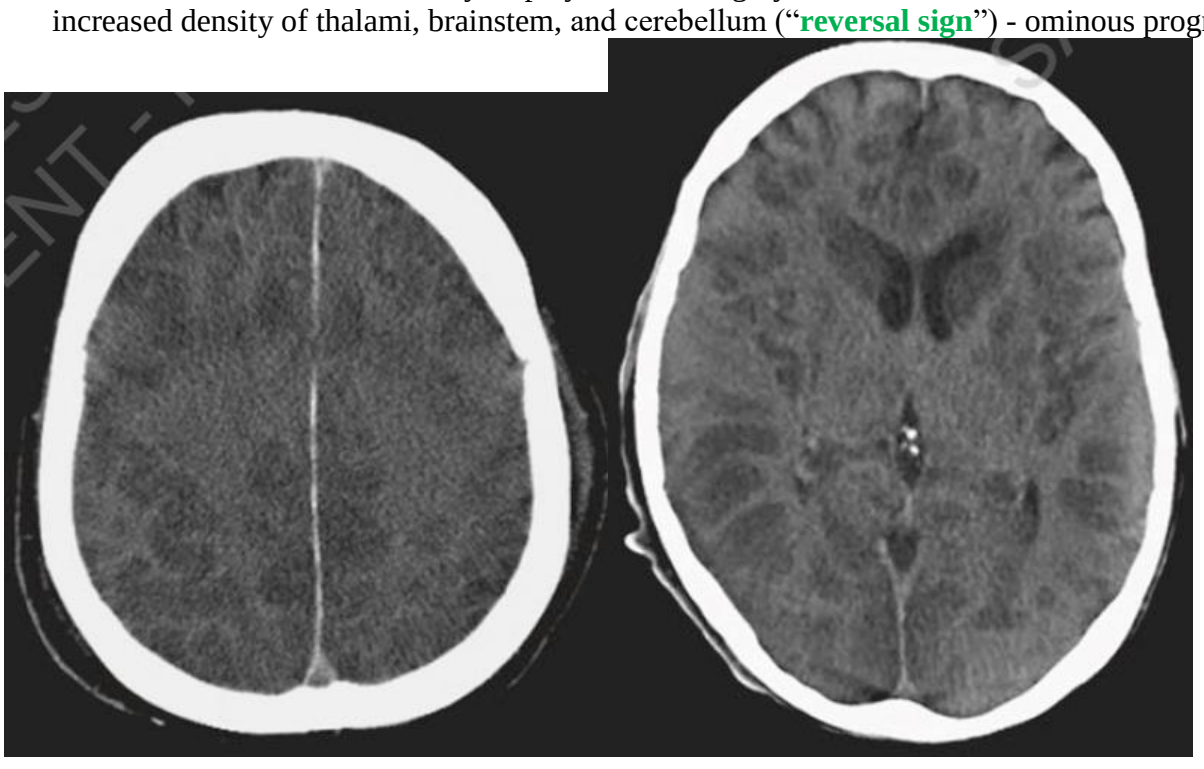
Basal ganglia + perirolandic & occipital cortex

N.B. although it is commonly held that hippocampi in mesial temporal lobes are areas most susceptible to anoxia, radiological evidence of damage to these structures is much less common!

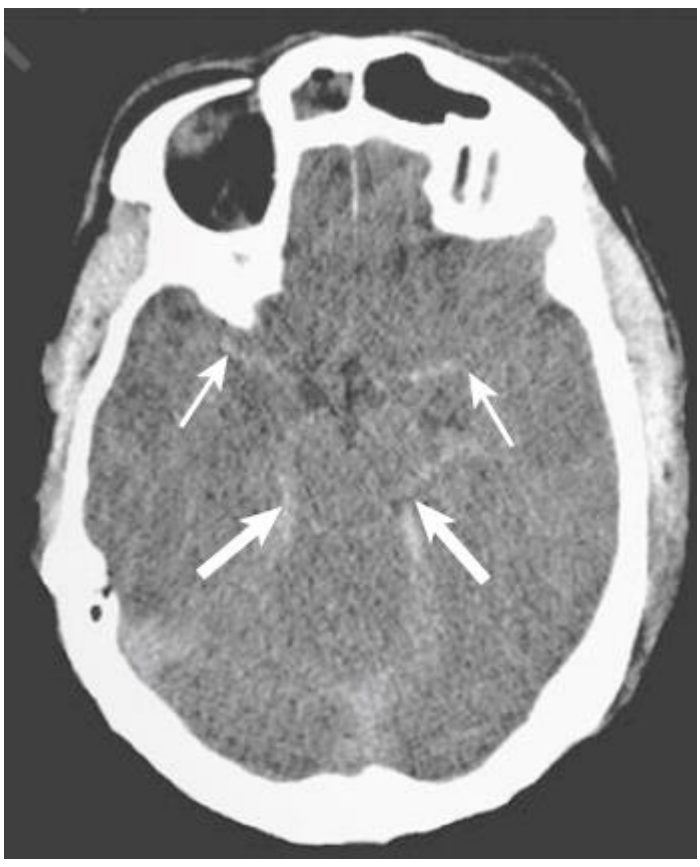
CT – diffuse cerebral edema, basal ganglia hypodensities, linear hyperdensity outlining cortex:



- in the most severe cases, CT may display reversal of gray/white matter densities with relatively increased density of thalami, brainstem, and cerebellum ("**reversal sign**") - ominous prognosis:

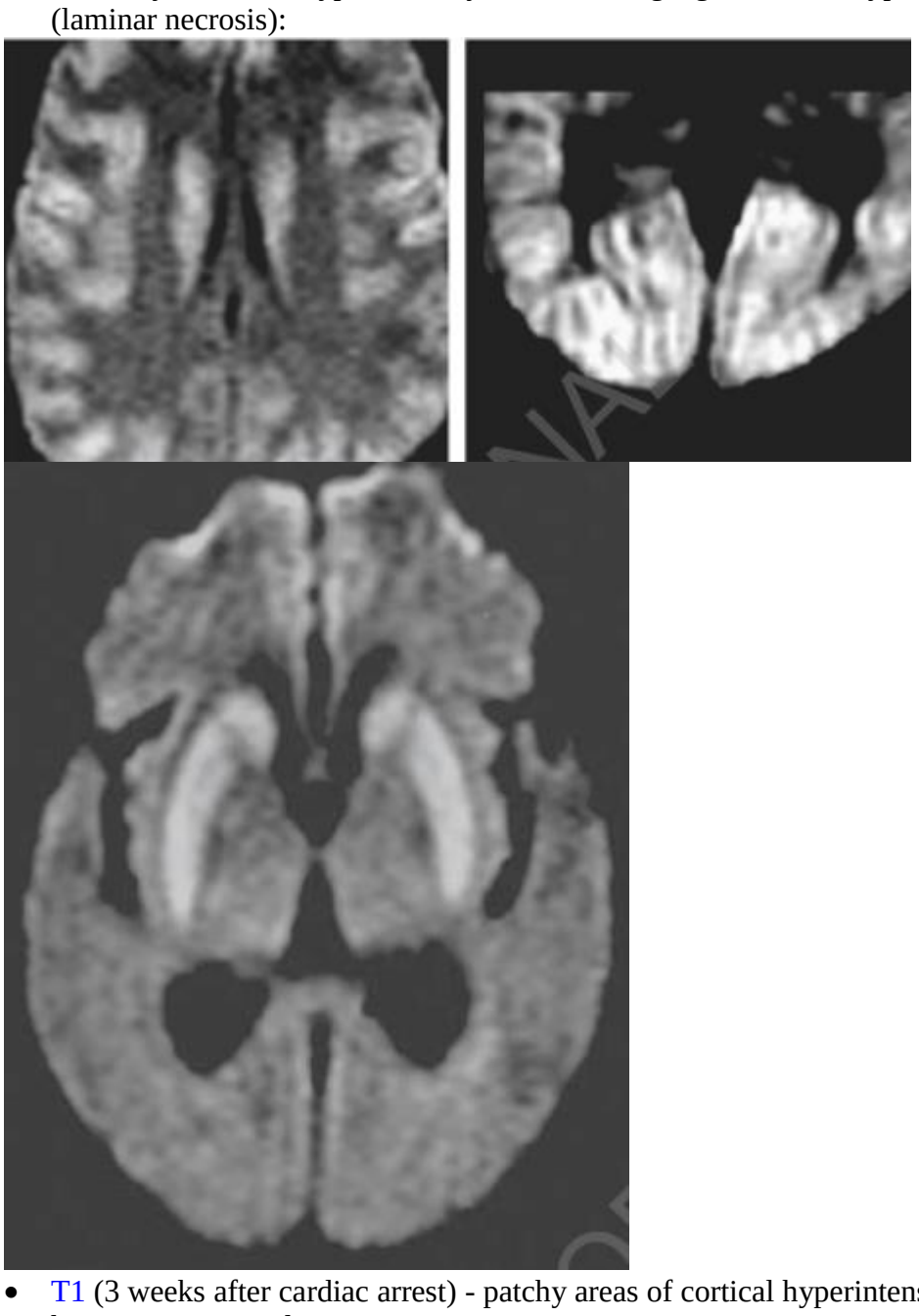


False CT signs after severe brain anoxia: *pseudo-subarachnoid hemorrhage* (H: attention to attenuation values in basal cisterns - much lower than in true cases of SAH), *false hyperdense MCA sign* (H: diffuse cerebral edema beyond MCA territory):

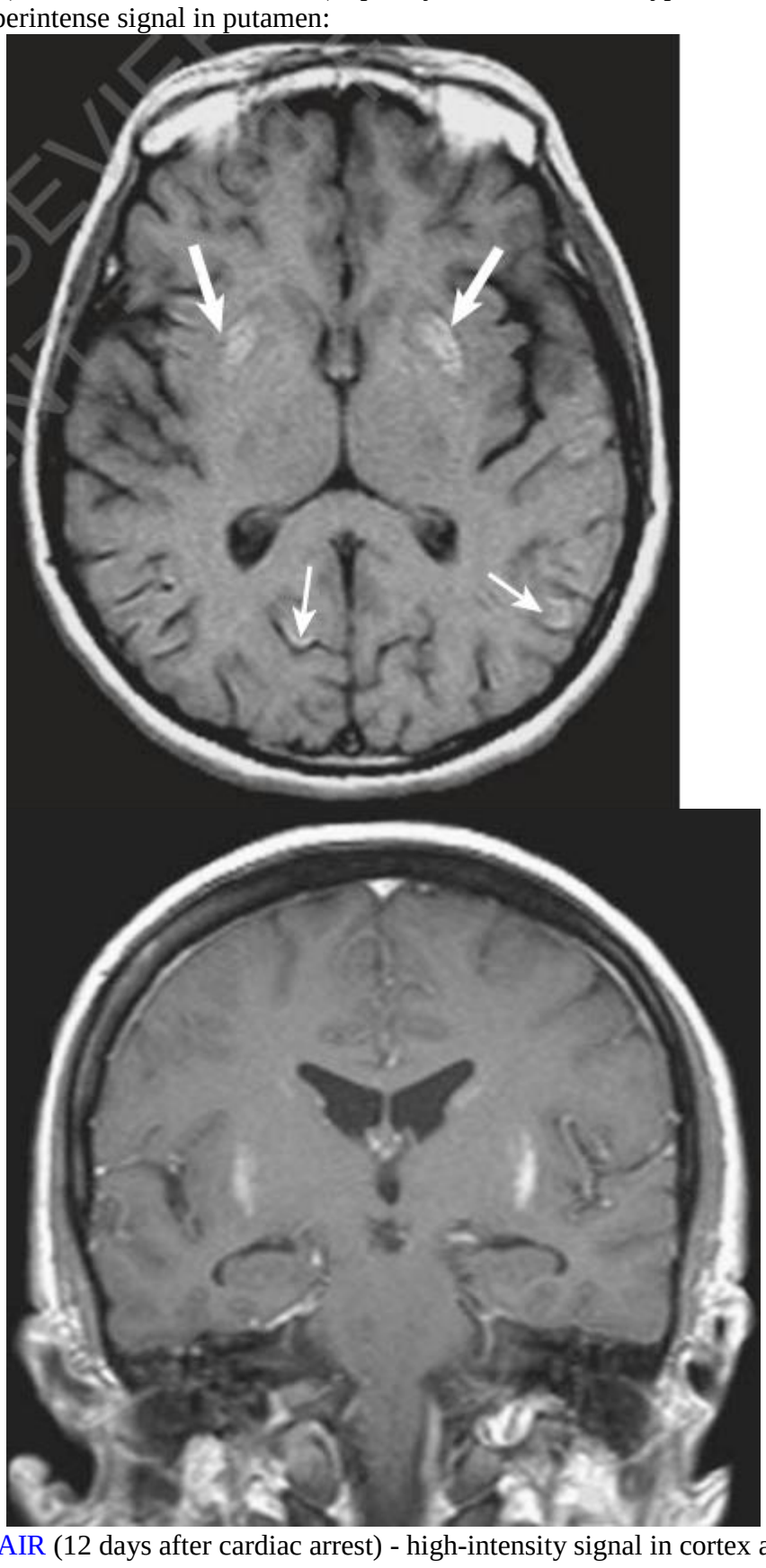


MRI :

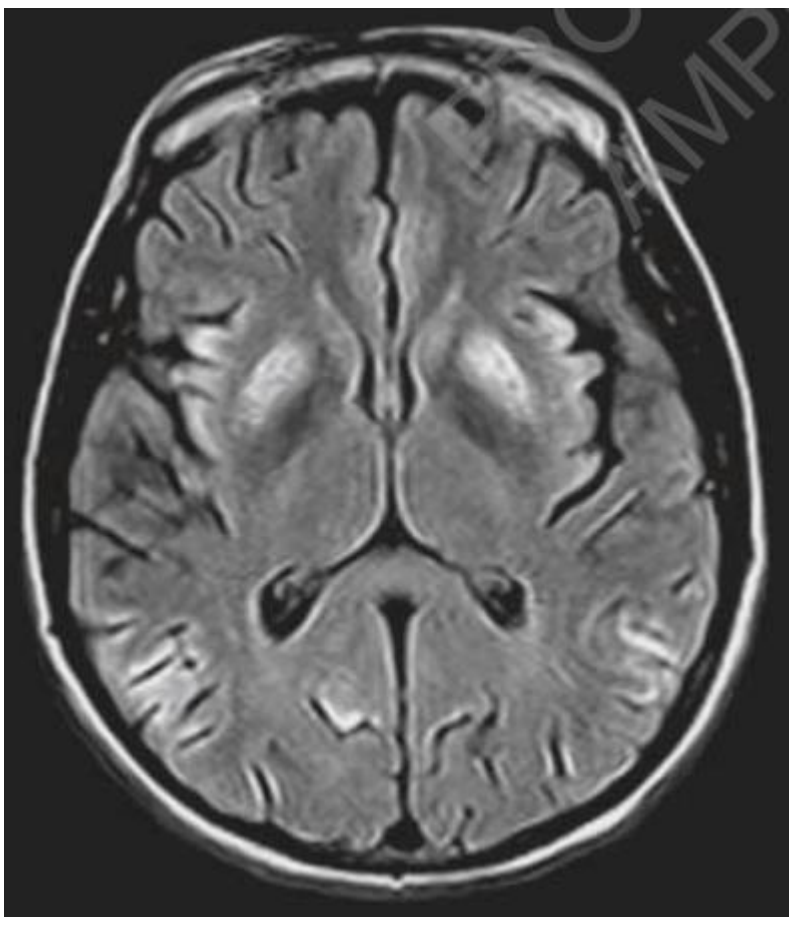
- DWI - symmetrical hyperintensity within basal ganglia, diffuse hyperintense signal in cortex (laminar necrosis):



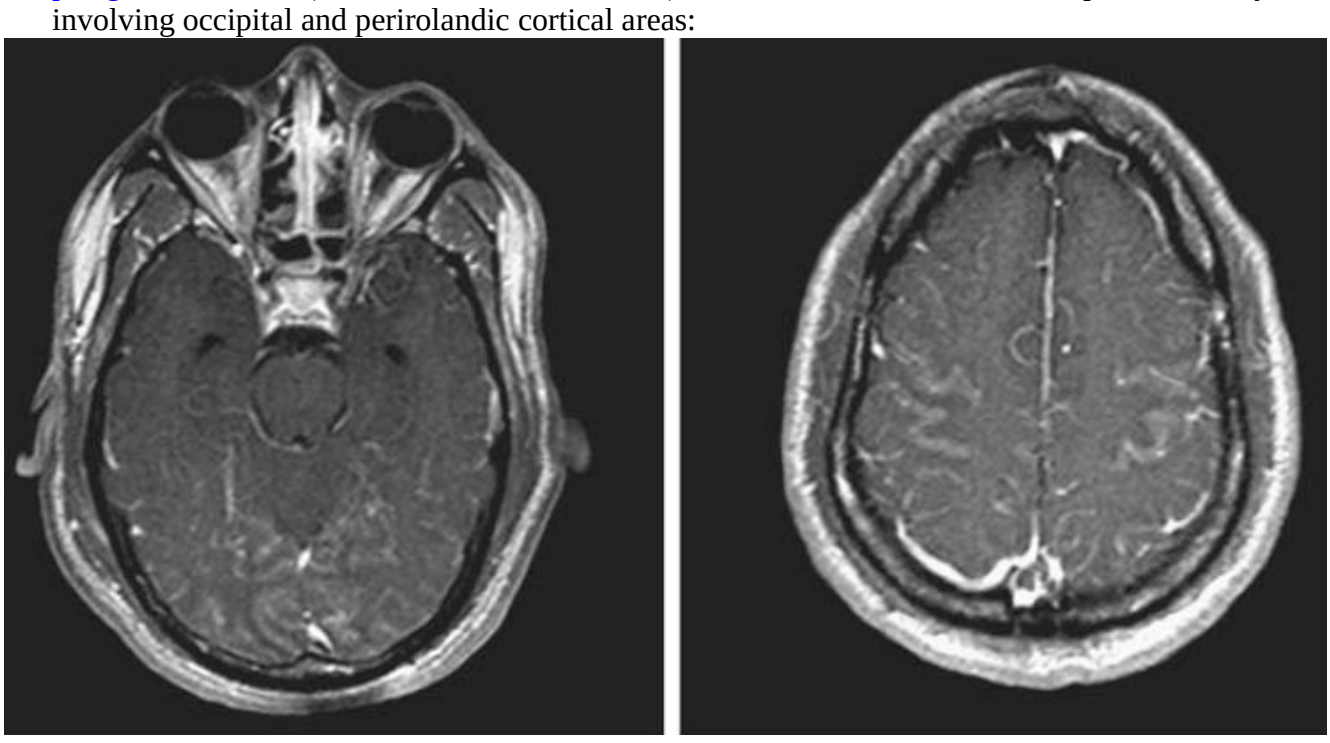
- T1 (3 weeks after cardiac arrest) - patchy areas of cortical hyperintensity (laminar necrosis), hyperintense signal in putamen:



- FLAIR (12 days after cardiac arrest) - high-intensity signal in cortex and lenticular nuclei:



- postgadolinium-T1 (1 month after cardiac arrest) - diffuse cortical enhancement predominantly involving occipital and perirolandic cortical areas:



COMPLICATIONS

ACUTE complications (typically within 72 hours):

1. ICP↑ due to edema – may be life-threatening! see p. Vas5 "Malignant MCA stroke" >>
   Edema and herniation are *most common causes of early death*!
2. Hemorrhagic transformation – within first 24-48 hrs
3. Seizures
4. Aspiration pneumonia

SUBACUTE complications:

1. Complications of bedridden patients: pneumonia*, UTI, deep venous thrombosis → pulmonary emboli, decubitus ulcers, spasticity, joint problems (e.g. contractures, shoulder-hand syndrome), malnutrition.
   *most common cause of *non-neurological death in first 2-4 weeks*
2. Epilepsy (risk 3.3% within 2 years, vs. 7.8% if patient had hemorrhagic transformation); postictal state often represents relapse of original stroke syndrome.
   – risk is increased if patient had intervention (such as tPA or thrombectomy) – reperfusion injury?
   – many cases of idiopathic epilepsy in elderly are probably result of silent cortical infarction.
3. Post-stroke depression
   – occurs in 30-50% patients within 2 years.
   – ½ meet criteria for major depression - may have major impact on recovery.
   – more common with lesions affecting *frontal lobe*, *head of caudate nucleus* - such lesions may interrupt noradrenergic and serotoninergic pathways.
   – responds to tricyclic antidepressants and SSRIs.

PROGNOSIS

RECOVERY

Complete NEUROLOGIC RECOVERY occurs in about 10%.
- most functional recovery occurs during first 3 months.
- most deficits that remain after 12 mo are permanent.

STATE AFTER STROKE – 1 month ÷ 1 year
RESIDUA AFTER STROKE – after 1 year

- older age, impaired consciousness, aphasia, brain stem signs suggest poor prognosis.
- of all stroke types, **lacunar strokes** have best prognosis.
  - recurrence rate 10% / yr (but only minority of recurrent strokes are of lacunar etiology!).

Modified Rankin Scale (mRS) (originally introduced in 1957 by *Rankin*; modified by *Lindley et al* in 1994) - degree of disability / dependence in daily activities:

mRS ≤ 2 means independent

0 - No symptoms.
1 - No significant disability. Able to carry out all usual activities, despite some symptoms.
2 - Slight disability (functionally still independent). Able to look after own affairs without assistance, but unable to carry out all previous activities.
3 - Moderate disability. Requires some help, but able to walk unassisted.
4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6 - Dead.

RECURRENCE

- after TIA or minor stroke, risk for recurrent stroke within 90 days is ≈ 10%.*
  N.B. most of recurrent strokes occur within 48 hours!
  – risk is greatest in *atherosclerotic* infarction and lowest in lacunes

– risk of recurrence does not depend if tPA was used

Early CT/CTA and DWI-MRI are not significantly different in predicting recurrent stroke:

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
CT/CTA	67%	68%	14%	96%
DWI-MRI	75%	43%	9%	96%

N.B. avoid of iodine contrast in diabetics who are getting oral antidiabetic agents like metformin - risk of **lactic acidosis**!!!

- long-term stroke recurrence rates 4-14% / yr.

PEDIATRIC & YOUNG PATIENTS

INCIDENCE - 2.5 per 100 000 children.

- hemorrhages comprise much higher percentage of strokes than in adults.
- 3% of ischemic strokes occur in patients < 40 yrs.

Pathophysiology:

- collateral circulation over convexities is abundant - infarcts tend to be limited to ***deeper regions*** of cerebral hemispheres (esp. striatocapsular areas).
- vascular occlusions are more often intracranial.
- extracranial lesions usually involve pharyngeal portions of carotid and vertebral arteries (vs. arterial origins as in adults) – traumatic dissection (!), contiguous infection, vasoconstriction, fibromuscular dysplasia.

  Atherosclerosis is very rare in youth!

Etiologies:

1) ***trauma*** (22% strokes in patients < 45 yrs) → vascular dissection
2) ***cardiac disorders*** (cyanotic heart disease, mitral valve prolapse are most common).
3) ***vascular disorders***: moyamoya disease, migraine, amphetamine* or cocaine** abuse, premature atherosclerosis (esp. in DM + HTN + smoking), homocystinuria

   *may cause vasculitis (vs. cocaine)

   **50% ischemic strokes, 50% hemorrhagic
4) ***hematologic disorders***: antiphospholipid antibodies, leukemia, sickle cell disease, oral contraceptives (risk↑ 9-fold).
5) amniotic fluid embolism
6) ***infections***: herpes zoster ophthalmicus (ischemic stroke risk↑ 3-fold), mucormycosis

   N.B. obtain VDRL in all patients!

Risk factors:

1. Diabetes: odds ratio 12
2. HTN: odds ratio 6.8
3. Current cigarette smoking: odds ratio 2.5
4. Long-term heavy alcohol consumption: odds ratio 15 (heavy alcohol ingestion within 24 hrs preceding stroke is not risk factor)

Most common causes for hemorrhagic stroke – AVMs, aneurysms.

Clinical Features - often subtle and nonspecific in young child or infant;

- ischemic stroke in ***newborns*** can occur without any acute clinical evidence;
  - **seizures** are common presenting symptom.
  - **hemiparesis** is not early feature – develops only when CNS is sufficiently mature (6-12 months of age) for effects of brain damage to become evident - clinical situation is often referred to as *CONGENITAL HEMIPLEGIA* (form of cerebral palsy).
  - patients develop **pathological early hand preference**.
  - imaging often demonstrates *porencephalic widening* of contralateral ventricle.

Prognosis is better than in adults - abundant collateral circulation, plasticity of developing brain.

e.g. if child < 4 yrs has stroke, speech is invariably recovered (permanent aphasia does not occur).

DYKE-DAVIDOFF syndrome: intrauterine ICA infarction → cerebral hemiatrophy → decreased size of half of cranium along with compensatory ipsilateral skull thickening.

CEREBELLAR INFARCTION

Early findings are due to intrinsic **cerebellar lesion**: vertigo, nausea-vomiting, ataxia (up to inability to get up), nystagmus, dysarthria

Later findings (12-96 hrs following onset) are due to **increased pressure within posterior fossa** – brainstem compression (particularly posterior pons).

- 80% of patients developing signs of brain stem compression will die, usually within hours to days.

CT findings of tight posterior fossa: obliteration of basal cisterns and 4th ventricle.

Surgical treatment – see p. Vas5 >>

BIBLIOGRAPHY for ch. "Neurovascular Disorders" → follow this LINK >>