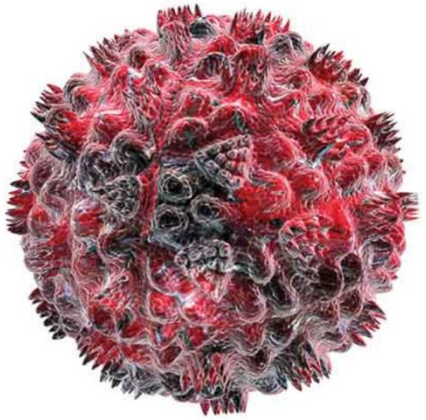


Infectious causes of stroke

Dell Seton Medical School Neurology Residency Lecture

05/02/2023

Rachel Pearson, MD



No financial disclosures

Objectives

- HIV
- Neurosyphilis
- Tb and fungals
- Cysticercosis
- Herpes viruses



True or False

After controlling for traditional risk factors and demographics, HIV infection remains an independent predictor of stroke

HIV and Stroke

- Cardiovascular disease (includes stroke) is the primary cause of death among HIV infected patients in high income countries (Shahbaz et al., 2015)

- HIV positive patients have an increased risk of ischemic stroke independent of traditional risk factors compares to HIV negative patients

- Stroke risk is associated with increased viral load. (Chow et al., 2012)

Proposed Stroke Mechanisms in HIV + patients

- Cardioembolic (CHF, IE)
- Prothrombotic state
- Accelerated atherosclerosis
- HIV vasculopathies
- CNS infections

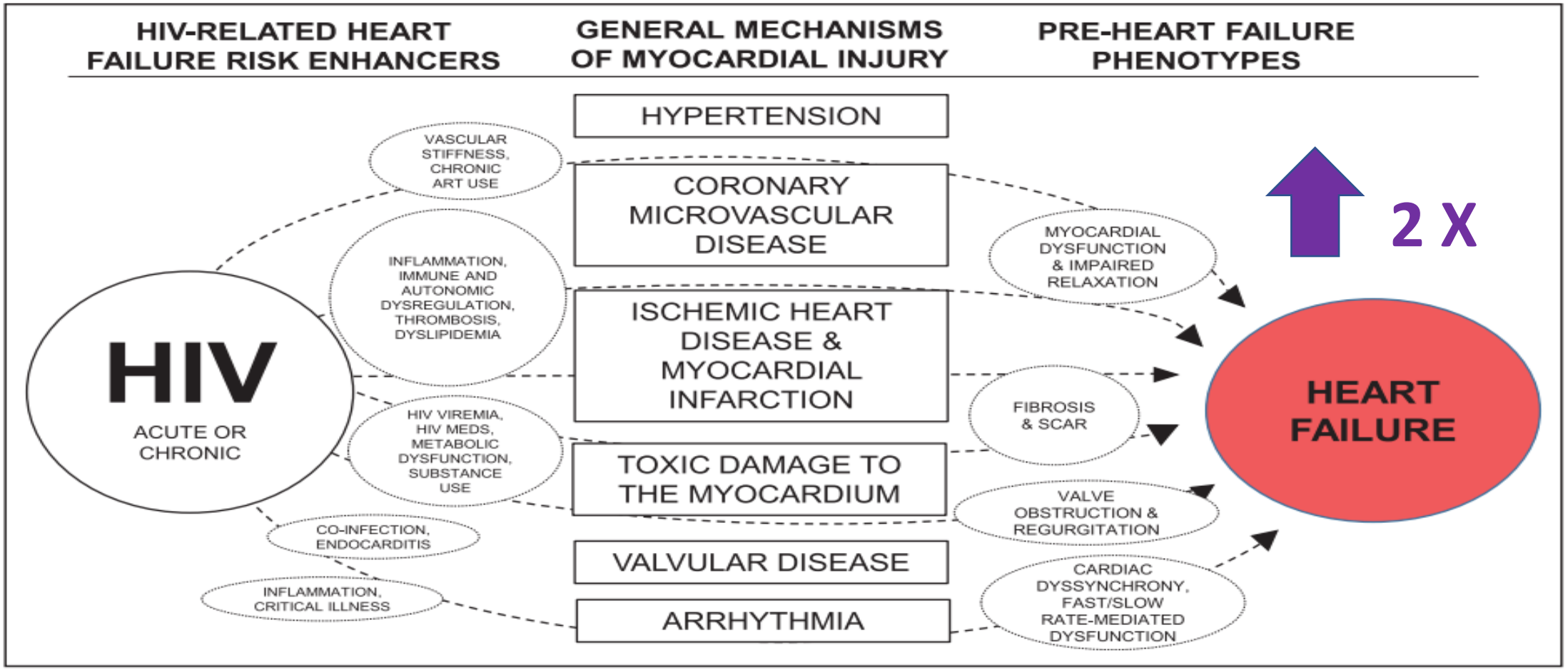
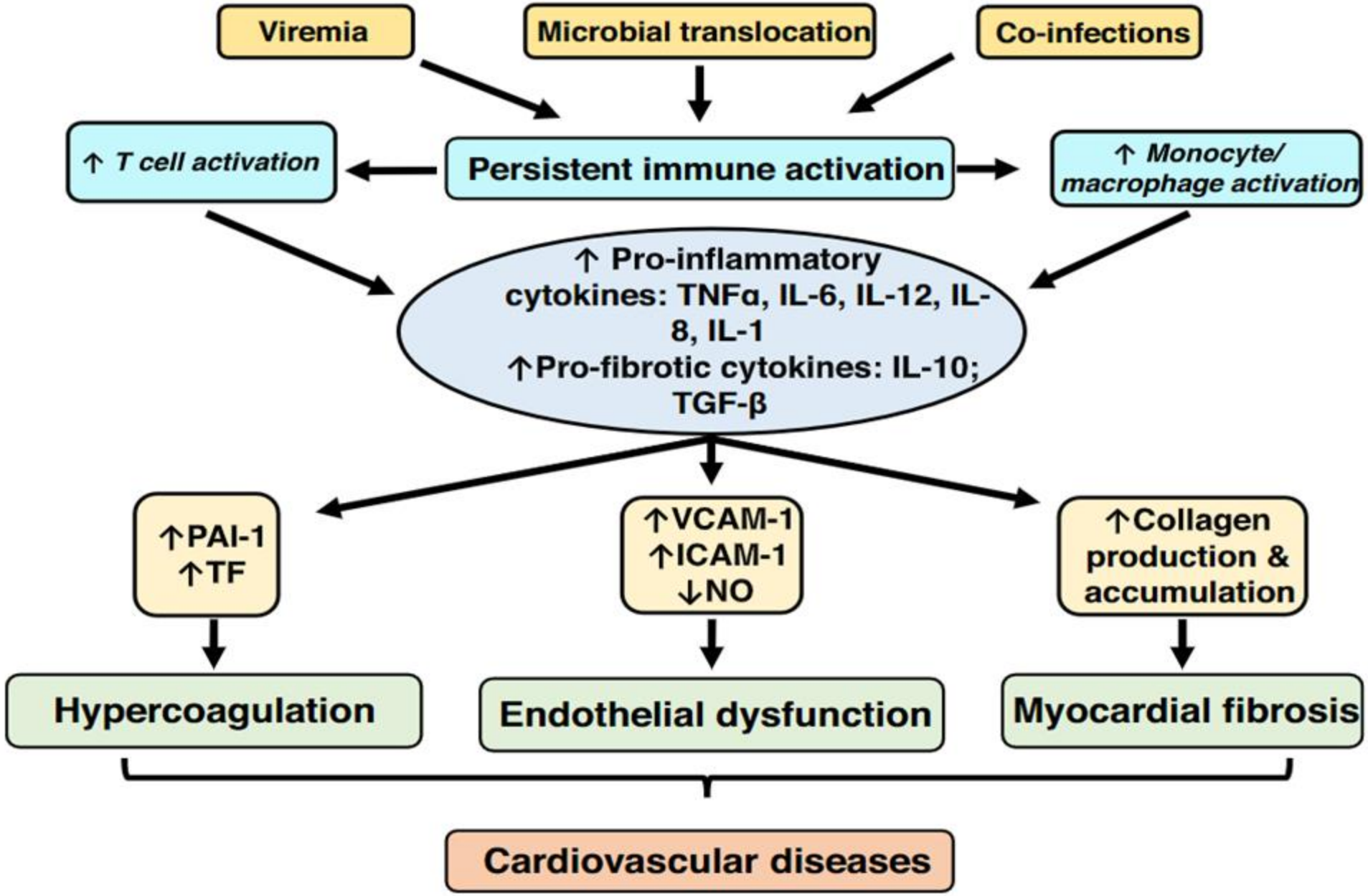


Figure 3. Proposed mechanisms of myocardial dysfunction and heart failure in HIV.
ART indicates antiretroviral therapy.

Prothrombotic State

- Protein S deficiency is frequently found, however it is not a likely cause of stroke (Qureshi, 2005)
- HIV patients have elevated fibrinogen, D –dimer, P-selectin, tissue factor, and vWF
- Elevated levels of IL-1, IL-6, TNF-alpha 1 and 2, CD163, and CD14 are associated with atherosclerotic disease and carotid plaque progression

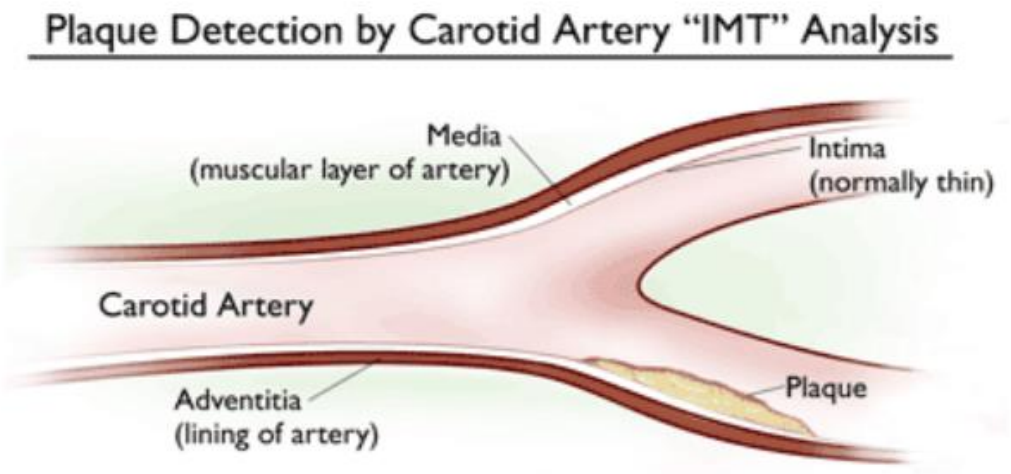
Circulation. 2019;140:e98–e124. DOI: 10.1161/CIR.0000000000000695

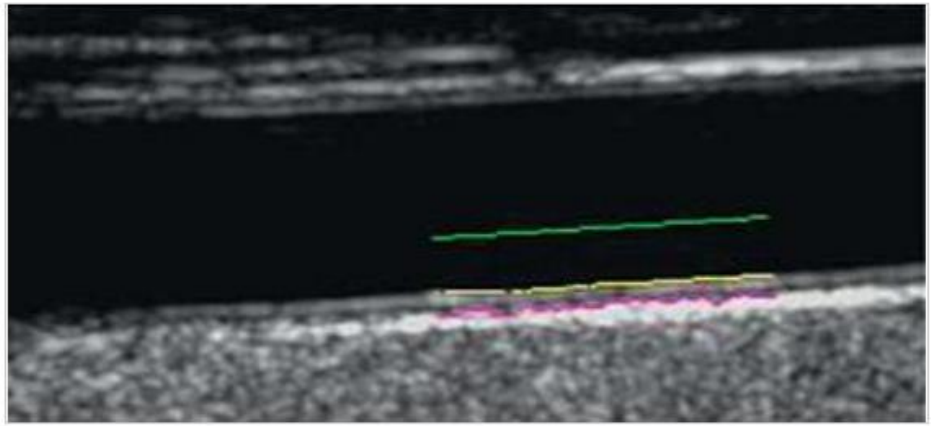

Viremia
Microbial translocation
Co-infections
↑ T cell activation
Persistent immune activation
↑ Monocyte/ macrophage activation
↑ Pro-inflammatory cytokines: TNFα, IL-6, IL-12, IL-8, IL-1
↑Pro-fibrotic cytokines: IL-10; TGF-β
↑PAI-1
↑TF
↑VCAM-1
↑ICAM-1
↓NO
↑Collagen production & accumulation
Hypercoagulation
Endothelial dysfunction
Myocardial fibrosis
Cardiovascular diseases

True or False

HIV + patients have more carotid plaques and higher intima-media thickness compared to uninfected individuals

Accelerated Atherosclerotic disease



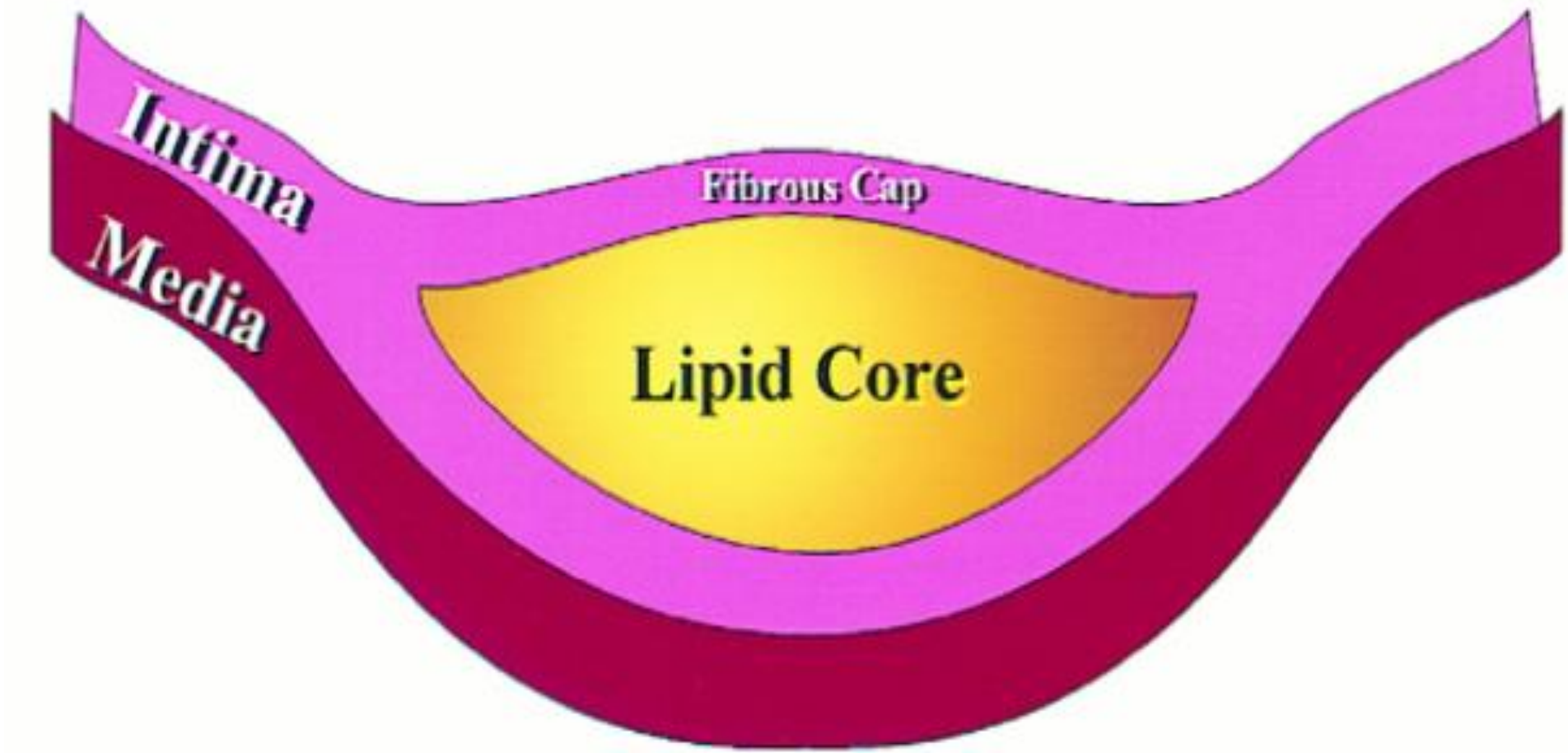


Which plaque is most likely to rupture?

A. Thin fibrous cap, lipid rich core

B. Thick fibrous cap, lipid rich core

C. Thin fibrous cap, calcium rich core


Intima
Media
Fibrous Cap
Lipid Core

Which statins are safest in patients on protease inhibitors?

- A. Atorvastatin and Simvastatin
- B. Simvastatin and Lovastatin
- C. Pitavastatin and Pravastatin
- D. Rosuvastatin
- E. Statins should be avoided in patients on protease inhibitors

Statin selection in HIV

- Prava and Pitava are very safe when administered with Protease Inhibitors (PI) and Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

- When a higher intensity statin is needed

Atorvastatin 20mg or less

Rosuvastatin 10mg or less

Avoid lovastatin and simvastatin with PI and cobicistat routines as levels may increase by 32-fold.

Drug Interactions with Antiretroviral Medications. National HIV curriculum, University of Washington. August 30, 2020.

Management of atherosclerotic disease in HIV + patients

HIGH RISK APPROACH

Consider referral to cardiologist; patient-clinician discussion re: benefit vs. risk, patient preference

LIFESTYLE OPTIMIZATION

(Particularly Smoking Cessation)

+

LIPID LOWERING DRUG THERAPY

*Atorvastatin 10-80 mg**

*Rosuvastatin 5-40 mg**

Pitavastatin 2-4 mg

Statin Dosing: START LOW, GO SLOW

Decrease dose or discontinue if severe myalgia or unexplained muscle weakness, LFTs >3x the upper limit of normal, or CK >10x the upper limit of normal

**Exercise caution due to drug interactions at high end of dose range; consider if very high risk and/or known CAD. If familial hypercholesterolemia, severe statin intolerance, or insufficient response to statin as determined by clinician: consider ezetimibe +/- PCSK9 inhibitor on an individualized basis.*

Circulation. 2019;140:e98–e124. DOI: 10.1161/CIR.0000000000000695

Cerebral Vasculopathy in HIV Infection Revealed by Transcranial Doppler (TCD)

Small pilot study looking at 31 HIV + patients and 10 age-matched healthy controls

None had a history of CNS infection, dementia, or cerebrovascular disease

7/31 were classified as AIDS

Average CD4 count of 217 +- 169

All had CRP, RF, ANA, anti-cardiolipin labs drawn

All had brain and vessel imaging (mostly MRI) to rule out prior stroke and atherosclerotic disease

Stroke 1999 Apr;30(4):811-3.

doi: 10.1161/01.str.30.4.811.dd text

Table 1. Baseline BFV and CRC in HIV-Infected Individuals (n=31) and Healthy Control Subjects (n=10)

	HIV-Infected (n=31)	Controls (n=10)	*P*
Baseline BFV right MCA, cm/s	63 ±16 (n=29)	79±16	<0.005
Baseline BFV left MCA, cm/s	65±15 (n=29)	75±16	<0.05
CRC right MCA, %	31±11 (n=29)	46±13	<0.001
CRC left MCA, %	33±13 (n=29)	47±11	<0.005
Mean CRC of both MCA, %	31±11 (n=27)	46±13	<0.0005

Stroke 1999 Apr;30(4):811-3.
doi: 10.1161/01.str.30.4.811.dd text

Conclusion

- Independent of CD4 count and autoimmune labs, HIV + individuals have reduced cerebrovascular reserve

Stroke
Volume 31, Issue 9, September 2000; Pages 2117-2126
https://doi.org/10.1161/01.STR.31.9.2117

ORIGINAL CONTRIBUTIONS

Cerebral Infarction in Adult AIDS Patients

Observations From the Edinburgh HIV Autopsy Cohort

M.D. Connor, G.A. Lammie, J.E. Bell, C.P. Warlow, P. Simmonds, and R.D. Brettle

183 autopsy cases reviewed

Included: Cerebral infarction

Excluded: Those with opportunistic infections, or CNS lymphoma

Sample size of 10

Non-vasculitic vasculopathy

- 9/10 cases showed mild-moderate concentric hyaline thickening and perivascular space dilation and vessel wall mineralization AKA **SMALL VESSEL DISEASE**

- Aneurysms and occlusive disease may also be seen (common carotid, abdominal aorta, common iliac, femoral, popliteal) AKA LARGE AND MEDIUM VESSEL DISEASE

J Clin Pathol 2001;54:275–278

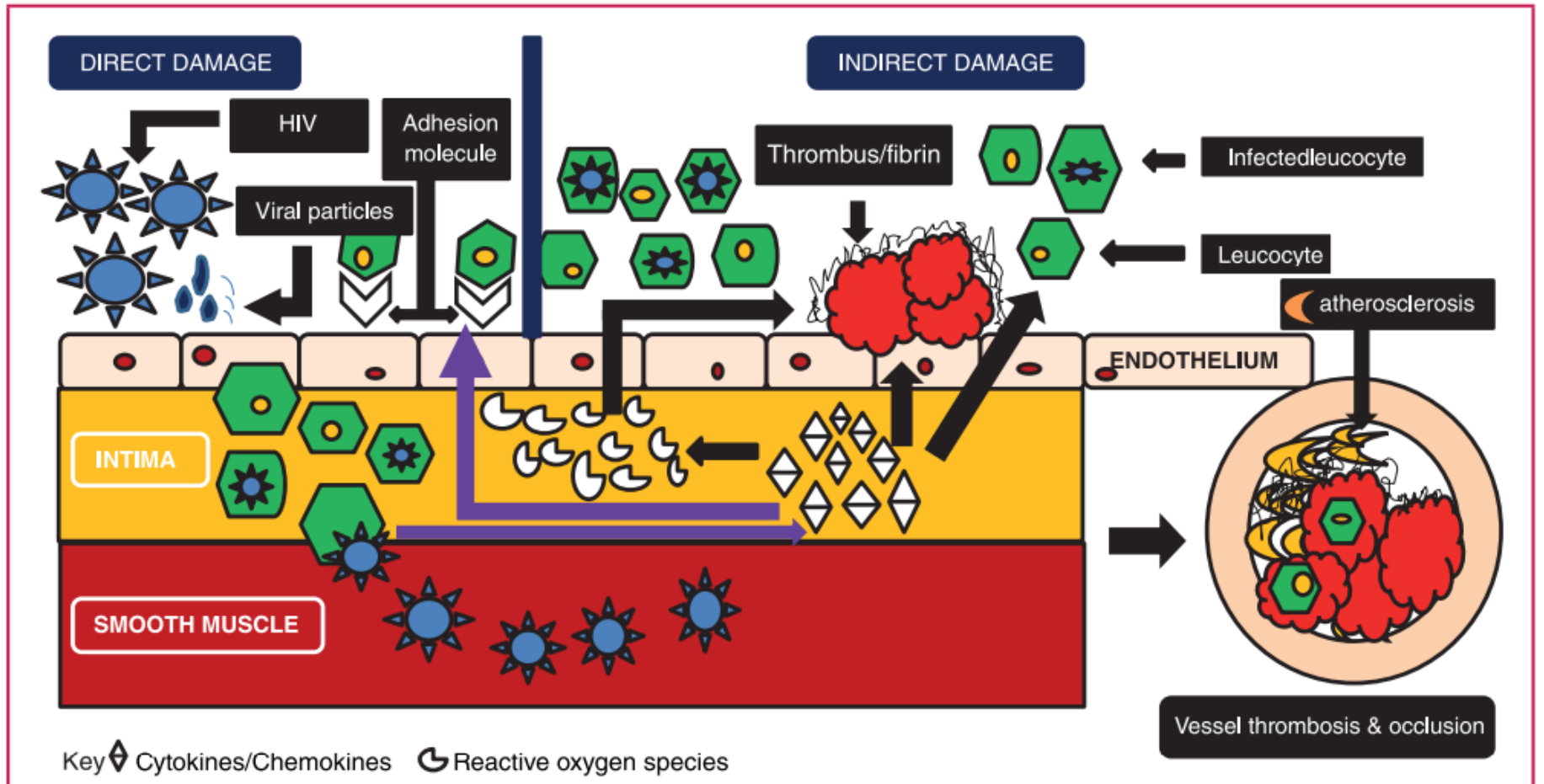
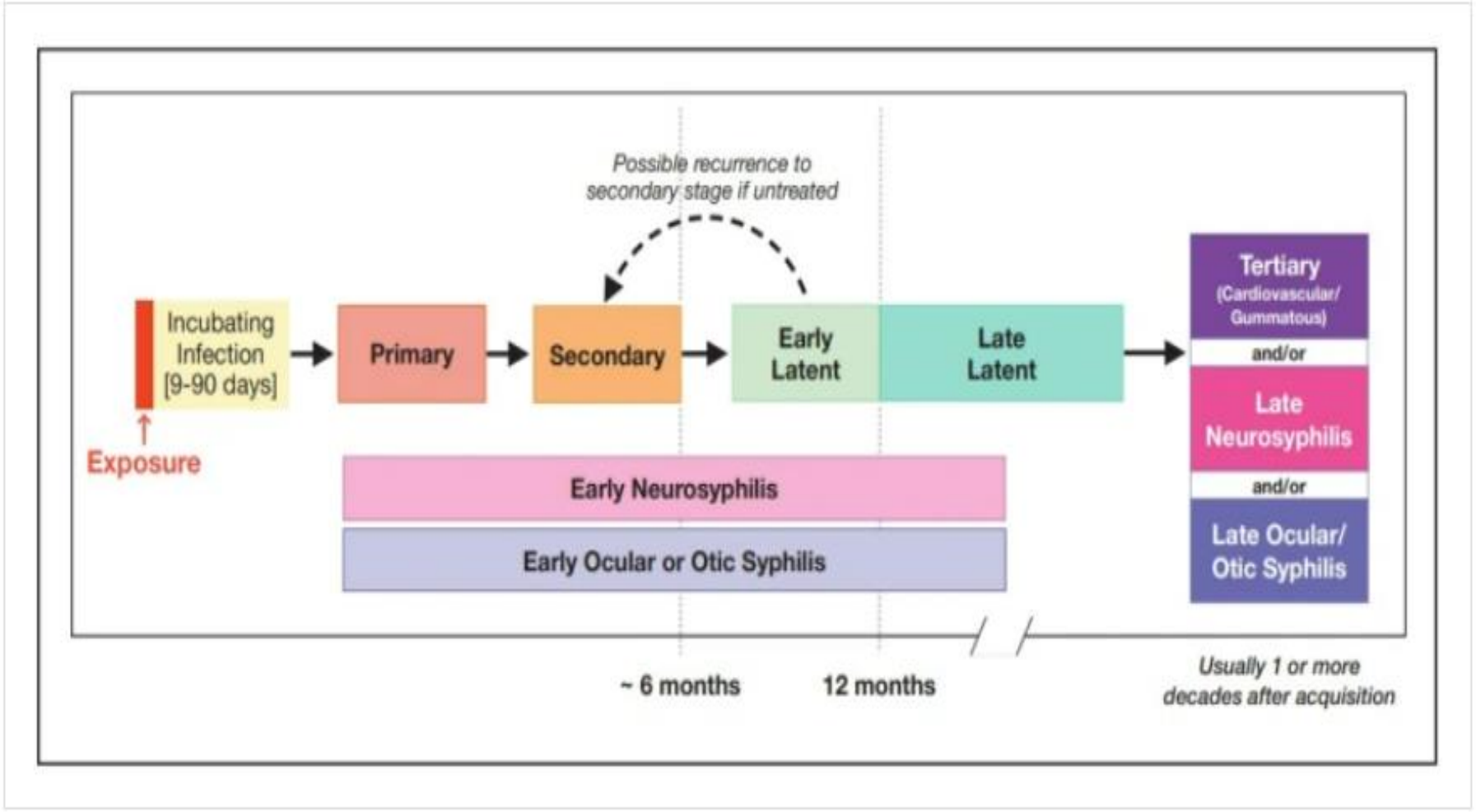


Fig. 1A. Schematic illustration of direct and indirect endothelial damage. The former is characterised by viral endothelial invasion, upregulation of adhesion molecules, generation of reactive oxygen species and varied cytokine and chemokine responses. The latter encompasses continued viral invasion, generation of an inflammatory cascade that leads to a vicious circle of endothelial injury, activation and remodelling, culminating in thrombosis and occlusion.

HIV Vasculitis

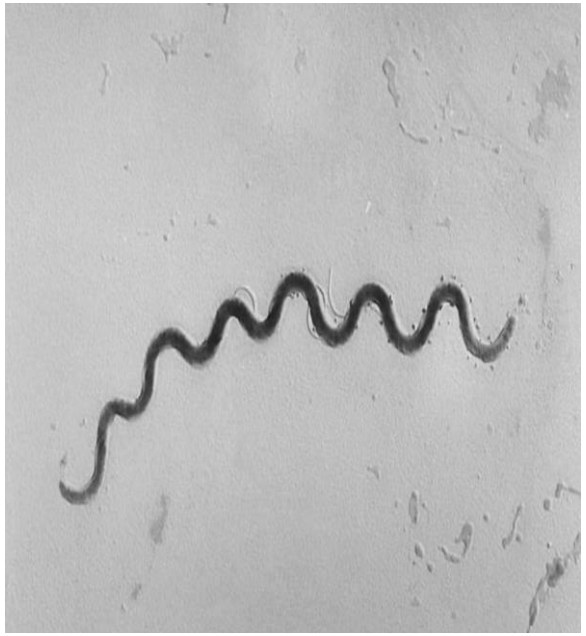
- VZV, HSV, EBV
- Tb, Cryptococcus, Syphilis
- Aspergillosis, Candida, Coccidioidomycosis, Mucormycosis, Toxoplasmosis, Trypanosomiasis

Neurosyphilis



NYC Department of Health and Mental Hygiene, and the NYC STD Prevention Training Center. The Diagnosis and Management of Syphilis: An Update and Review. March 2019.

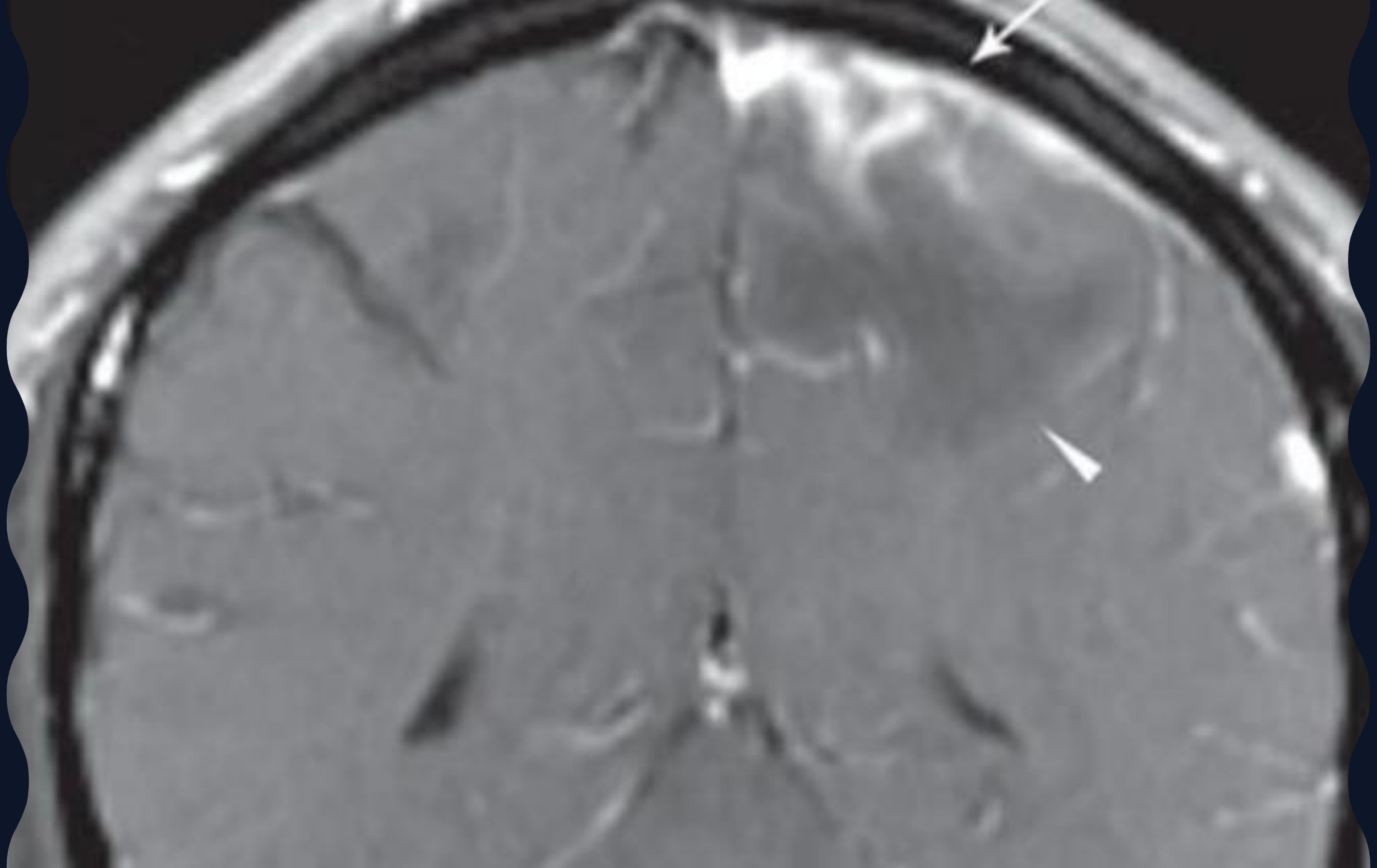
Meningovascular Syphilis

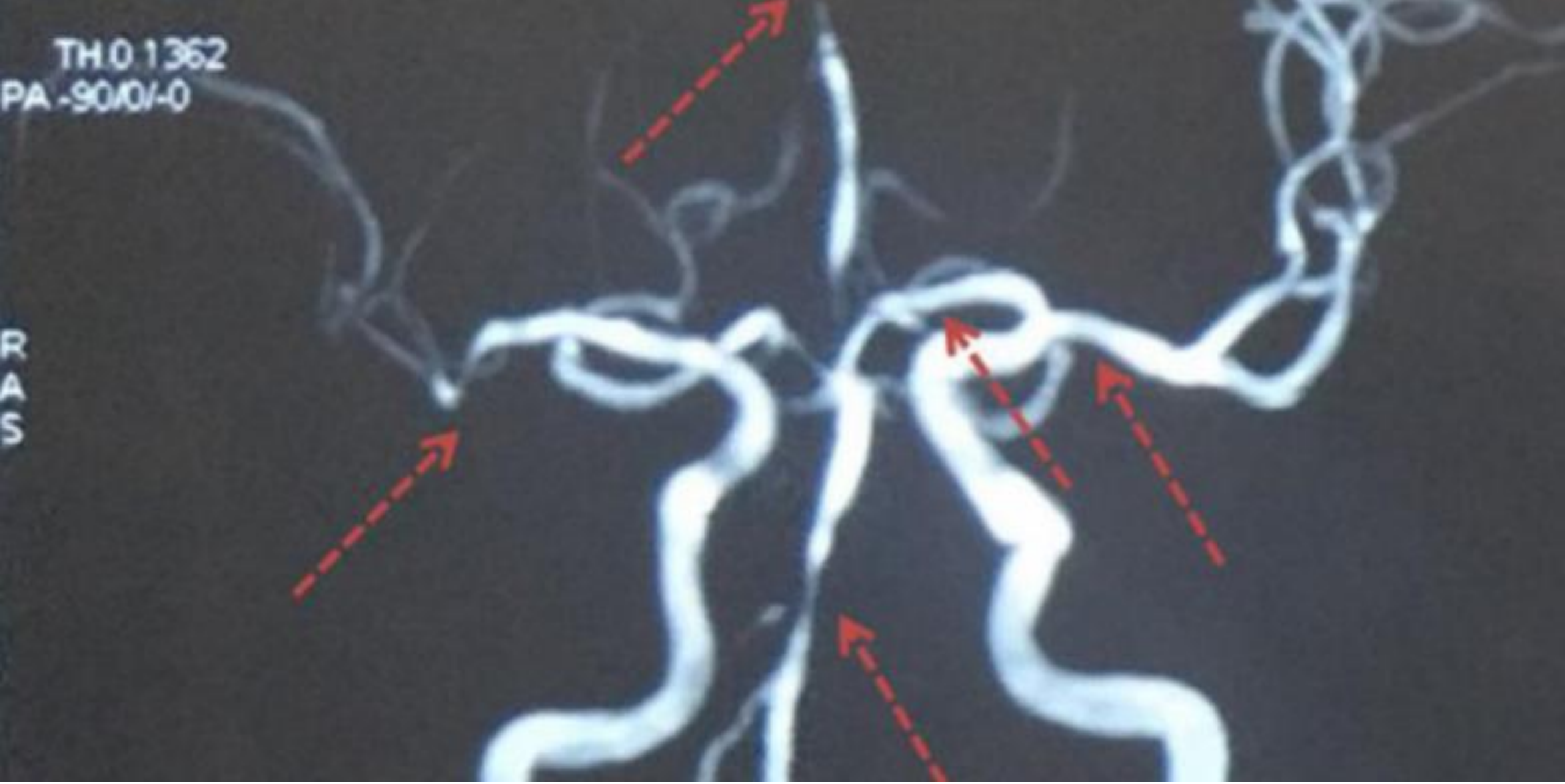


- Stroke incidence (in the post-abx era) in patients with meningovascular syphilis ranges from 7-23%.

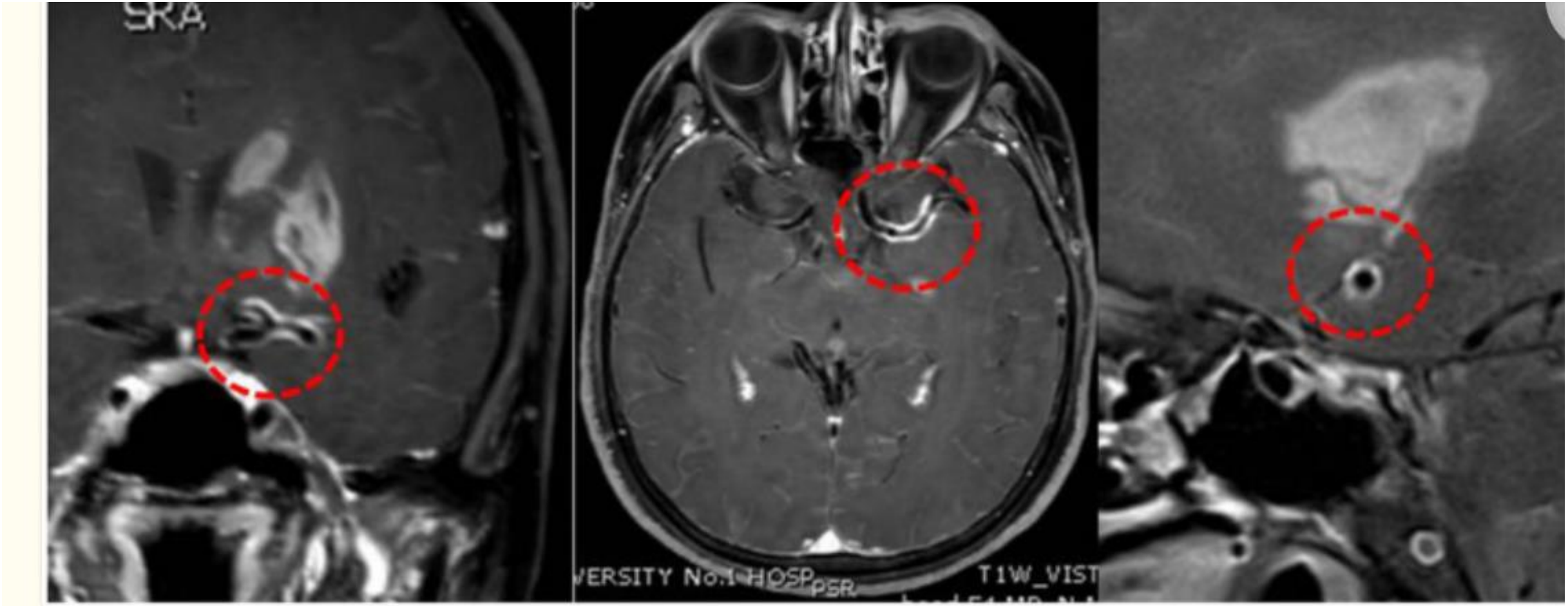
<u>Pathology features</u>

- Endarteritis of the medium and large arteries
- Endarteritis of the small arteries
- Intima thickening
- Media thinning
- Vaso vasorum cuffed by inflammatory cells





Front Neurol. 2021; 12: 675083.
Published online 2021 Aug 30. doi: 10.3389/fneur.2021.675083



Enhancement on High-resolution MRI

Front Neurol. 2021; 12: 675083.
Published online 2021 Aug 30. doi: 10.3389/fneur.2021.675083

Neurosyphilis Workup

-Check Serum RPR (> 95% of neurosyphilis patients will be +)

-If positive, confirm with Serum FTA-Abs

LP Profile

-Lymphocytic pleocytosis, elevated protein, normal glucose

-May have elevated oligoclonal bands

-CSF VDRL

Which of the following are risk factors for CNS Tb?

- A. HIV
- B. Alcoholism
- C. Malignancy
- D. Immune Suppression
- E. All of the Above



Tb Meningitis

Presentation varies from fever, vomiting, and apathy to cranial nerve palsies

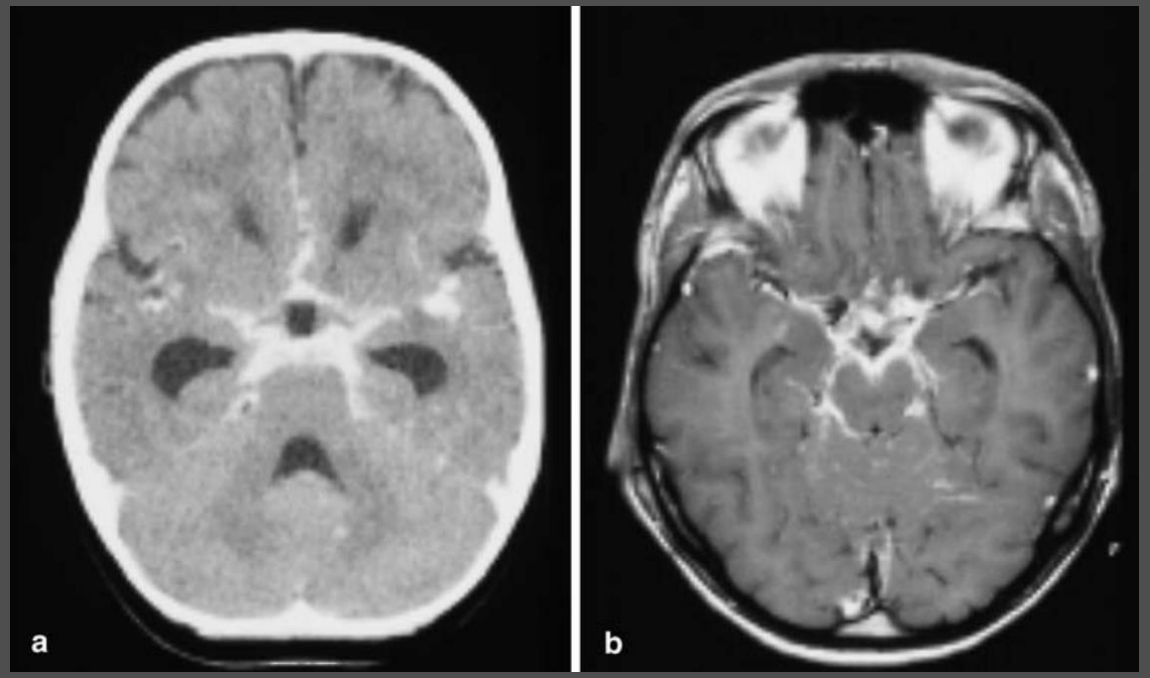
LP profile shows : very high protein, low glucose, may have elevated WBC with lymphocytic predominance

- AFB cultures may take weeks
- Corticosteroids reduce mortality

■ Table 16.14 Tuberculous Meningitis: Stages of Severity at Presentation

Stage I	Fever, irritability, lethargy, headache Regression of developmental milestones
Stage II	Nuchal rigidity, seizures, focal neurologic deficits, vomiting Movement disorders, cranial nerve palsies (predilection of *Mycobacterium tuberculosis* for basilar portion of brain) Cerebral edema, infarction
Stage III	Paraplegia, cardiovascular instability Posturing, eventual death

Source: Adapted from Council MR. Streptomycin treatment of tuberculous meningitis: report of the committee on Streptomycin in Tuberculosis Trials. *Lancet*. 1948;1:582–597.



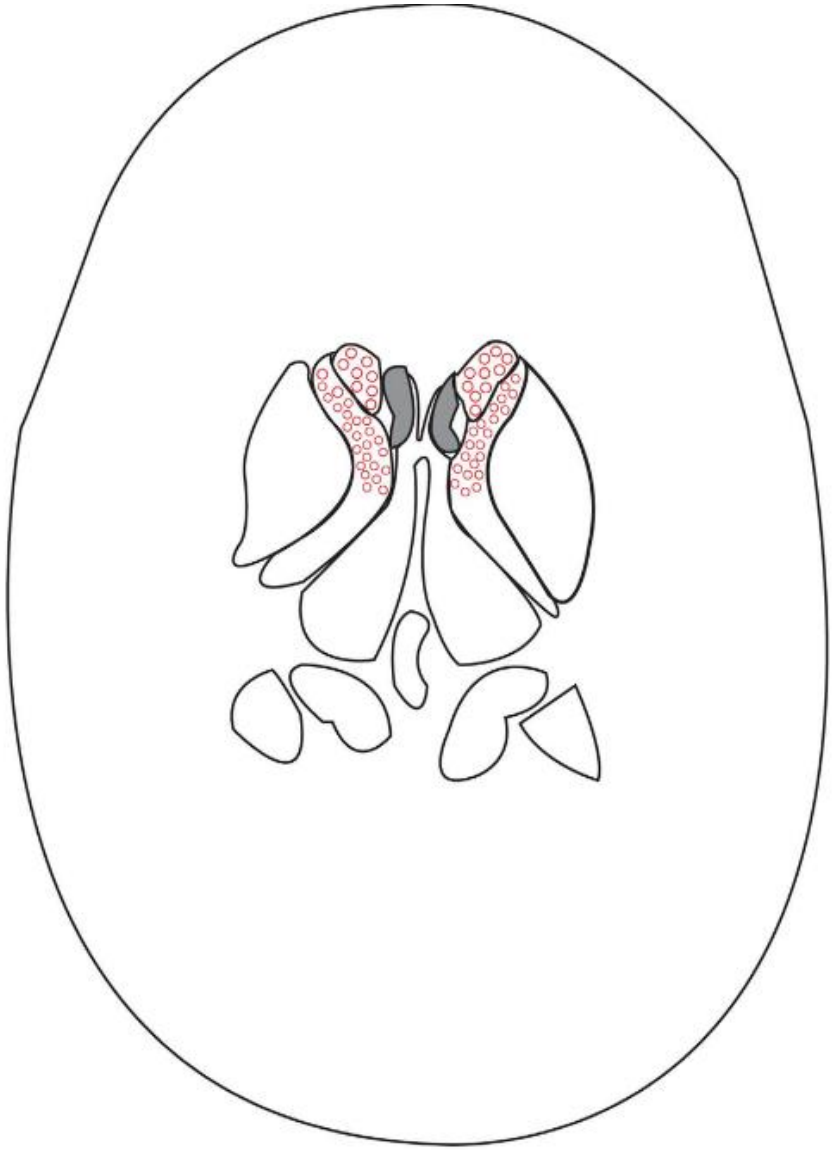
Tuberculosis of the Central Nervous System: Overview of Neuroradiological Findings

September 2003 · European Radiology 13(8):1876-90

DOI:10.1007/s00330-002-1608-7

Source · PubMed

"Tb Zone"



Other Fungals

- Aspergillus (inhalation)
- Mucormycoses (sinuses)
- Candida (hematogenously)
- Cryptococcus (inhalation)
- Coccidioidomycosis (inhalation)

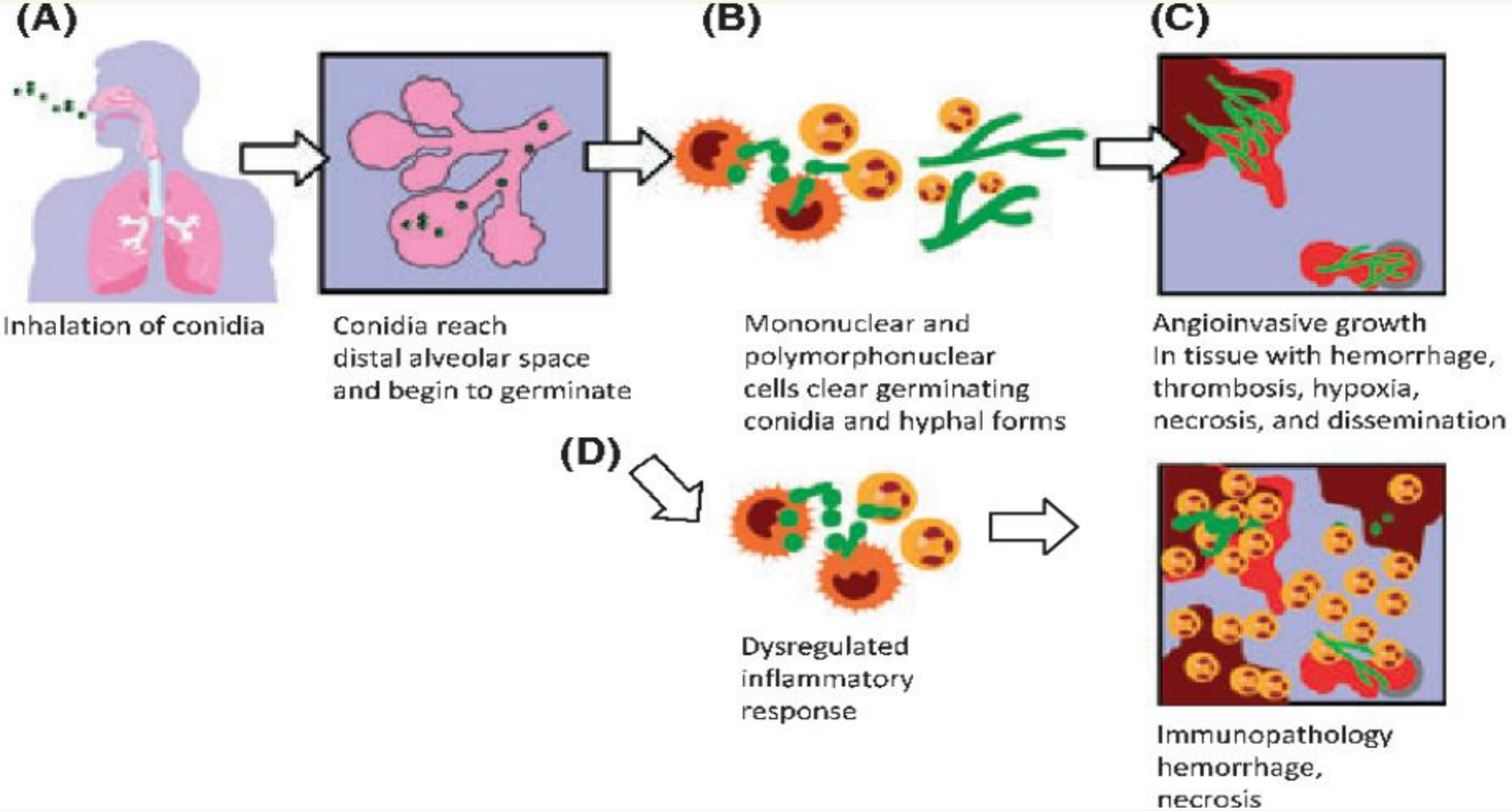
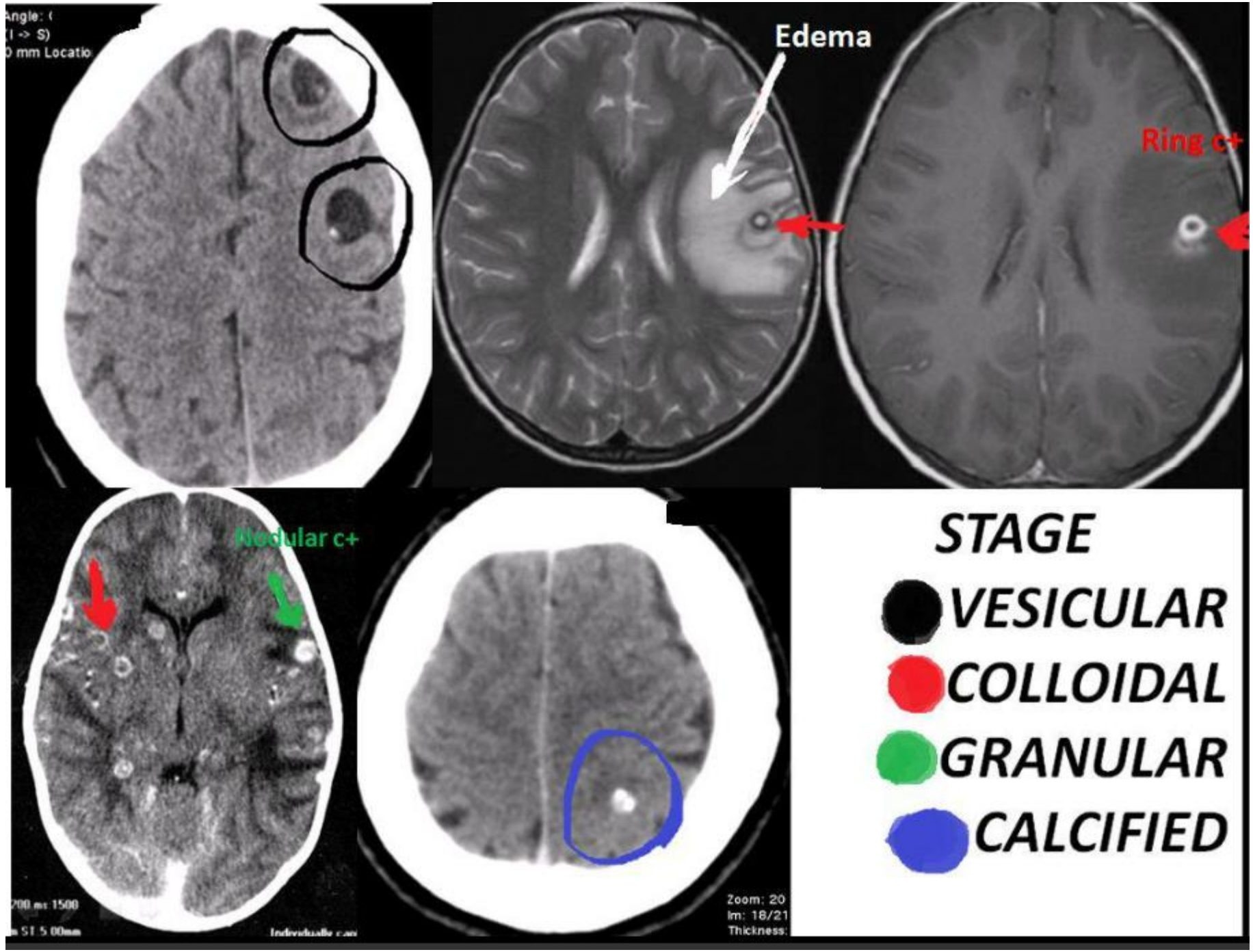
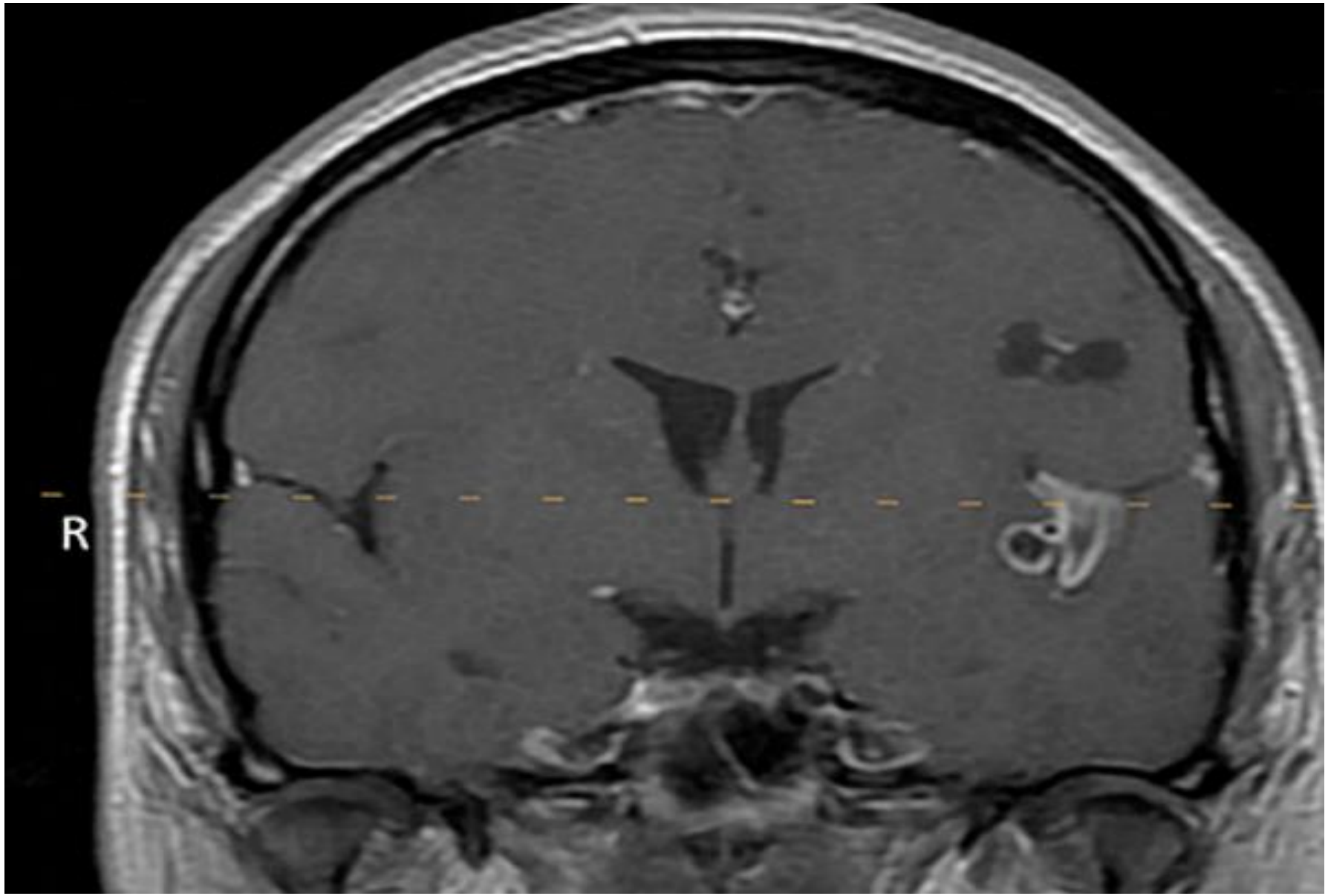


Fig1. Pathogenesis of invasive aspergillosis in different immunological settings. (Ben-Ami, 2010)

Cysticercosis

- Small-vessel disease
- Large-vessel disease
- Hemorrhagic stroke
- Mycotic aneurysm rupture


Edema
Ring c+
Nodular c+
STAGE
VESICULAR
COLLOIDAL
GRANULAR
CALCIFIED


R

True or False

VZV infection is a risk factor for stroke

VZV Vasculopathy

- Two studies using the Taiwan National Health Research Institute records revealed a 30% increased risk of stroke within 1 year following zoster (Kang et al., 2009) and a 4.5-fold increased risk if zoster occurred in the ophthalmic division of the trigeminal nerve (Lin et al., 2010).

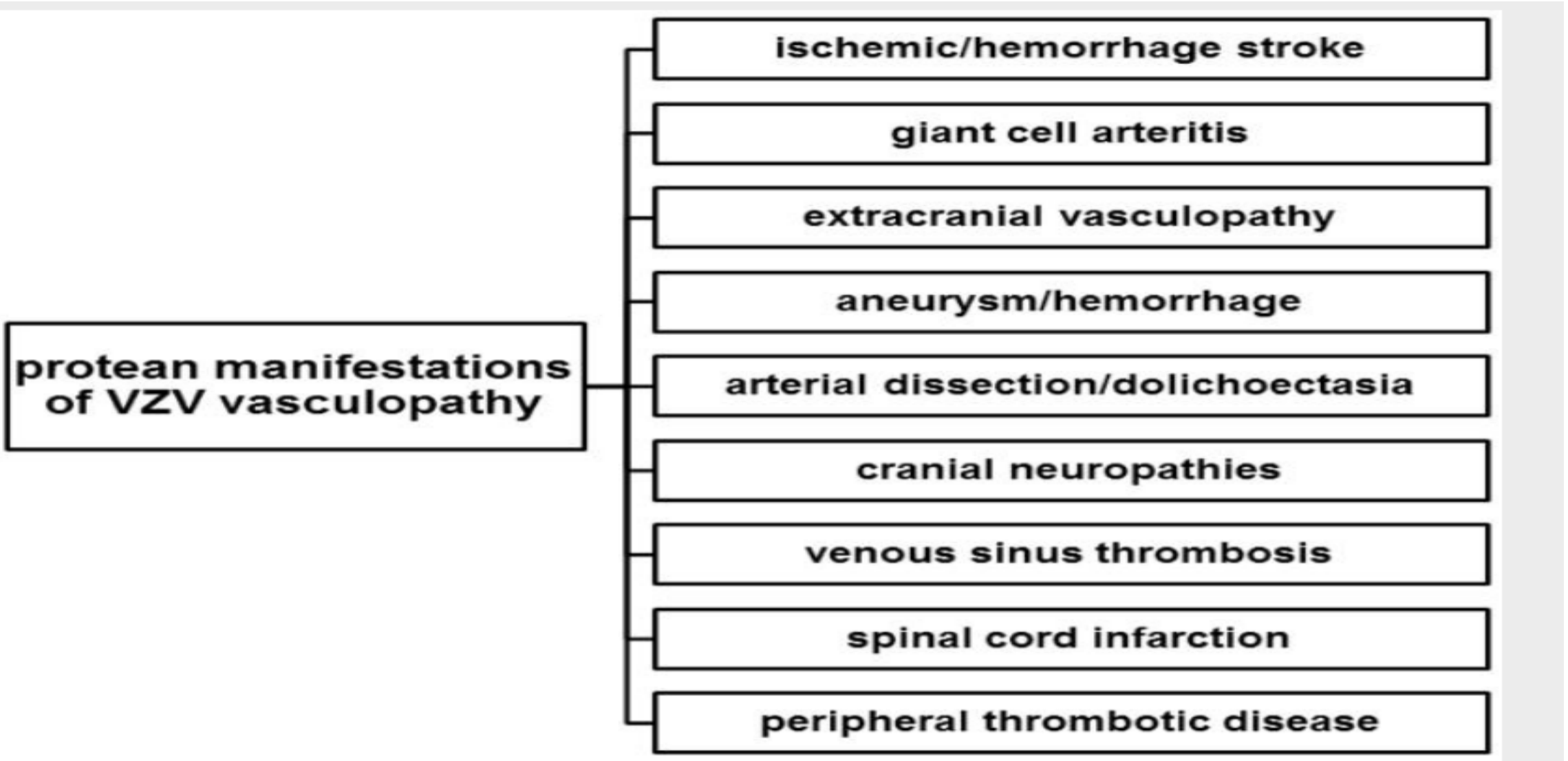
- Increased risk of stroke within the 1-6 months of infection

When to Suspect VZV Vasculitis as an Etiology of Ischemic Stroke.

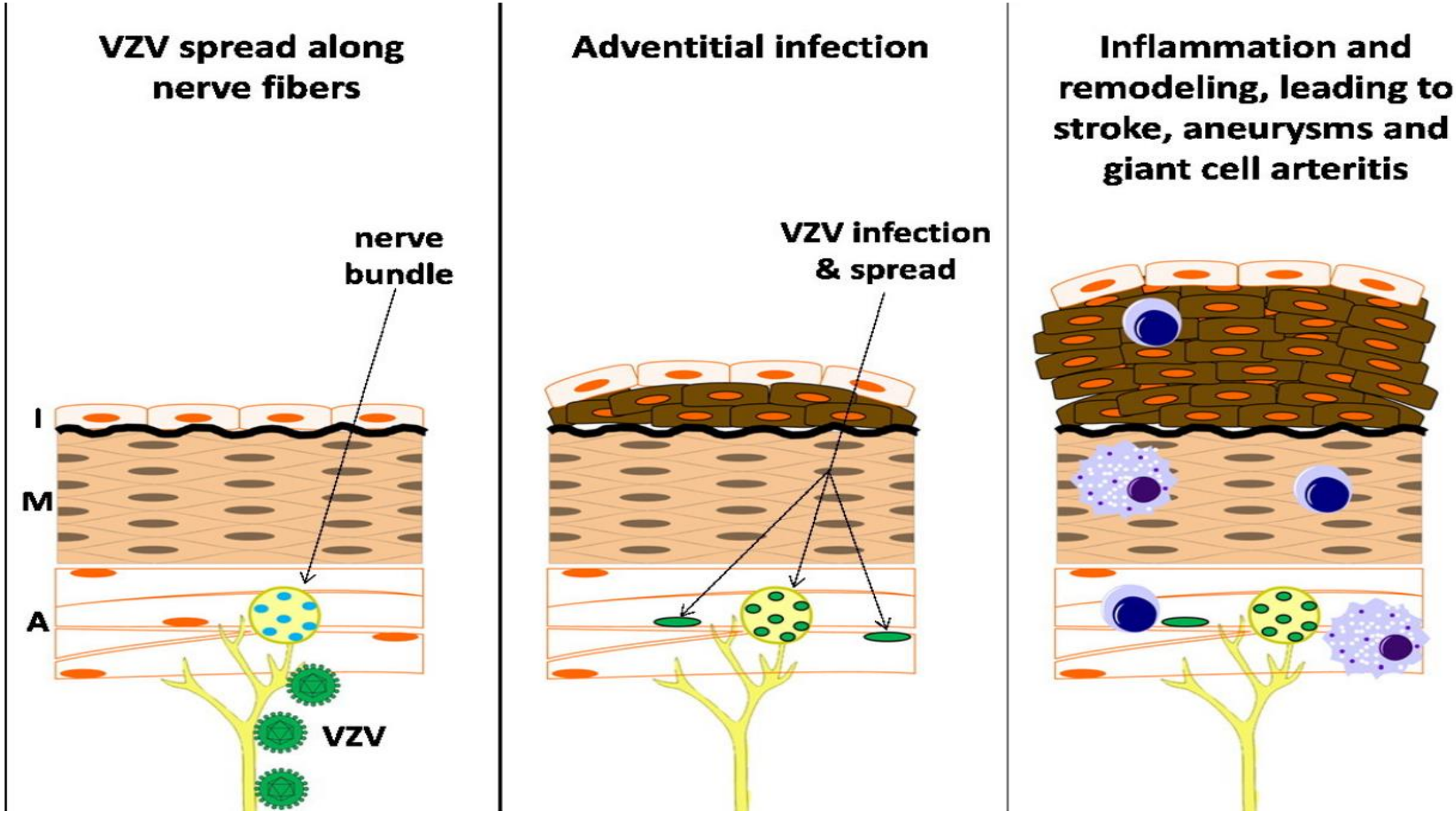
Cryptogenic stroke after detailed workup
• Recent history of varicella or zoster with/without rash
• Paucity of traditional vascular risk factors
• Recurrent stroke despite optimal medical therapy
• Infarcts at gray-white matter junction on MRI
• Arterial narrowing in distribution atypical for atherosclerosis
• Immunocompromised individual (eg, HIV, DM, elderly)

Neurohospitalist. 2019 Oct; 9(4): 203–208.

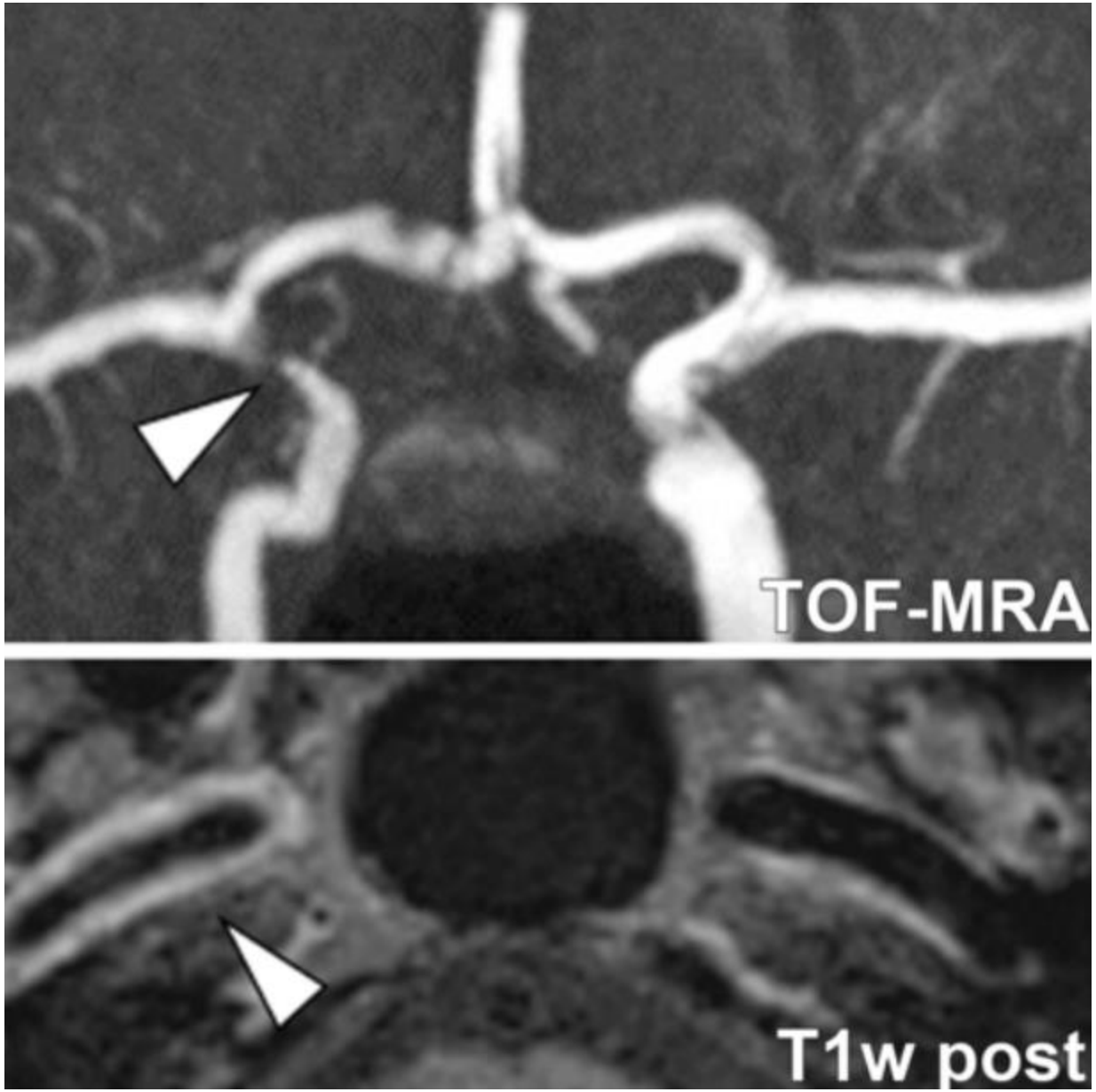
Published online 2019 Apr 28. doi: 10.1177/1941874419845732



Curr Infect Dis Rep. 2014 Jun; 16(6): 407.
doi: 10.1007/s11908-014-0407-z

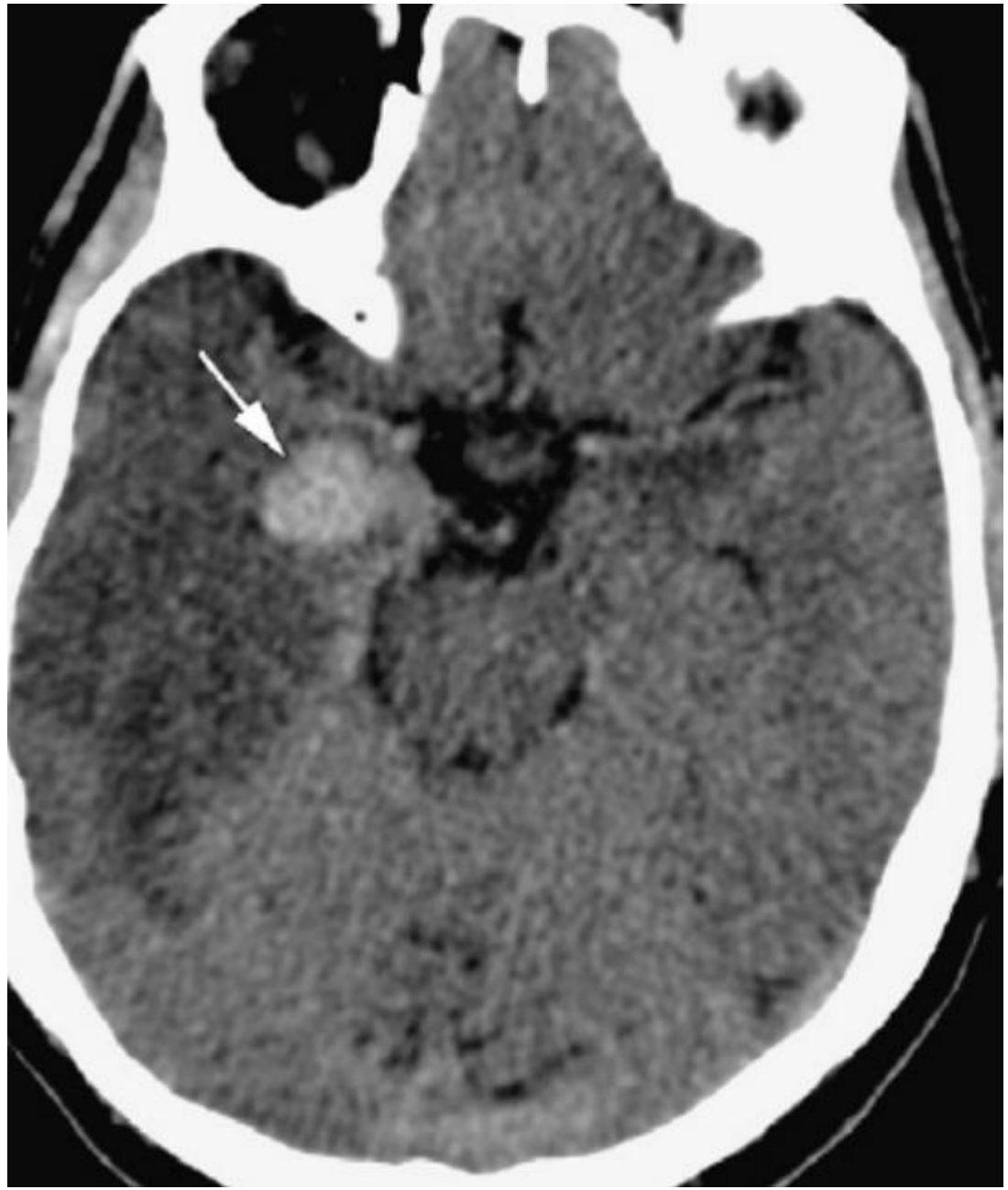


Journal of Neuroimmunology
Volume 308, 15 July 2017, Pages 112-117


TOF-MRA
T1w post

Diagnosis and Treatment

- Cover with antivirals while LP results
- Check CSF VZV-IgG
- If there is concern for vasculopathy, treat with prednisone 1mg/kg/day X 5 days.



Cerebrovascular HSV

- Lobar ICH
- Ischemic CVA (large vessels)
- SAH
- Venous Sinus Thrombosis

What about antiplatelet agent use with infectious vasculopathies?

- Not well studied

- It is probably reasonable to use antiplatelet agents for secondary stroke prevention in patients with traditional stroke risk factors

Which of the following syphilitic manifestations can commonly be seen in early infection?

- A. general paresis
- B. meningovascular disease
- C. syphilitic amyotrophy
- D. syphilitic cerebellar ataxia
- E. tabes dorsalis

Continuum Neuroinfectious Disease. August 2021. Vol. 27. No. 4

A 65 year old female with long-standing rheumatoid arthritis on methotrexate and steroids presents with her 3rd stroke within 7 months. MRI shows several infarcts of varying ages involving multiple vascular territories. These are located at the grey-white matter junction with the most recent infarct showing contrast enhancement. The patient likely has a vasculopathy related to which of the following infections?

- A. BK virus
- B. CMV
- C. HSV
- D. HHV 6
- E. VZV

Continuum Neuroinfectious Disease. August 2021. Vol. 27. No. 4

References

Caplan, L. R., & Biller José. (2018). In *Uncommon causes of stroke* (pp. 1–76). essay, Cambridge University Press.

Continuum Neuroinfectious Disease. August 2021. Vol. 27. No. 4

Thank you