CNS infections causing ischemic and /or hemorrhagic stroke

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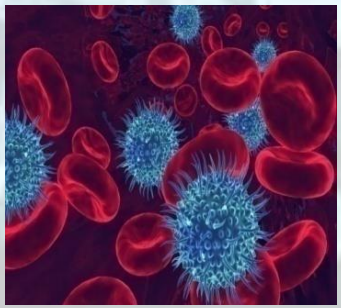


Background

- Infections in SSA are frequent
- Stroke is frequent with a higher incidence in **younger** population
- **Microrganisms** leading to Infection are NUMEROUS and variable in each region
- Numeous **etiologies** leading to Stroke
- BOTH share challenge in epidemiology diagnosis management and prognosis

Fernandes et al. Ischemic stroke and infectious diseases in low-income and middle-income countries. Curr Opin Neurol. (2019)

Jillella et al. Infectious causes of stroke. Curr Opin Infect Dis. Jun;32(3):285-292. (2019)

Stroke and Infection

- Stroke and Infection: **Complex** relationship:

NEUROLOGY REVIEWS

ARTICLE

Stroke and Infection—A Complex Association

Neurology Reviews. 2009 April;17(4):1, 27, 28

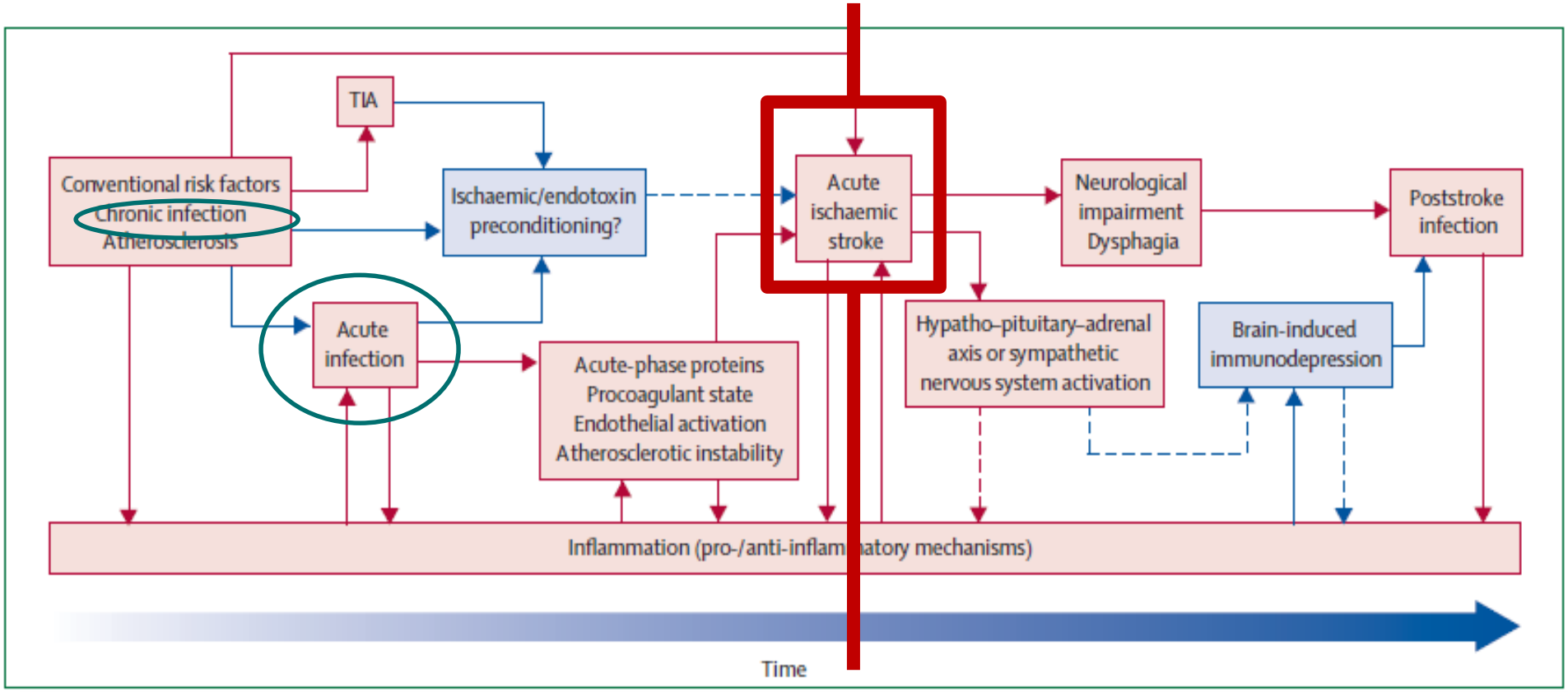
  - ***Pre-stroke***:
    - Infection= risk factor/Trigger: **1/3** ischemic stroke
    - Infection=cause
  - ***Post-stroke***:
    - Secondary immunosuppressive state: impaired immunity or brain-induced immunodepression after stroke
    - Infection=Complication (bacterial pneumonia and urinary tract infections)

Engel et al, Models of infection before and after stroke: investigating new targets.. Infect Disord Drug Targets.(2010)

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

Stroke and Infection

- Stroke and Infection: Complex relationship:



Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

Studies on infections preceding stroke: 5-43%

	Study design	Type of infection(s)	Number of patients with infection (%)	Prestroke interval (for prevalence estimate)	Number of patients (controls)	Prestroke interval (for risk analysis)	Outcome statistic (95% CI)	Description of outcome statistic
Syrjänen and co-workers[7]	Case–control	Infections (80% respiratory)	19 (35%)	1 m	54 (54)	1 m	RR 9·0 (2·2–80·0)	RR of stroke after infection
Ameriso and co-workers[8]	Consecutive series	Mostly respiratory tract infections	17 (34%)	1 m	50	..	..	..
Grau and co-workers[9]	Case–control	Mostly respiratory tract bacterial infections	31 (16%) 38 (19%)	1 w ≤4 w	197 (197)	1 w	OR 4·6 (1·9–11·3)*	Estimated OR for stroke after infection
Macko and co-workers[10]	Case–control	Infections or inflammatory events (mostly upper respiratory tract)	13 (35%)	1 w	37 (47, 34)†	..	..	..
Bova and co-workers[11]	Case–control	Infections (mostly respiratory tract or urinary tract)	41 (23%) 44 (24%)	1 w 2 m	182 (194)	2 m	OR 2·9 (1·6–5·3)	Risk of preceding infection in patients with acute ischaemic stroke
Grau and co-workers[12]	Case–control	Infections (bacterial or viral)	27 (27%) 8 (5%) 45 (27%)	1 w 2–4 w 4 w	166 (166)	1 w	OR 2·9 (1·3–6·4)	Risk of cerebrovascular ischaemia after infection
Nagaraja and co-workers[13]	Case–control	Infections (bacterial or viral)	6 (10%) 20 (33%) 26 (43%)	1 w ≤2 w >2 w	60 (60)	..	..	..
Paganini-Hill and co-workers[14]	Case–control and crossover	Infectious or inflammatory events	43 (18%)	1 m	233 (363)	1 m	RR 1·8 (0·6–3·6)	RR of large-vessel or cardioembolic stroke after respiratory tract infection
Nencini and co-workers[15]	Case–control	Infective or non-infective inflammatory events	17 (18%) 37 (40%)	7 d 30 d	93 (200)	7 d 30 d	OR 2·5 (1·1–5·4) OR 2·2 (1·3–4·0)	Risk of ischaemic stroke after inflammatory event
Smeeth and co-workers[16]	Case series	Systemic respiratory tract infections‡	..	..	244 237 368 561 1650	1–3 d 4–7 d 8–14 d 15–28 d 29–91 d	IR 3·2 (2·8–3·6) IR 2·3 (2·1–2·7) IR 2·1 (1·9–2·3) IR 1·7 (1·5–1·8) IR 1·3 (1·3–1·4)	IR for first stroke after systemic respiratory tract infections
		Urinary tract infections§	..	..	152 158 245 445 1250	1–3 d 4–7 d 8–14 d 15–28 d 29–91 d	IR 2·7 (2·3–3·2) IR 2·1 (1·8–2·5) IR 1·9 (1·7–2·1) IR 1·7 (1·6–1·9) IR 1·2 (1·2–1·3)	IR for first stroke after urinary tract infections

OR=odds ratio. RR=relative risk. IR=incidence ratio. * By conditional logistic regression analysis; a later report by the same group used a different statistical model resulting in an OR of 4·3, 95% CI 1·8–10·5.[17] †Two control groups (47 community, 34 hospitalised). ‡22 400 participants exposed. §14 603 participants exposed.

Table 1: Studies that report infections preceding stroke

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

Potential New Risk Factors for Ischemic Stroke

What Is Their Potential?

Graeme J. Hankey, MD, FRCP, FRACP

TABLE 5. Potential New Risk Factors for Ischemic Stroke

Genetic factors/genotypes
Angiotensin-converting enzyme genotype
Factor V Leiden
Prothrombin G20210A
MTHFR
Human platelet antigen type 1
Factor XIII
Apo E
Plasminogen activator inhibitor-1 4G/5G genotypes
Phosphodiesterase 4D
5-Lipooxygenase–activating protein
Inflammatory markers
Leucocyte count
Monocyte count
High-sensitivity C-reactive protein
Soluble CD40 ligand
Serum amyloid A
Interleukins (IL-6, IL-18)
Vascular and cellular adhesion molecules
Myeloperoxidase
Matrix metalloproteinase-9
Infectious agents
Cytomegalovirus
Herpes simplex virus
Chlamydia pneumonia
Helicobacter pylori
Legionella sp
Periodontal disease

Hankey et al, Potential New Risk Factors for Ischemic Stroke What Is Their Potential? Stroke (2006)

Organisms implicated in stroke

Table 2 Selected organisms implicated in stroke pathogenesis

Organism	Infection	Mechanism
Bacterial infections		
Treponema pallidum	Neurosyphilis	Vasculitis/arteritis
Mycobacterium tuberculosis	Tuberculous meningitis	Arteritis; meningitis
Chlamydia pneumoniae	Acute or chronic respiratory infections	Accelerated atherogenesis, enhanced platelet aggregation
Helicobacter pylori	Gastritis, peptic ulcer disease	Enhanced platelet aggregation, prothrombotic state
Porphyromonas gingivalis (and other periodontal pathogens)	Periodontal disease	Chronic inflammation due to infectious burden; prothrombotic state
Parasitic infections		
Trypanosoma cruzi	Chagas disease, Heart failure	Cardioembolism
Taenia solium	Neurocysticercosis	Arachnoiditis/small artery vasculitis; direct compression of large arteries by cysts
Plasmodium falciparum	Cerebral malaria	Occlusion of cerebral arteries by infected erythrocytes
Echinococcus granulosis	Cardiac hydatidosis; cerebral cystic echinococcosis	Cardioembolism; arterial compression from cerebral cysts
Schistosoma mansoni	Schistosomiasis	Microembolic borderzone infarction
Toxocara canis	Toxocariasis	Arachnoiditis; vasculitis
Spirometra species (tapeworm)	Cerebral sparganosis	Vasculitis
Trichinella spiralis	Neurotrichinelliasis	Microinfarction due to direct obstruction of small vessels with larvae; vasculitis
Fungal infections		
Cryptococcus	Systemic and CNS infections (usually immunocompromised)	Meningitis; vasculitis
Aspergillus	Systemic and CNS infections	Arteritis, vasculopathy
Mucorales (including *Rhizopus*, *Mucor*, etc.)	Mucormycosis	Vascular invasion of fungus, aneurysmal dilatation, vascular necrosis
Viral infections		
Human immunodeficiency virus (HIV)	HIV disease/AIDS	Vasculopathy; susceptibility to opportunistic CNS infections
Cytomegalovirus	Often asymptomatic, latent; occasional mononucleosis-like syndrome	Inflammatory response with accelerated atherogenesis
Varicella zoster virus	Chickenpox, shingles	Vasculitis/vasculopathy
Herpes simplex virus (types 1 and 2)	Oral and genital infections	Vasculopathy; possible stroke trigger in young people
Parvovirus B19	"Fifth disease"	Possible arteriopathy

Infections and Mechanism of pathogenesis

Curr Neurol Neurosci Rep
DOI 10.1007/s11910-015-0602-9

INFECTION (J HALPERIN, SECTION EDITOR)

Infection and Stroke: an Update on Recent Progress

Eliza C. Miller[1] · Mitchell S. V. Elkind[2]

Mechanism of pathogenesis	Examples
Direct invasion of arterial wall, endotheliopathy	Syphilis, VZV, HSV, HIV, parvovirus B19
Acceleration of atherosclerosis through induction of cytokines (TNF-alpha, interleukin 2) in response to specific antigenic stimulus	Herpesviruses, *Chlamydia pneumoniae*
Acute systemic infection as stroke trigger (platelet activation, dehydration, infection-induced cardiac arrhythmias)	Influenza, upper respiratory infections, urinary tract infections
Chronic inflammation due to multiple infections (infectious burden)	Periodontal infection, *Chlamydia pneumoniae*, herpesviruses
Post-stroke infection due to stroke-induced reduction in cell mediated immunity; increased antigen presentation leading to autoimmune inflammatory response against damaged brain tissue → poor stroke recovery, worse functional outcomes	Urinary tract infections, pneumonia, hospital acquired line infections

Miller et al, Infection and Stroke: an Update on Recent Progress. Curr Neurol Neurosci Rep (20015

Acute infection preceding stroke

- *Retrospective series* of 64 young adults (16–40 years) with ischemic stroke:
  - Unexpected **seasonal variations** in stroke incidence
  - ➔ Identification of 18 patients (**28%**) with a history of possible acute infection at the time of stroke
- *Systematic study*: ↑ **serum bacterial antibody** levels in:
  - **44%** of patients with stroke (<45 years)
  - 9% of controls

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

Acute infection preceding stroke

- Acute infection=significant risk factor for stroke(all age):
  - ***Respiratory***
  - ***Bacterial***
  - ***<1 week*** preceding stroke

- Relative risk [RR] of stroke after infection in the preceding month: **1.8** (95% CI 0.6–3.6) to **9.0** (2.2–80.0)

- Prevalence of infection preceding ischemic stroke:
- <1 month: **18% to 40%**
- <1week: **10% to 35%**

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

Chronic infection and conventional stroke risk factors

- Chronic infections: ↑stroke risk if association with:
  - **Conventional** stroke risk factors
  - **Genetic** predisposition
- Lead to: ↑ plasma fibrinogen,CRP,IL-6➔↑stroke risk
- Complex interactions between:
  - Conventional stroke risk factors
  - Systemic inflammation
  - Chronic infections
    - (*Chlamydia pneumoniae, Helicobacter pylori, periodontal disease,…)*

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

Acute infection: Effects on stroke subtypes

- Respiratory tract infection
  - ➔ ***large-vessel*** and ***cardioembolic*** ischemic stroke (particularly in patients without vascular risk factors)
- Infection <1 month:
  - Ischemic stroke (***atherothrombotic*** +***cardioembolic***)
  - Bacterial and viral infection (+ atrial fibrillation++):

    ➔ ↑ risk for cardioembolic stroke (↑ prothrombotic state)
- Viral infection: H.Influenza++ vaccination
  - Lavallée et al.: Reduced risk of stroke: 0.5 at 1year and 0.4 at 5years
  - Grau et al.: Reduced risk of ***stroke or transient ischaemic attack*** (OR 0·46, 0·27–0·77), no protective effect in summer months

Stroke. 2002 Feb;33(2):513-8.

Association between influenza vaccination and reduced risk of brain infarction.

Lavallée P[1], Perchaud V, Gautier-Bertrand M, Grabli D, Amarenco P.

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

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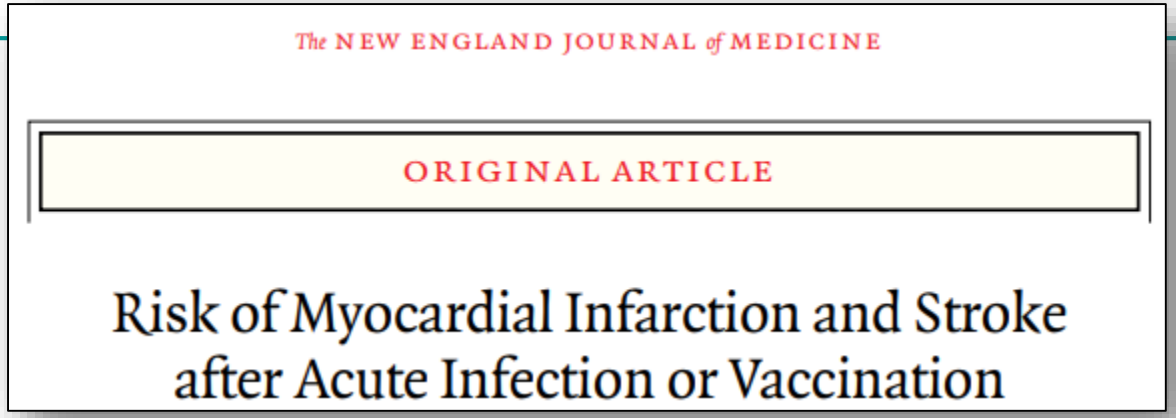


- UK General Practice Research Database (UKGPRD):
  - Most robust evidence for acute infection as a trigger for stroke
  - ***50 000*** patients (first or subsequent stroke)
  - Risk of first stroke:
    - substantially higher after acute infection
    - highest risk during the ***first 3 days***
    - incidence ratio (IR):
      - ***3·2*** (2·8–3·6) after systemic ***respiratory*** tract infection
      - ***2·7*** (2·3–3·2) after ***urinary*** tract infection
      - significantly raised for ***3 months*** (effect gradually reduced)
      - Vaccination: small protective effect

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

Smeeth et al, Risk of myocardial infarction and stroke after acute infection or vaccination. N Engl J Med. (2004)

Table 1. Age-Adjusted Incidence Ratios of a First Myocardial Infarction and a First Stroke in Risk Periods after Exposure to Vaccination or Infection.*

Outcome and Risk Period	Influenza Vaccination (N=20,486)		Tetanus Vaccination (N=7966)		Pneumococcal Vaccination (N=5925)		Systemic Respiratory Tract Infection (N=20,921)		Urinary Tract Infection (N=10,448)	
	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)
Myocardial infarction										
1–3 days	77	0.75 (0.60–0.94)	12	1.10 (0.62–1.92)	4	0.49 (0.19–1.32)	322	4.95 (4.43–5.53)	58	1.66 (1.28–2.14)
4–7 days	94	0.68 (0.56–0.84)	17	1.16 (0.72–1.87)	12	1.11 (0.63–1.96)	276	3.20 (2.84–3.60)	75	1.61 (1.28–2.02)
8–14 days	176	0.73 (0.63–0.85)	25	0.97 (0.66–1.44)	23	1.22 (0.81–1.84)	422	2.81 (2.54–3.09)	100	1.22 (1.00–1.49)
15–28 days	417	0.87 (0.79–0.96)	46	0.89 (0.66–1.19)	43	1.15 (0.85–1.55)	576	1.95 (1.79–2.12)	217	1.32 (1.16–1.52)
29–91 days	2,154	1.03 (0.98–1.08)	253	1.07 (0.94–1.21)	177	1.10 (0.95–1.28)	1,658	1.40 (1.33–1.48)	820	1.23 (1.14–1.33)
Baseline period	17,533	1.00	7605	1.00	5662	1.00	17,099	1.00	9079	1.00
	Influenza Vaccination (N=19,063)		**Tetanus Vaccination (N=6155)**		**Pneumococcal Vaccination (N=4416)**		**Systemic Respiratory Tract Infection (N=22,400)**		**Urinary Tract Infection (N=14,603)**	
	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)
Stroke										
1– 3 days	76	0.77 (0.61–0.96)	11	1.33 (0.74–2.41)	9	1.29 (0.67–2.49)	244	3.19 (2.81–3.62)	152	2.72 (2.32–3.20)
4–7 days	95	0.72 (0.59–0.88)	15	1.36 (0.82–2.26)	10	1.08 (0.58–2.01)	237	2.34 (2.05–2.66)	158	2.12 (1.81–2.48)
8–14 days	194	0.84 (0.73–0.96)	15	0.77 (0.46–1.28)	19	1.18 (0.75–1.85)	368	2.09 (1.89–2.32)	245	1.89 (1.65–2.13)
15–28 days	409	0.88 (0.80–0.97)	40	1.02 (0.74–1.39)	29	0.90 (0.63–1.30)	561	1.68 (1.54–1.82)	445	1.71 (1.55–1.88)
29–91 days	2,051	1.01 (0.96–1.06)	209	1.15 (1.00–1.32)	160	1.15 (0.98–1.35)	1,650	1.33 (1.26–1.40)	1,250	1.22 (1.15–1.30)
Baseline period	16,188	1.00	5853	1.00	4184	1.00	18,056	1.00	12,164	1.00

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

Smeeth et al, Risk of myocardial infarction and stroke after acute infection or vaccination. N Engl J Med. (2004)

Table 2. Age-Adjusted Incidence Ratios of a Recurrent Myocardial Infarction or Stroke during Risk Periods after Exposure to Vaccination or Infection.*

Outcome and Risk Period	Influenza Vaccination (N=4010)		Tetanus Vaccination (N=1889)		Pneumococcal Vaccination (N=1686)		Systemic Respiratory Tract Infection (N=5259)		Urinary Tract Infection (N=2408)	
	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)
Myocardial infarction										
1–3 days	11	0.34 (0.19–0.61)	1	0.42 (0.06–2.87)	2	0.70 (0.18–2.81)	61	3.14 (2.43–4.05)	12	1.38 (0.78–2.43)
4–7 days	34	0.77 (0.55–1.09)	2	0.63 (0.16–2.51)	2	0.53 (0.13–2.10)	59	2.26 (1.74–2.93)	18	1.55 (0.97–2.47)
8–14 days	71	0.93 (0.73–1.18)	7	1.24 (0.59–2.62)	9	1.34 (0.69–2.60)	78	1.71 (1.36–2.14)	35	1.72 (1.23–2.42)
15–28 days	146	0.97 (0.82–1.16)	7	0.61 (0.29–1.28)	14	1.05 (0.62–1.79)	131	1.45 (1.21–1.73)	51	1.25 (0.94–1.66)
29–91 days	607	0.97 (0.88–1.06)	58	1.04 (0.79–1.36)	79	1.42 (1.12–1.79)	488	1.38 (1.24–1.52)	172	1.04 (0.88–1.23)
Baseline period	3131	1.00	1812	1.00	1578	1.00	4339	1.00	2097	1.00

	Influenza Vaccination (N=4139)		Tetanus Vaccination (N=1355)		Pneumococcal Vaccination (N=1117)		Systemic Respiratory Tract Infection (N=6016)		Urinary Tract Infection (N=4273)	
	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)
Stroke										
1–3 days	19	0.56 (0.35–0.89)	3	2.05 (0.66–6.41)	2	1.01 (0.25–4.04)	70	2.57 (2.03–3.27)	37	1.65 (1.19–2.28)
4–7 days	33	0.74 (0.52–1.05)	1	0.49 (0.07–3.52)	3	1.13 (0.36–3.52)	80	2.23 (1.78–2.80)	52	1.72 (1.31–2.28)
8–14 days	56	0.72 (0.55–0.94)	2	0.54 (0.13–2.20)	3	0.64 (0.21–2.00)	94	1.51 (1.23–1.86)	72	1.35 (1.06–1.72)
15–28 days	105	0.69 (0.57–0.85)	5	0.63 (0.26–1.55)	10	1.06 (0.57–2.00)	145	1.27 (1.07–1.50)	124	1.15 (0.96–1.39)
29–91 days	516	0.79 (0.71–0.87)	38	0.96 (0.67–1.37)	46	0.99 (0.72–1.35)	501	1.27 (1.15–1.41)	470	1.16 (1.04–1.29)
Baseline period	3396	1.00	1301	1.00	1053	1.00	4617	1.00	3472	1.00

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

Smeeth et al, Risk of myocardial infarction and stroke after acute infection or vaccination. N Engl J Med. (2004)

Acute infection as a trigger for stroke

- Highest stroke risk: **<1week** after
  - acute infection
  - transient ischemic attack

} « **stroke-prone state** »
(acute susceptibility to stroke)

- Acute infection

➔activation of immune cells in atherosclerotic plaques

➔plaque rupture

➔ embolic events

(transient ischemic attack and ischemic stroke)

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

Acute infection as a trigger for stroke

- Disturbances in **immunohaematological mechanisms**:
  - ↑anticardiolipin antibodies (young and middle-aged patients)
  - ↑ ↑ fibrin D-dimer concentration, cardiolipin immunoreactivity, and fibrinogen concentrations
  - ↑ C4b-binding protein (a main inhibitor of the anticoagulant protein S)
  - ↓activated protein C
  - ↓ ratio of active tissue plasminogen activator to plasminogen activator inhibitor
  - Systemic infection➔↑ CRP+ proinflammatory cytokines ➔ procoagulant state
  - ↑IL6➔ ↓ProtS
  - ↑Platelet activation (if infection <1 week from stroke)
  - Infections ➔transient impairment of endothelium-dependent relaxation

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

Acute infection as a trigger for stroke

- **Seasonal variations** in concentrations of fibrinogen and factor VIIc:
  - higher in winter
  - attributed to **respiratory infections** by way of the acute-phase response activation ➔ seasonal variation in stroke incidence

Lancet. 1994 Feb 19;343(8895):435-9.

Seasonal variations of plasma fibrinogen and factor VII activity in the elderly: winter infections and death from cardiovascular disease.

Woodhouse PR[1], Khaw KT, Plummer M, Foley A, Meade TW.

⊕ Author information

Abstract

There are approximately 20,000 excess deaths from cardiovascular disease each winter in England and Wales. The reasons for the excess have not been fully elucidated. For one year, we studied 96 men and women aged 65-74 living in their own homes in order to examine seasonal variation in plasma fibrinogen and factor VII clotting activity (FVIIc), and to investigate relationships with infection and other cardiovascular-disease risk factors. Both fibrinogen and FVIIc plasma values were greater in winter with estimated winter-summer differences (confidence intervals) of 0.13 (0.05-0.20) g/L for fibrinogen and 4.2 (1.2-7.1)% of standard for FVIIc. These differences could account for 15% and 9% increases in ischaemic heart disease risk in winter respectively. After adjustment for confounding by season, fibrinogen was strongly related to neutrophil count ($p < 0.0001$), C-reactive protein ($p < 0.0001$), alpha 1-antichymotrypsin ($p < 0.0001$), and self-reported cough ($p < 0.0001$) and coryza ($p = 0.0004$), but not to ambient temperature. Therefore, we suggest that seasonal variation in fibrinogen might be induced by winter respiratory infections via activation of the acute phase response. Seasonal variations in the cardiovascular risk factors fibrinogen and FVIIc provide further possible explanations for the marked seasonal variation in death from ischaemic heart disease and stroke in the elderly.

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

Woodhouse et al, Seasonal variations of plasma fibrinogen and factor VII activity in the elderly: winter infections and death from cardiovascular disease. Lancet.(1994)

Chronic infection and conventional stroke risk factors

- Observational studies:
  - Infection = risk factor for **stroke and coronary** events
- Chlamydia pneumoniae:
  - DNA and/or antigen: detected in **> 40% of atherosclerotic plaques**
  - Rabbits inoculated with C pneumoniae ➔ developed inflammatory lesions in arteries
- Randomized Controlled Trials (RCTs): antibiotic therapy:
  - **No prevention** of serious cardiovascular events (patients with coronary artery disease)

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

Hankey et al, Potential New Risk Factors for Ischemic Stroke What Is Their Potential? Stroke (2006)

Previous infection and the risk of ischaemic stroke in Italy: the IN2 study

Conclusions: Early previous infections and persistent chronic infection of *C. pneumoniae* could contribute to increase the risk of ischaemic stroke significantly, in the elderly especially.

Table 2 Odds ratio (OR) for stroke in relation to IgA and IgG anti-*Chlamydia pneumoniae* seropositivity in case–control studies

Study	Age (years)	Case/control	OR for IgA	OR for IgG
Wimmer *et al.* [24]	18–50	58/52	1.71 (1.08–2.70)	1.91 (1.06–3.47)
Cook *et al.* [25]	16–88	176/1518	4.4 (3.0–6.5)	4.2 (2.5–7.1)
Elkind and Cole [11]	> 39	89/89	4.51 (1.44–14.06)	2.59 (0.87–7.75)
Heuschmann *et al.* [26]	74.6 ± 10.4	145/260	NA	0.86 (0.44–1.67)
Anzini *et al.* [27]	18–46	141/192	8.8 (3.9–19.1)	2.2 (1.5–3.9)
Ngeh *et al.* [28]	65–98	95/82	0.63 (0.26–1.52)	1.32 (0.66–2.64)
Johnsen *et al.* [8]	50–64	254/254	1.54 (0.96–2.47)	1.28 (0.83–1.95)
Njamnishi *et al.* [29]	26–80	64/64	4.29 (1.84–11.56)	1.46 (0.68–3.22)
Elkind *et al.* [30]	> 55	246/474	1.5 (1.0–2.2)	1.2 (0.8–1.8)
Piechowski-Jozwiak *et al.* [7]	< 55	94/103	8.65 (4.44–18.07)	0.85 (0.53–1.63)
Glader *et al.* [31]	55.6	97/197	0.4 (0.2–0.9)	0.9 (0.5–1.6)
Alamowitch *et al.* [32]	18–85	483/483	1.54 (0.84–2.81)[a]	1.10 (0.80–1.51)
Rai *et al.* [33]	53.6 ± 14.7	51/48	4.72 (1.161–13.83)	0.25 (0.08–1.83)
Bandaru *et al.* [34]	> 65	100/100	12.2 (1.5–96.6)	2.1 (1.0–4.2)
Present study	69 ± 13	749/253	2.12 (1.25–3.58)	1.56 (0.88–2.14)

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

Hankey et al, Potential New Risk Factors for Ischemic Stroke What Is Their Potential? Stroke (2006)

Stroke

Journal of the American Heart Association

American Heart Association | American Stroke Association

Infection and the Risk of Spontaneous Cervical Artery Dissection: A Case-Control Study

Benoît Guillon, Karine Berthet, Lamia Benslamia, Marion Bertrand, Marie-Germaine Bousser and Christophe Tzourio

Recent infection (+ Pre-existing abnormalities of extracellular matrix proteins++)

➔ ↑ risk **cervical artery dissection**

Results—Acute infection was more frequent in patients with SCAD (31.9%) than in control subjects (13.5%) (crude odds ratio, 3.0; 95% confidence interval, 1.1 to 8.2; $P=0.032$). This association was stronger in patients with multiple (odds ratio, 6.4) than single artery (odds ratio, 2.1) dissection.

Conclusions—Recent infection is a risk factor and could be a trigger for SCAD. **(*Stroke*. 2003;34:e79-e81.)**

TABLE 3. Type of Infections Diagnosed in Cases and Controls

	Cases	Controls
Respiratory tract		
Upper respiratory tract*	8	3
Bronchitis	3	3
Pneumonia	. . .	1
Gastrointestinal tract	2	. . .
Flu syndrome	2	. . .

*Including rhinopharyngitis (n=3), tonsillitis (n=5), sinusitis (n=2), and laryngitis (n=1).

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

Guillon et al, Infection and the risk of spontaneous cervical artery dissection: a case-control study. Stroke. (2003)

Effects of preceding infection on stroke outcome

- Severity and clinical outcome of ischemic stroke: worse when preceded by infection: Greater severity of ***neurological deficit at presentation*** (discordant results)

Cerebrovascular Diseases

Original Paper

Cerebrovasc Dis 2012;33:310–315
DOI: 10.1159/000335306

Received: June 9, 2011
Accepted: November 17, 2011
Published online: February 15, 2012

Previous Infection and Stroke: A Prospective Study

outcome (OR = 1.15; p = 0.564). ***Conclusions:*** PI are observed in 9.7% of stroke cases without differences according to the TOAST subtype. PI are associated with previous poor functional status and with stroke severity, but have no independent influence on the 3-month outcome.

Table 4. Demographics, vascular risk factors and characteristics of patients with acute IS and ICH according to the PI

	Ischemic stroke (n = 1,703)					Intracerebral hemorrhage (n = 278)				
	n	PI cases	non-PI cases	p	OR	n	PI cases	non-PI cases	p	OR
Age, years	1,703	79 [71–84][a]	77 [67–83][a]	0.025[b]		278	79 [66–86][a]	75 [63–82][a]	0.369	
Male %	1,703	46.6	50.8	0.299		278	47.4	55.2	0.634	
Arterial hypertension, %	1,689	76.4	70.7	0.132	1.35 (0.93–1.94)	275	52.6	62.1	0.467	0.68 (0.27–1.73)
Diabetes, %	1,703	32.8	32.2	0.932	1.02 (0.73–1.43)	277	26.3	26.0	1.0	1.02 (0.35–2.93)
Dyslipidemia, %	1,676	33.1	38.2	0.213	0.88 (0.61–1.26)	273	26.3	25.6	1.0	1.04 (0.36–3.0)
Coronary artery disease, %	1,696	16.1	16.2	1.0	0.99 (0.65–1.52)	278	5.3	10.0	1.0	0.50 (0.06–3.88)
Peripheral artery disease, %	1,679	10.1	9.5	1.0	0.99 (0.57–1.70)	272	10.5	5.5	0.309	2.01 (0.42–9.57)
Atrial fibrillation, %	1,703	27.6	29.3	0.661	0.92 (0.65–1.30)	278	47.4	13.5	0.001[b]	5.76 (2.19–15.17)
Previous stroke/TIA, %	1,695	25.0	27.5	0.528	0.86 (0.60–1.24)	274	31.6	30.6	1.0	1.05 (0.38–2.86)
Current smoking, %	1,650	12.5	21.0	0.008[b]	0.54 (0.34–0.86)	262	5.3	19.0	0.213	0.24 (0.03–1.82)
Previous mRS score >2, %	1,696	26.4	16.4	0.002[b]	1.89 (1.32–2.69)	274	38.9	18.0	0.039[b]	2.89 (1.06–7.86)
NIHSS score	1,702	6 [3–16][a]	4 [2–11][a]	0.002[b]		277	17 [8–21][a]	13 [4–21][a]	0.438	
mRS score >2 at 3 months, %	1,703	58.6	44.6	0.001	1.83 (1.27–2.63)	278	73.7	72.2	1.0	1.08 (0.38–3.10)
Death at 3 months, %	1,703	23.6	16.2	0.019	1.59 (1.09–2.32)	278	36.8	44.0	0.635	0.73 (0.28–1.92)

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

Roquer et al, Previous Infection and Stroke:A Prospective Study . Cerebrovasc Dis (2012)

Effects of preceding infection on stroke outcome

- Severity and clinical outcome of ischemic stroke: worse when preceded by infection: Greater severity of ***neurological deficit at presentation*** (discordant results)

Stroke. 2003 Feb;34(2):452-7.

Infection and risk of ischemic stroke: differences among stroke subtypes.

Paganini-Hill A[1], Lozano E, Fischberg G, Perez Barreto M, Rajamani K, Ameriso SF, Heseltine PN, Fisher M.

RESULTS: Infections, either total or specific, were not found more frequently in cases than controls. However, patients with a recent respiratory tract infection suffered more often from large-vessel atherothromboembolic or cardioembolic stroke than did patients without infection (48% vs 24%, P=0.07). The age- and sex-adjusted relative risk estimate for these subtypes was 1.75 (95% CI, 0.86 to 3.55). The risk was notably high for those without stroke risk factors: 4.15 (95% CI, 1.22 to 14.1) for normotensives, 2.71 (95% CI, 1.04 to 7.06) for nondiabetics, and 1.74 (95% CI, 0.74 to 4.07) for nonsmokers. Patients with a recent respiratory infection also had a more severe neurological deficit on admission than those without infection (P=0.05).

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

Paganini-Hill et al, Infection and risk of ischemic stroke: differences among stroke subtypes. Stroke. (2003)

European Neurology

Original Paper

Eur Neurol 2005;53:188–193
DOI: 10.1159/000086355

Assessment of Relations between Clinical Outcome of Ischemic Stroke and Activity of Inflammatory Processes in the Acute Phase Based on Examination of Selected Parameters

Preceding infection

- Higher ***inflammatory markers*** (CRP, white blood cell count)
- Worse ***neurological impairment*** (at day1 and day4)

Parameters	Patients with stroke			Control (C) (n = 15)	p
	total (n = 36)	without infection before stroke (A) (n = 21)	with infection before stroke (B) (n = 15)		
Sex					
Female	17	13	4	9	
Male	19	8	11	6	
Age, years					
Mean ± SD	68.8 ± 9.7	68.7 ± 9.8	69.1 ± 9.9	67.2 ± 14.9	NS[1]
Range	37–80	37–79	2–80	36–85	
Chito 1, µmol/l/h					
Mean ± SD	100.4 ± 55.3	76 ± 34.9	134.6 ± 61.4	91.1 ± 40.8	B/C: $p < 0.01$[2]
Range	25.0–238.0	25–155	59–238	27.0–164.0	B/A: $p < 0.0009$[2]
Chito 2, µmol/l/h					
Mean ± SD	94.2 ± 47.6	78.8 ± 33.9	115.8 ± 56.1	–	
Range	26.0–229.0	27–146	26–229		B/A: $p < 0.02$[2]
IgG 1, mg%					
Mean ± SD	1,293.9 ± 394.4	1,229.3 ± 447.6	1,384.5 ± 296	1,143.9 ± 234	B/C: $p < 0.03$[2]
Range	613–2,400	613–2,400	957–1,850	619–1,500	B/A: NS[2]
IgG 2, mg%					
Mean ± SD	1,295 ± 442.1	1,307.7 ± 549.6	1,277.3 ± 237.9	–	B/A: NS[2]
Range	397–3,020	397–3,020	1,000–1,703		
CRP 1, mg/l					
Mean ± SD	7.5 ± 4.3	4.7 ± 1.3	11.3 ± 4.1	3.29 ± 1.3	B/C: $p < 0.000001$[2]
Range	2.0–20.0	2–7	5–20	1.6–6.0	B/A: $p < 0.000001$[2]
CRP 2, mg/l					
Mean ± SD	23.5 ± 33.5	11.8 ± 12.3	39.9 ± 45.9	–	B/A: $p < 0.01$[2]
Range	3.0–189.0	3–45	10–189		
Fibr 1, g/l					
Mean ± SD	4.3 ± 1.1	4.2 ± 1.0	4.5 ± 1.2	3.46 ± 1.08	B/C: $p < 0.01$[2]
Range	2.0–7.0	2.6–6.7	2.0–7.0	2.0–5.6	B/A: NS[2]
Fibr 2, g/l					
Mean ± SD	4.6 ± 1.2	4.4 ± 1.1	5.0 ± 1.3	–	B/A: NS[2]
Range	2.2–7.6	2.2–7.6	2.9–7.3		
WBC 1, $\times 10^3/\mu l$					
Mean ± SD	8.6 ± 2.8	7.2 ± 1.6	10.5 ± 3.1	7.3 ± 1.9	B/C: $p < 0.002$[2]
Range	4.5–20.3	4.5–9.8	5.6–20.3	4.6–9.9	B/A: $p < 0.0002$[2]
WBC 2, $\times 10^3/\mu l$					
Mean ± SD	10.0 ± 3.2	8.4 ± 1.8	12.6 ± 3.5	–	B/A: $p < 0.0001$[2]
Range	5.7–24.0	5.7–12.8	9.0–24.0		
SSS 1, points					
Mean ± SD	31.9 ± 10.8	35.4 ± 10.1	27.3 ± 10.2	–	B/A: $p < 0.02$[2]
Range	8.0–51.0	15–51	8–47		
SSS 2, points					
Mean ± SD	38.9 ± 13.2	43.7 ± 10.7	32.1 ± 13.8	–	B/A: $p < 0.008$[2]
Range	12.0–54.0	20–54	12–54		

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts. Lancet Neurol (2008)

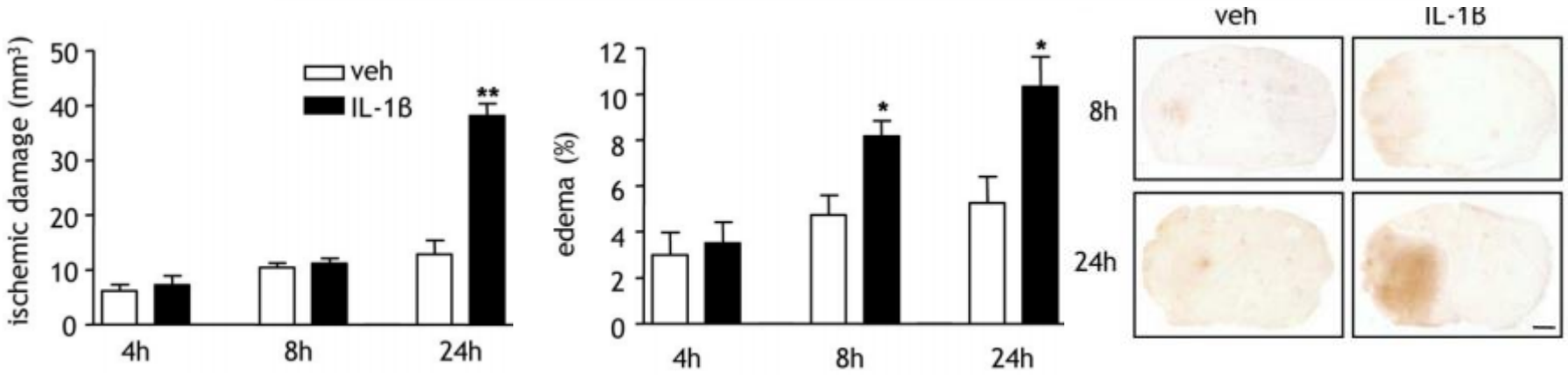
Palasik et al, Assessment of relations between clinical outcome of ischemic stroke and activity of inflammatory processes in the acute phase based on examination of selected parameters. Eur Neurol.(2005)

Effects of preceding infection on stroke outcome

- Systemic **lipopolysaccharide** [endogenous, exogenous (**bacterial**)] (acute systemic inflammatory stimulus) through **IL-1++** ➔ detrimental effect on outcome:
  - brain damage +neurological deficit

Neurobiology of Disease

Systemic Inflammatory Stimulus Potentiates the Acute Phase and CXC Chemokine Responses to Experimental Stroke and Exacerbates Brain Damage via Interleukin-1- and Neutrophil-Dependent Mechanisms



Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

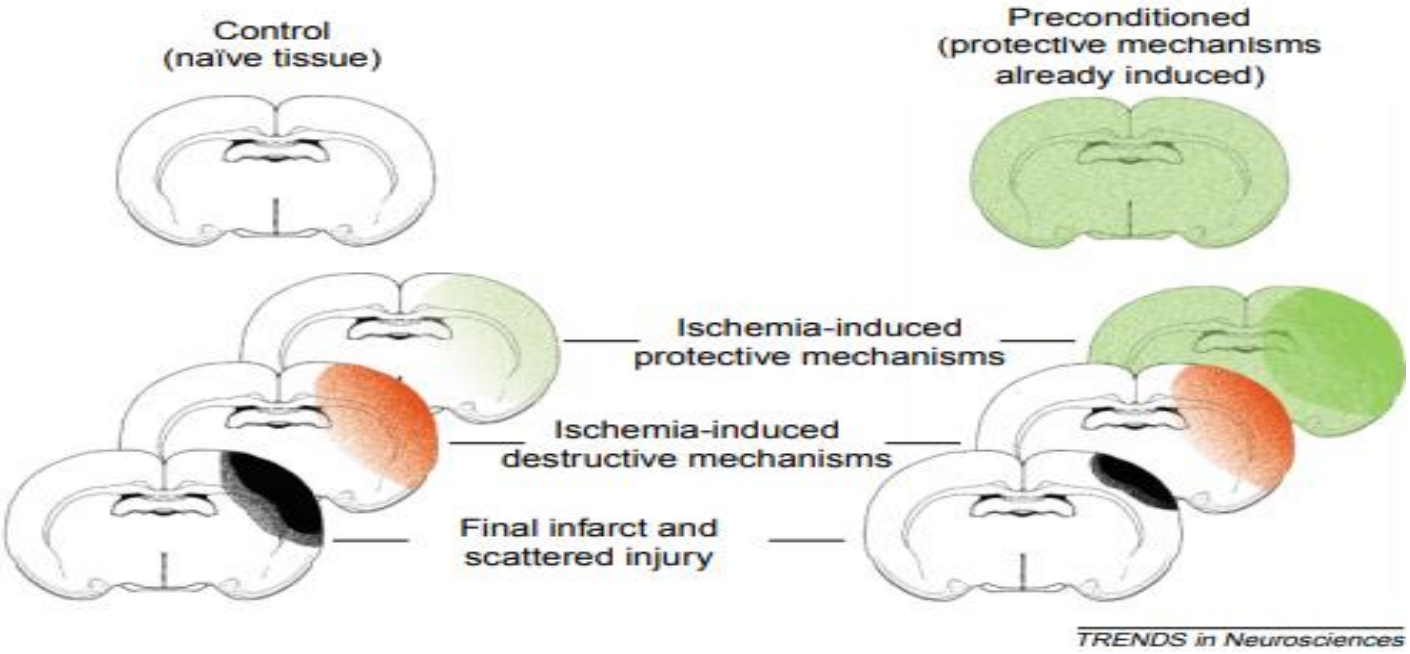
McColl et al, Systemic inflammatory stimulus potentiates the acute phase and CXC chemokine responses to experimental stroke and exacerbates brain damage via interleukin-1- and neutrophil-dependent mechanisms. J Neurosci.(2007)

Effects of preceding infection on stroke outcome

- But++++: Preceding infection: Not always deleterious effect on outcome
  - prior subthreshold insults ➔ endogenous neuroprotection

248 Review TRENDS in Neurosciences Vol.26 No.5 May 2003

Ischemic tolerance and endogenous neuroprotection



Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

Dirnagl et al, Ischemic tolerance and endogenous neuroprotection. Trends Neurosci. (2003)

Effects of preceding infection on stroke outcome

- Lipopolysaccharide priming: protective eff ects in experimental models of stroke, with reductions in infarct volume and infl ammatory cell activation and infiltration.

Lipopolysaccharide pre-treatment induces resistance against subsequent focal cerebral ischemic damage in spontaneously hypertensive rats

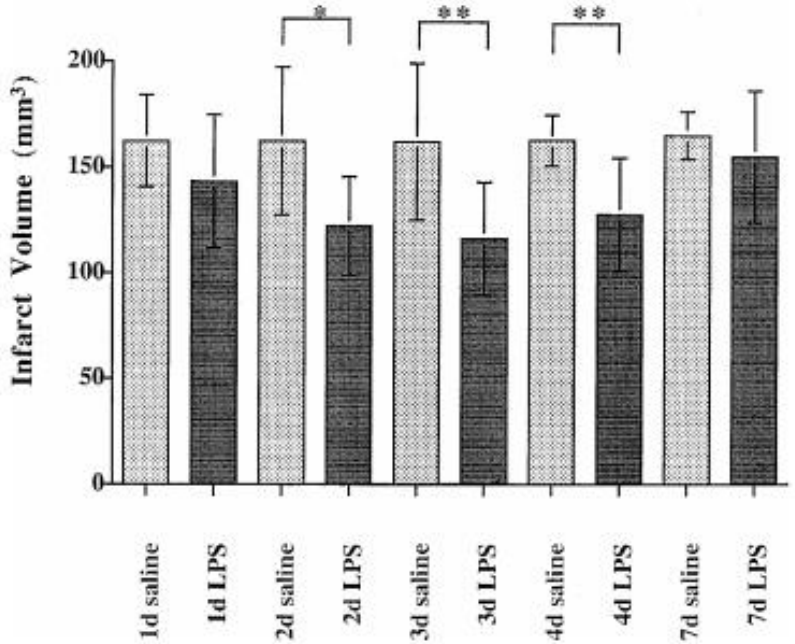


Fig. 1. Infarct volumes: LPS (0.9 mg/kg) or saline i.v. at several times before MCAO. * $P < 0.05$; ** $P < 0.02$.

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

Tasaki et al, Lipopolysaccharide pre-treatment induces resistance against subsequent focal cerebral ischemicdamage in spontaneously hypertensive rats. Brain Res. (1997)

Implications for treatment strategies in preceding infection

- Recognition of vulnerable individuals and **prevention of infection** (ex.: stroke-prone state in patients with transient ischaemic attack)

- Pleiotropic effects of **statins**(stabilisation of atherosclerotic plaques, modulation of immune and inflammatory responses):
  - Protection against endothelial dysfunction related to acute infection)
  - BUT: simvastatin:
    - Improvement of clinical outcomes in stroke
    - increasing poststroke infection

  } Balance

- **Influenza vaccination** in patients:
  - History of cerebrovascular disease
  - at high risk of stroke

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

Implications for treatment strategies in preceding infection

Influenza Vaccination for Secondary Prevention of Cardiovascular Events: A Systematic Review

JCPH – Vol. 70, n° 1 – janvier–février 2017

Conclusions: Given the limitations of these data, it is unclear whether the cardiovascular benefit with influenza vaccination in patients with cardiovascular disease is a true effect. Nevertheless, because of the potential benefit and the low risk of adverse events, the annual influenza vaccine should be recommended for all patients with established cardiovascular disease.

Study (Year)	GRADE Score	Design	Country	No. of Patients	Baseline Characteristics	Intervention	Control	Duration
FLUVACS (2002 and 2004)[29,30]	Low	Randomized, single-blind	Argentina	301	Mean age 65 years, 66% with acute MI, 34% with elective PCI	Single 0.5-mL IM dose of A/Moscow/ 10/99-like virus, A/New Caledonia/ 20/99 (H1N1)-like virus, and AB/Sichuan/ 379/99-like virus	Saline	6 months
FLUCAD (2008)[31]	Moderate	Randomized, double-blind	Poland	658	Median age 60 years, 73% male, 56% with stable CAD, 24% with PCI for ACS, 20% with PCI for stable angina	Single 0.5-mL IM dose of A/New Caledonia/ 20/99 (H1N1), A/Christchurch/ 28/03 (H3N2), and B/Jiangsu/ 10/03	Placebo	14 months
Phrommintikul et al. (2011)[32]	Moderate	Randomized, open-label	Thailand	439	Mean age 66 years, 57% male, 47% NSTEMI, 36% STEMI, 16% with unstable angina	Single 0.5-mL IM dose of split, inactivated influenza vaccine (type not reported)	No treatment	12 months
IVCAD (2009)[33]	NA	Randomized, single-blind	Iran	281	NR	Single 0.5-mL IM dose of 2007/2008 influenza vaccine	Placebo	6 months
FLUVACS-IC*[34]	NA	Randomized, single-blind	Argentina	117	NR	Single IM dose of influenza vaccine	Conventional medical therapy	6 months

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

LeBras et al, Influenza Vaccination for Secondary Prevention of Cardiovascular Events: A Systematic Review. Can J Hosp Pharm. (2017)

Bacterial Infections and Stroke

Bacterial infections implicated in stroke

Organism	Infection	Mechanism
Bacterial infections		
Treponema pallidum	Neurosyphilis	Vasculitis/arteritis
Mycobacterium tuberculosis	Tuberculous meningitis	Arteritis; meningitis
Chlamydia pneumoniae	Acute or chronic respiratory infections	Accelerated atherogenesis, enhanced platelet aggregation
Helicobacter pylori	Gastritis, peptic ulcer disease	Enhanced platelet aggregation, prothrombotic state
Porphyromonas gingivalis (and other periodontal pathogens)	Periodontal disease	Chronic inflammation due to infectious burden; prothrombotic state

Miller et al, Infection and Stroke: an Update on Recent Progress. Curr Neurol Neurosci Rep (20015

Neurosyphilis

- "The Great Masquerader »
- Two types of symptomatic neurosyphilis:
  - paranchymatous
  - Meningovascular: 2 types of vascular pathology:
    - Hübner arteritis
      - Most common type
      - Involves the large and medium sized vessels
    - Nissl's endarteritis:
      - Intimal and adventitial proliferation
      - Small vessels

Moghtaderi A.. Infective Causes of Stroke in Tropical Regions. Iran J Med Sci September (2012)

Neurosyphilis

- ***Mostly middle cerebral*** artery is affected
- Different types of atherosclerotic plaques reported
- Does not imply a cause-and-effect relationship

Moghtaderi A.. Infective Causes of Stroke in Tropical Regions. Iran J Med Sci September (2012)

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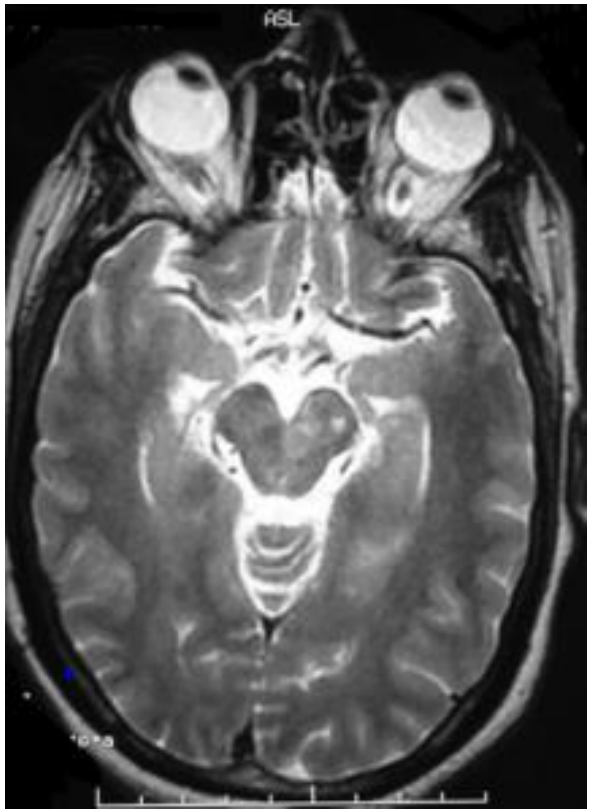
Revue neurologique

Original article

Stroke and syphilis: A retrospective study of 53 patients

Results. – A total of 53 patients with stroke met the diagnostic criteria for syphilitic arteritis. Their average age was 41 ± 12 years. Nine patients had a history of genital ulcer (17%), and the median duration of illness after presenting a chancre was 8 [range: 1–14] years. A prodromal syndrome was seen in 27 patients (50.9%) and included changes in mental status in 14 patients (26.4%), seizures in 10 cases (18.9%), headache in eight (15.1%) and memory loss in seven (13.2%). Neurological events included focal motor deficits in 29 cases (54.7%), ataxia in 11 (20.8%) and movement disorders in 15 (28.3%). HIV serology was performed in 31 patients and proved negative in every case. Disease evolution was generally favorable: 12 patients (22.6%) were autonomous at the time of hospital discharge; 29 (54.7%) had partially recovered; and only seven (13.2%) still had signs of severe sequelae.



Ahbeddou N et al., Stroke and syphilis: A retrospective study of 53 patients. Rev Neurol (Paris).(2018)

Tuberculosis

- **1/3** of the world's population: infected with *Mycobacterium tuberculosis (MTB)*
- *Highest* prevalence of tuberculosis in Southeast Asia
- Central nervous system tuberculosis (TB): serious type of extra-pulmonary TB

Moghtaderi A.. Infective Causes of Stroke in Tropical Regions. Iran J Med Sci September (2012)

Stroke in Tuberculosis (TB)

- Main cause: ***tuberculous meningitis*** (TBM)
- In ***15-75%*** of patients with TBM
- Especially in advanced stage of the disease with severe illness
- Majority of strokes: **asymptomatic** (silent area or deep coma)

Moghtaderi A.. Infective Causes of Stroke in Tropical Regions. Iran J Med Sci September (2012)

Mechanisms of stroke in TB

- ***Vasculitis*** involving perforating vessels of the brain: cerebrovascular complication of tuberculous meningitis

- Involvement of small, medium, and large arteries of the ***anterior circulation***

Carod-Artal FJ. Stroke in central nervous system infections. Ann Indian Acad Neurol (2008)

Stroke in Tuberculosis (TB)

- In all cases caused by MTB:

➔Pulmonary TB

➔Hematogenous dissemination to the CNS

➔Rupture of rich nodules into subarachnoid space

➔ Meningitis

➔ Lymphocytic infiltration around meningeal blood vessels

➔ **Arteritis + cerebral infarction**

Moghtaderi A.. Infective Causes of Stroke in Tropical Regions. Iran J Med Sci September (2012)

Incidence of stroke in neurotuberculosis

- Autopsied brain: 41%
- Post-computer tomography: 28 to 38%
- MRI: **>2/3** of patients

Moghtaderi A.. Infective Causes of Stroke in Tropical Regions. Iran J Med Sci September (2012)

Incidence of stroke in neurotuberculosis

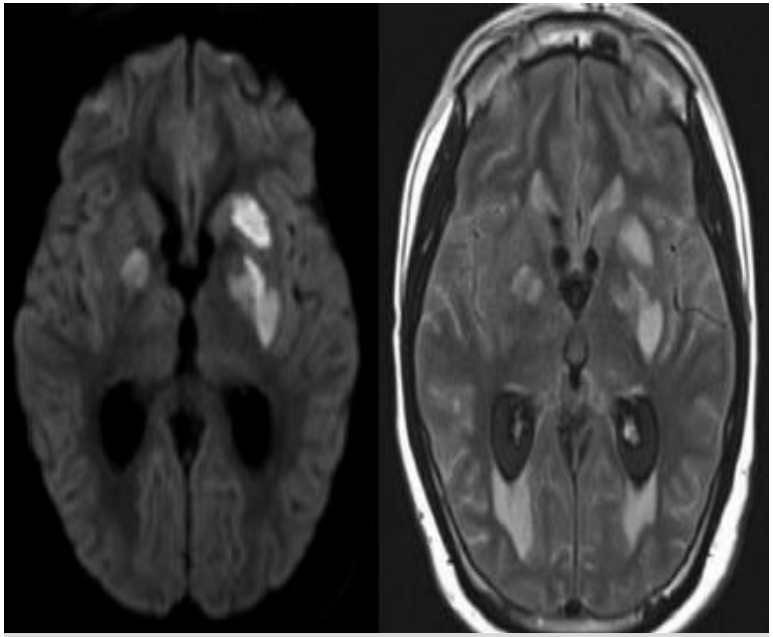
- **92%**: **anterior** cerebral circulation (carotid system)
- Lenticulostriate arteries of both **middle and anterior** cerebral arteries: mostly involved
- Large infarctions: due to middle cerebral artery involvement
- Brainstem infarction: due to occlusion of penetrating branches of basilar artery

Moghtaderi A.. Infective Causes of Stroke in Tropical Regions. Iran J Med Sci September (2012)

Stroke in neurotuberculosis
TUBERCULAR ZONE

- Tubercular zone=
  - Caudate nucleus
  - Anteromedial thalami
  - Anterior limb and genu of the internal capsule
- Mechanisms: involvement of:
  - Medial striate
  - Thalamotubular
  - Thalamoperforator

arteries



Stroke in the tubercular zone in tuberculous meningoencephalitis. (a) DWI and (b) FLAIR.

Jillella et al.. Infectious causes of stroke. Curr Opin Infect Dis. Jun;32(3):285-292. (2019)

Stroke
Journal of the American Heart Association

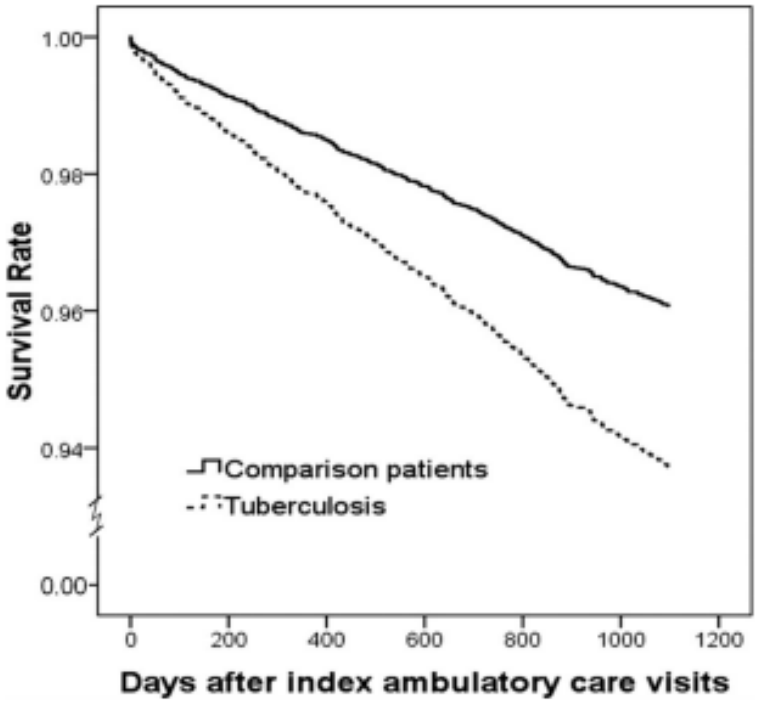
Tuberculosis and the Risk of Ischemic Stroke: A 3-Year Follow-Up Study

au-Jiuan Sheu, Hung-Yi Chiou, Jiunn-Horng Kang, Yi-Hua Chen and Herng-Ching Lin

American Heart Association | American Stroke Association

- 2283 TB patients; 6849 control subjects; 3 years: 2000 and 2003

Presence of Ischemic Stroke	Total Sample N=9132		Comparison N=6849		Tuberculosis N=2283	
	N	%	N	%	N	%
3-Year follow-up period						
Yes	392	4.3	256	3.7	136	6.0
No	8740	95.7	6593	96.3	2147	94.0
Crude HR (95% CI)	. . .		1.00		1.63 (1.32–2.02)	
Adjusted HR (95% CI)	. . .		1.00		1.52 (1.21–1.91)	



patients with a tuberculosis diagnosis are at an **increased risk for ischemic stroke but not hemorrhagic stroke** in the next 3 years

Sheu et al. Tuberculosis and the risk of ischemic stroke: a 3-year follow-up study. Stroke. (2010)

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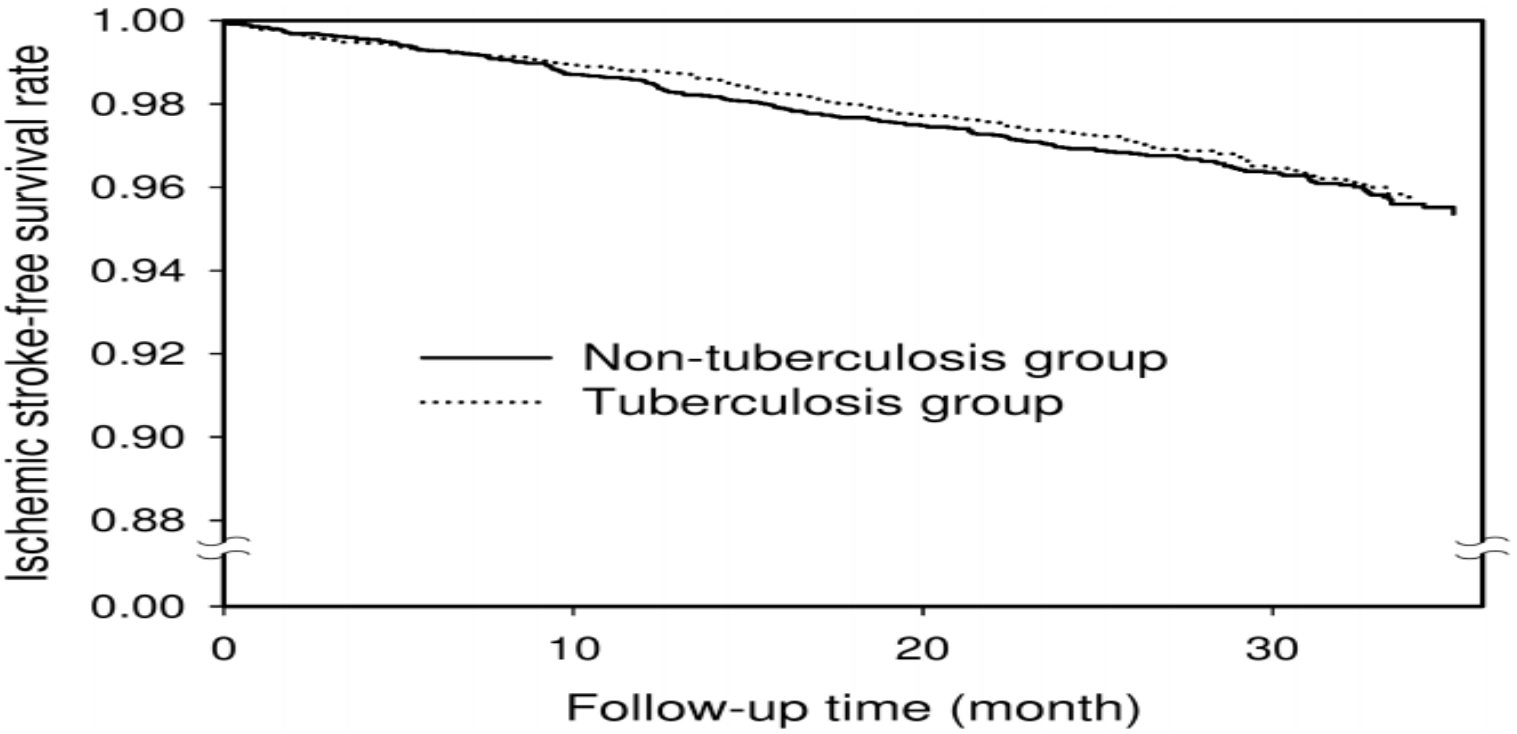
PLOS | ONE

Does Non-Central Nervous System Tuberculosis Increase the Risk of Ischemic Stroke? A Population-Based Propensity Score-Matched Follow-Up Study

- 5804 TB patients; 5804 control subjects; 3 years: 2000 and 2003



Non-CNS tuberculosis does not increase the risk of subsequent ischemic stroke

Wu et al. Does non-central nervous system tuberculosis increase the risk of ischemic stroke? A population-based propensity score-matched follow-up study. PLoS One.. (2014)

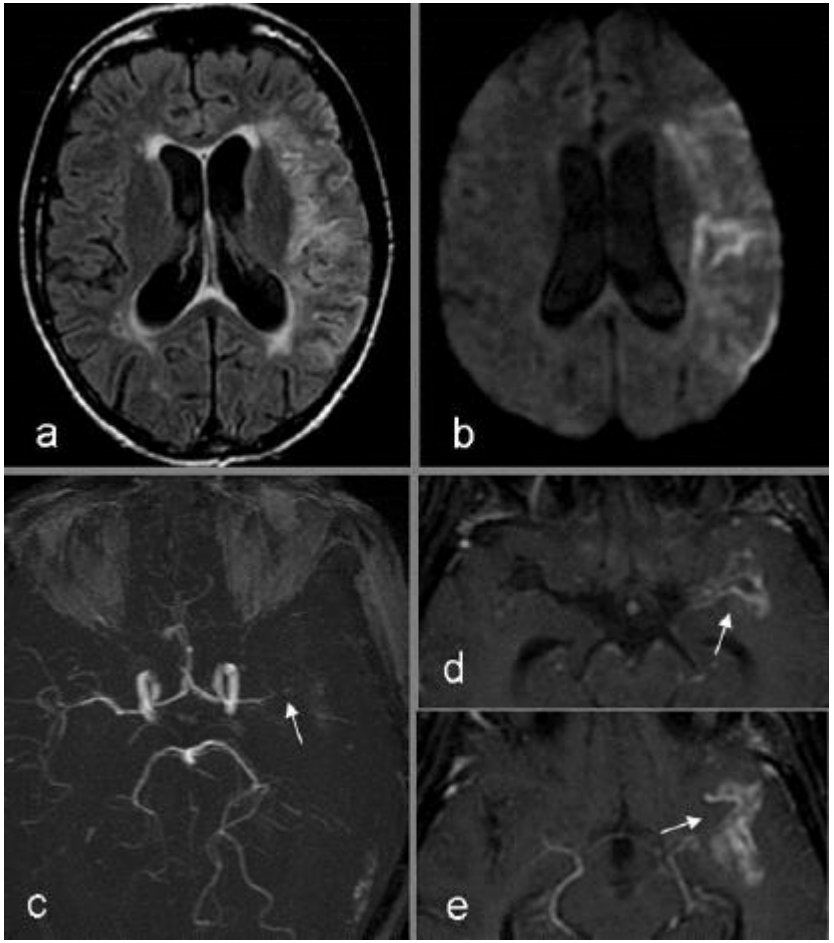
MEDITERRANEAN JOURNAL OF HEMATOLOGY AND INFECTIOUS DISEASES
www.mjhid.org ISSN 2035-3006

Case Report

Stroke in a Patient with Tuberculous Meningitis and HIV Infection

Co-infections++++

- 45 year old Caucasian female
- with **HIV** infection, CDC-A3 and **HCV**, genotype 1b co-infection
- Lung, meningeal tuberculosis
- Stroke due to a cortical sub-cortical ischemic lesion
- Anti-TB therapy
- Improvement



Brucellosis

- Incidence of CNS involvement in brucellosis: 0.5-25%

- Ischemic stroke:
  - Transient:
    - carotid or Vertebrobasilar artery
    - Monoparesis, hemiparesis, aphasia, vertigo…
  - Constituted stroke: motor impairment, visual impairment, aphasia
  - Cause : cerebral vasculitis, Brucella endocarditis

- Intracranial or subarachnoid hemorrhage : secondary to a **ruptured mycotic aneurysm**

Ay et al. Cerebral infarct due to meningovascular neurobrucellosis: a case report. Int J Infect Dis.(2010)

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Case Report

Cerebral infarct due to meningovascular neurobrucellosis: a case report

Saime Ay [a,*], Birkan Sonel Tur [b], Şehim Kutlay [b]

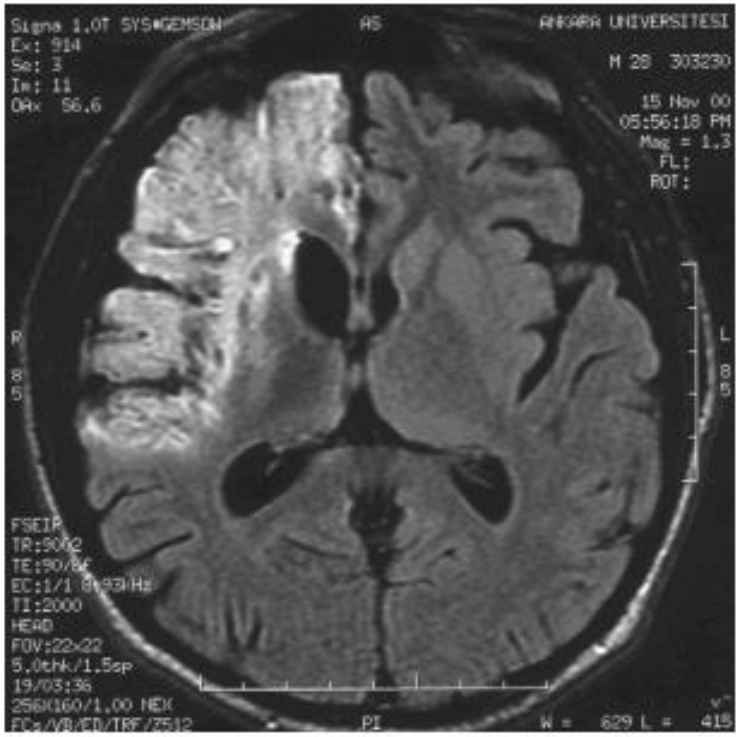


Figure 1. Magnetic resonance image of the brain: focal brain involvement of brucellosis.

Neurobrucellosis with thalamic infarction: a case report

- 56-year-old German male ; bilateral abducens nerve palsy, amblyacousia and intractable headaches
- Brucella:+ plasma and CSF
- Imaging: infarction of the left thalamus.

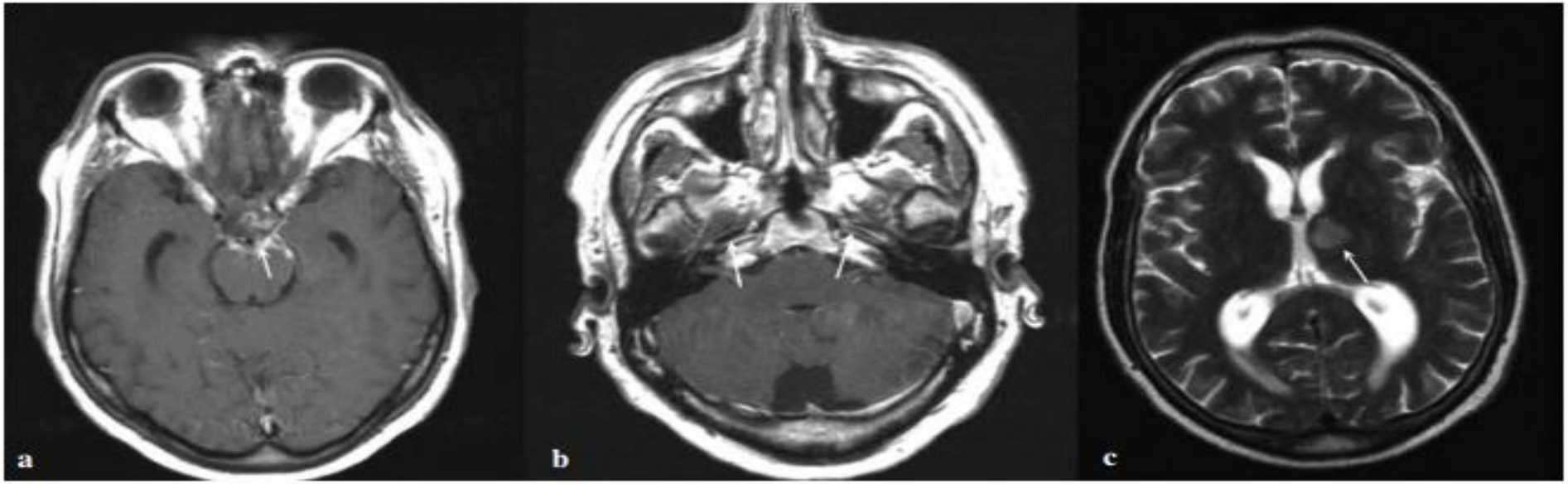


Fig. 1a CMRI (T1 sequences after gadolinium administration). Basal enhancement of leptomeninges (*arrowhead*, anterior). **b** CMRI (T1 sequences) after gadolinium administration with bilateral enhancement of vestibulocochlear nerves (*arrowhead*). **c** CMRI (T2 sequences) showing fresh infarction of left thalamus (*arrowhead*)

Jochum et al Neurobrucellosis with thalamic infarction: a case report. Neurol Sci.(2008)

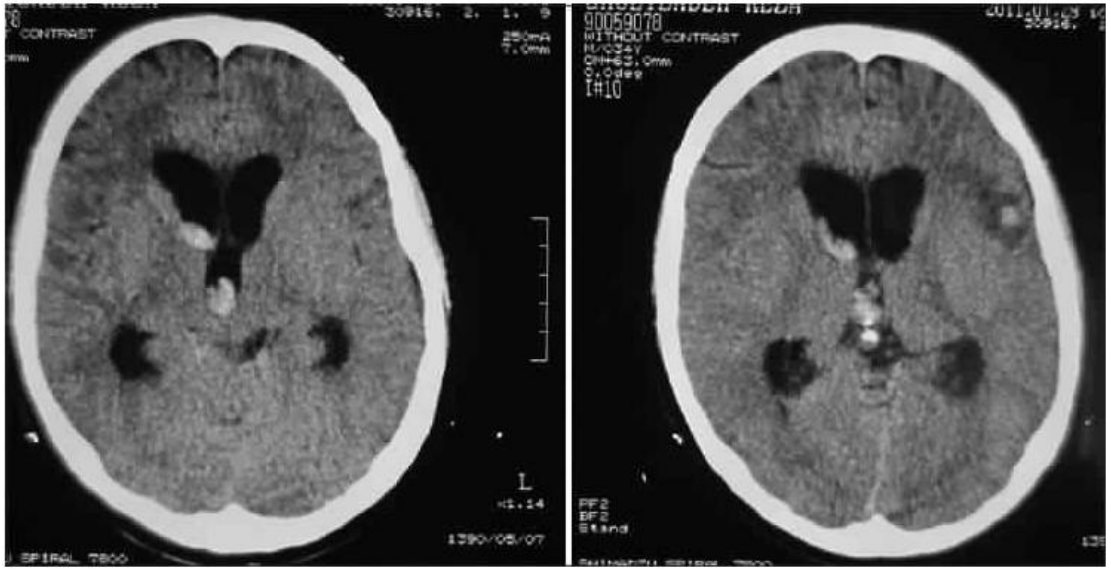
SURGICAL NEUROLOGY INTERNATIONAL

Surg Neurol Int. 2014 Oct 21;5:152. doi: 10.4103/2152-7806.143365. eCollection 2014.

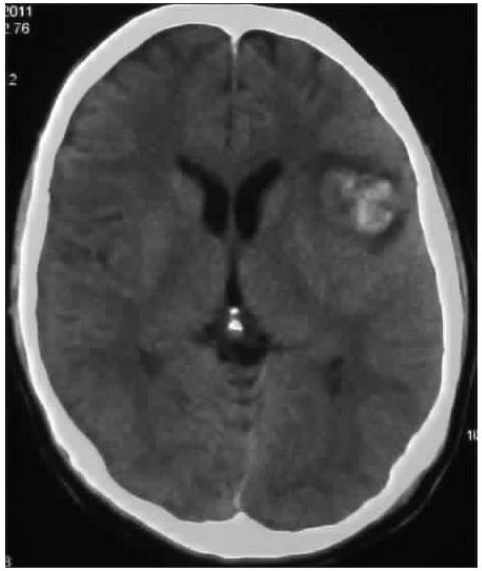
Brucella-related multiple cerebral aneurysms: Report of a case and review of the literature.

Amiri RS[1], Hanif H[2], Ahmadi A[3], Amirjamshidi A[2].

- A 34-year-old man with neurobrucellosis
- intracerebral haemorrhage (ICH)



Small hemorrhage within the Sylvian fissure and intraventricular hemorrhage in the right lateral and third ventricles associated with mild hydrocephalus



Second CT scan showing normal sized ventricles, but expanded left opercular ICH

Amiri et al Brucella-related multiple cerebral aneurysms: Report of a case and review of the literature. Surg Neurol Int. (2014)

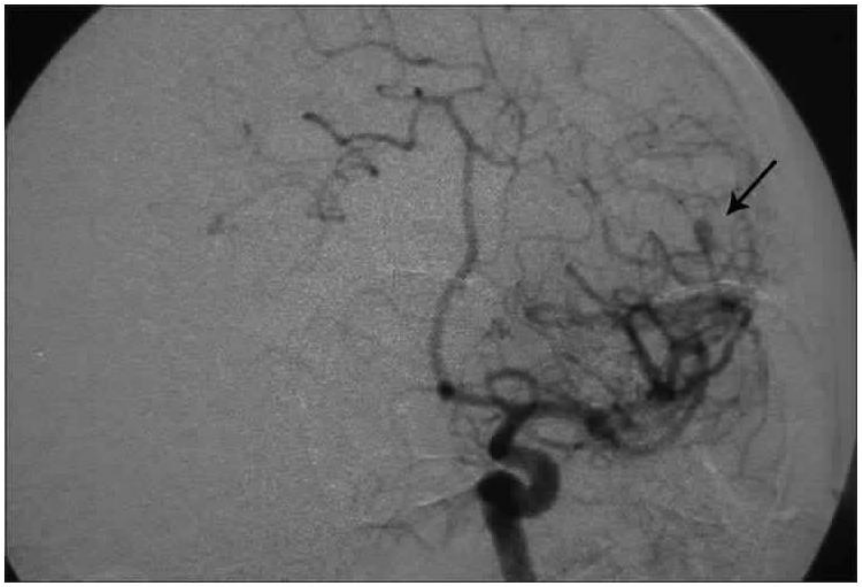
SURGICAL NEUROLOGY INTERNATIONAL

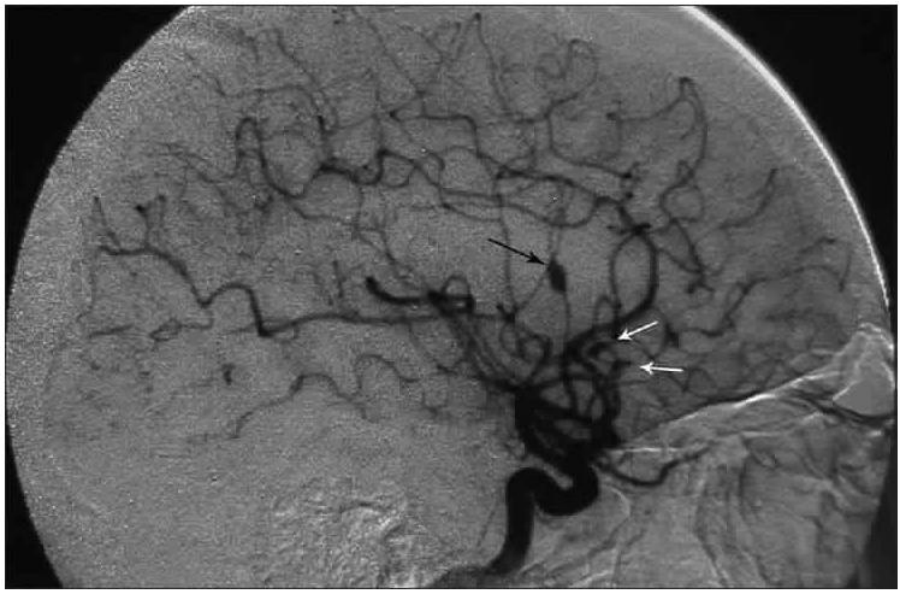
Surg Neurol Int. 2014 Oct 21;5:152. doi: 10.4103/2152-7806.143365. eCollection 2014.

Brucella-related multiple cerebral aneurysms: Report of a case and review of the literature.

Amiri RS[1], Hanif H[2], Ahmadi A[3], Amirjamshidi A[2].

- Three mycotic aneurysms were detected in the vicinity of middle cerebral artery (MCA)





AP view of the DSA showing distal MCA aneurysm

Amiri et al Brucella-related multiple cerebral aneurysms: Report of a case and review of the literature. Surg Neurol Int. (2014)

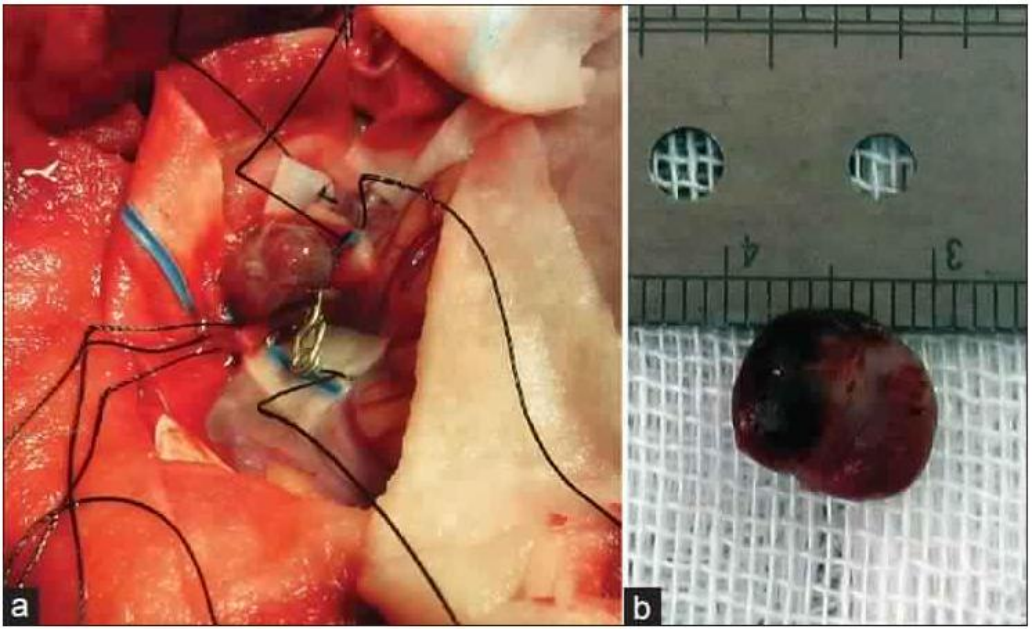
SURGICAL NEUROLOGY INTERNATIONAL

Surg Neurol Int. 2014 Oct 21;5:152. doi: 10.4103/2152-7806.143365. eCollection 2014.

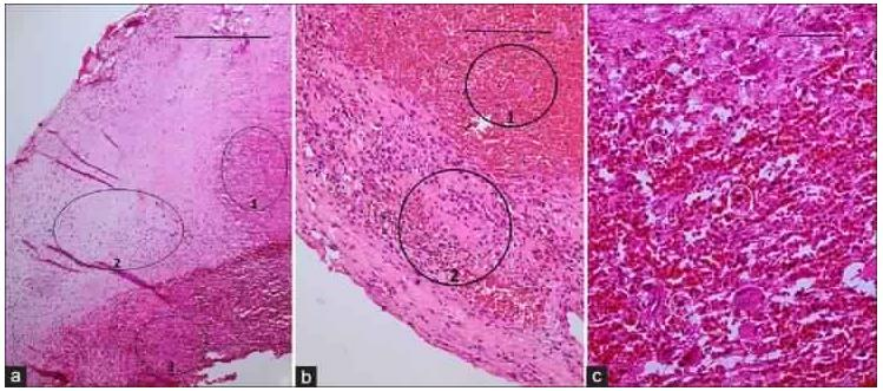
Brucella-related multiple cerebral aneurysms: Report of a case and review of the literature.

Amiri RS[1], Hanif H[2], Ahmadi A[3], Amirjamshidi A[2].

- . Medical treatment failed to treat them and aneurysms had to be managed surgically



(a) Intraoperative image of second MCA aneurysm clipped and (b) the second mid-size aneurysm resected



(a) H&E staining ×40 showing portions of vessel wall with necrotic (ring 1), fibrotic (ring 2), and thrombotic (ring 3) changes. Scale bar is 2 mm. (b) H and E, ×100 fibro-necrotic wall containing hemosiderin-laden macrophages (ring 2) admixed with many RBCs (ring 1). Scale bar is 1 mm. (c) H and E, ×400 showing white small rings encircling few foreign body type giant cells and inflammatory cells, interposed by thrombotic material. Periodic acid Schiff (PAS) staining (for fungi) and acid-fast bacillus (AFB) staining for mycobacteria show no specific microorganism. All these findings are compatible with "necrotizing vasculitis." Scale bar is 100 μm

ORIGINAL RESEARCH

WILEY Brain and Behavior Open Access

Vasculitis and neurobrucellosis: Evaluation of nine cases using radiologic findings

Case	Cranial imaging findings	Diagnosis
1	MRI: common T2W hyperintense signal change, subdural hygroma, and right frontal hygroma on postcontrast images with leptomeningeal contrast enhancement (Figure 1).	Neurobrucellosis small vessel vasculitis and granuloma
2	3D TOF MR angiography showed signal loss in the right ICA and right MCA (Figure 2).	Neurobrucellosis great vessel vasculitis
3	Lesion compatible with acute infarct that shows diffusion limitation in left frontoparietal region on MR. MR angiography showed a mild stenosis at the exit of the left main carotid artery, a contrast signal surrounding the exit of the left main carotid artery, and surrounding the brachiocephalic artery outlet (Figure 3).	Neurobrucellosis great vessel vasculitis
4	On cranial MRI, triventricular hydrocephalus and leptomeningeal contrast enhancement were detected, and a lesion consistent with abscess was detected in the right half of the pons (Figure 4).	Neurobrucellosis meningoencephalitis and pons abscess
5	Cranial MRI imaging revealed T2W hyperintense ischemic gliotic lesions of diffuse nodular appearance	Neurobrucellosis small vessel vasculitis
6	Cranial diffusion MRI revealed acute restriction of diffusion in the right precentral gyrus, cranial MRI revealed lesions compatible with small vessel disease, and saccular aneurysm was detected in the anterior communicating artery on MR angiography (Figure 5).	Neurobrucellosis great vessel vasculitis and saccular aneurysm
7	Widespread and large numbers of demyelinating plaques and amyloid angiopathy on Cranial MR (Figure 6).	Neurobrucellosis small vessel vasculitis
8	Cranial MR reveals T2W hyperintense lesions in bilateral frontal lobes in addition to findings consistent with diffuse small vascular disease and is significant for neurobrucellosis (Figure 7).	Neurobrucellosis small vessel vasculitis
9	Cranial MR reveals widespread T2W hyperintense lesions and a granuloma-compatible lesion with right frontal contrast involvement, and it partially regresses with treatment (Figure 8).	Neurobrucellosis small vessel vasculitis and granuloma

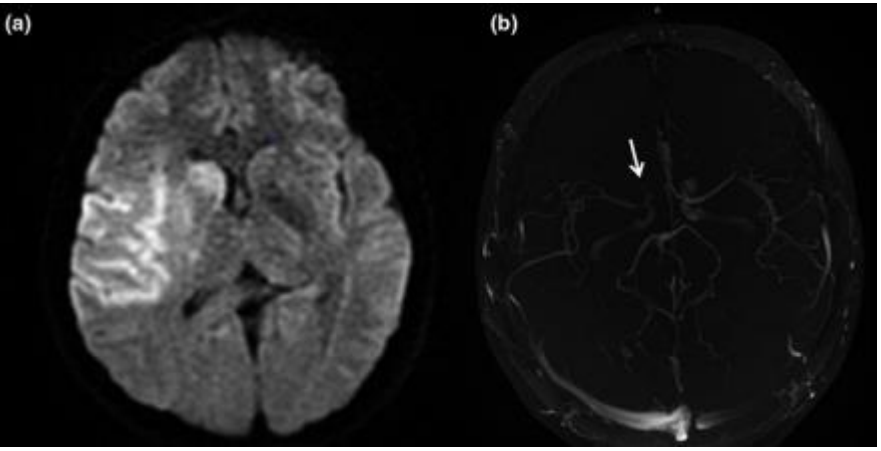
3D TOF MR angiography, three-dimensional time-of-flight magnetic resonance angiography; MRI, magnetic resonance imaging; T2W, T2-weighted.

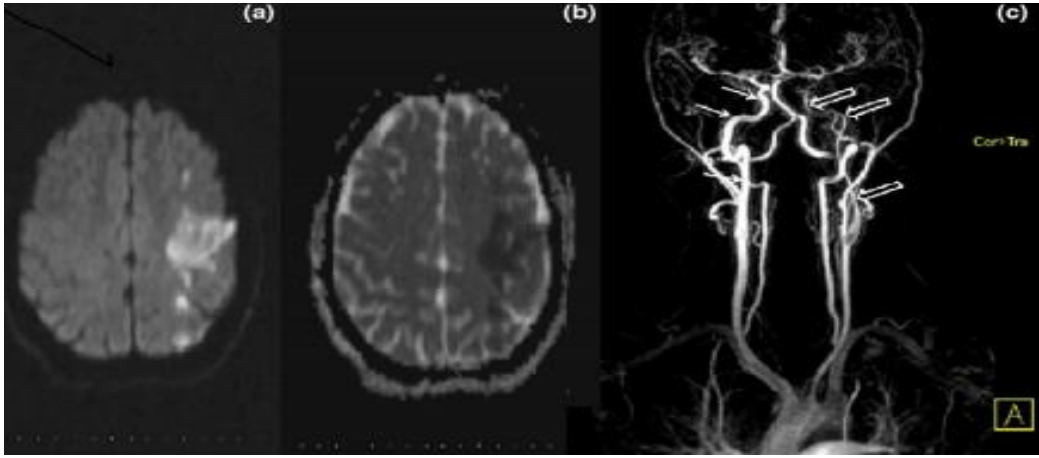
Turkoglu et al Vasculitis and neurobrucellosis: Evaluation of nine cases using radiologic findings. Brain Behav. (2018)

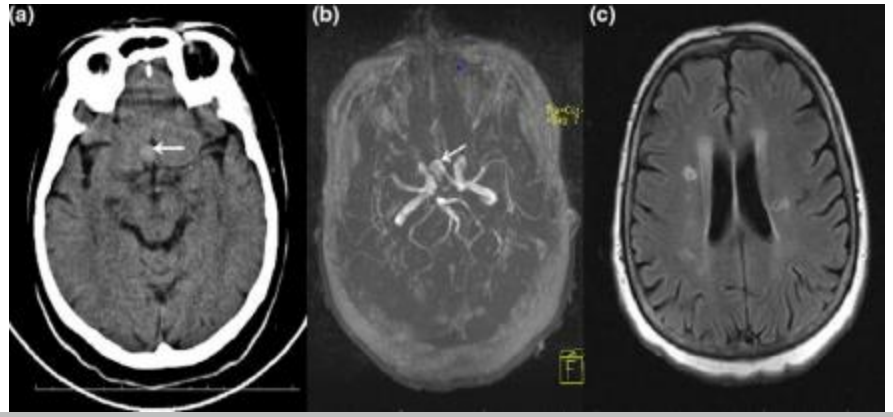
ORIGINAL RESEARCH

WILEY Brain and Behavior Open Access

Vasculitis and neurobrucellosis: Evaluation of nine cases using radiologic findings







Aneurysm in the anterior communicating artery location

Turkoglu et al Vasculitis and neurobrucellosis: Evaluation of nine cases using radiologic findings. Brain Behav. (2018)

Chronic *Chlamydia pneumoniae* Infection and Stroke in Cameroon

A Case-Control Study

Alfred K. Njamnshi, Kathleen Ngu Blackett, Josephine N. Mbuagbaw, Freedom Gumedze, Sandeep Gupta, Charles S. Wiysonge

TABLE 2. Seroprevalence of *C pneumoniae* Antibodies in Cases and Controls

Antibody Type	Stroke Cases	Controls	OR, 95% CI
All cases of stroke (64 case-control pairs)			
IgA	50 (78.1%)	27 (42.2%)	4.29, 1.84 to 11.56; $P=0.0002$
IgG	41 (64.1%)	35 (54.7%)	1.46, 0.68 to 3.22; $P=0.29$
Thrombotic stroke cases (35 case-control pairs)			
IgA	33 (94.3%)	13 (37.1%)	21.00, 3.38 to 868.45; $P<0.0001$
IgG	22 (62.9%)	16 (45.7%)	1.86, 0.69 to 5.50; $P=0.18$

- 64 stroke patients, Cameroon
- IgA antibodies were detected in 50 (78.1%) patients and 27 (42.2%) controls (odds ratio [OR] 4.29; 95% CI, 1.84 to 11.56; P=0.0002)
- strong statistical association between (IgA, and not IgG, as a serological marker of) chronic C pneumoniae infection and stroke

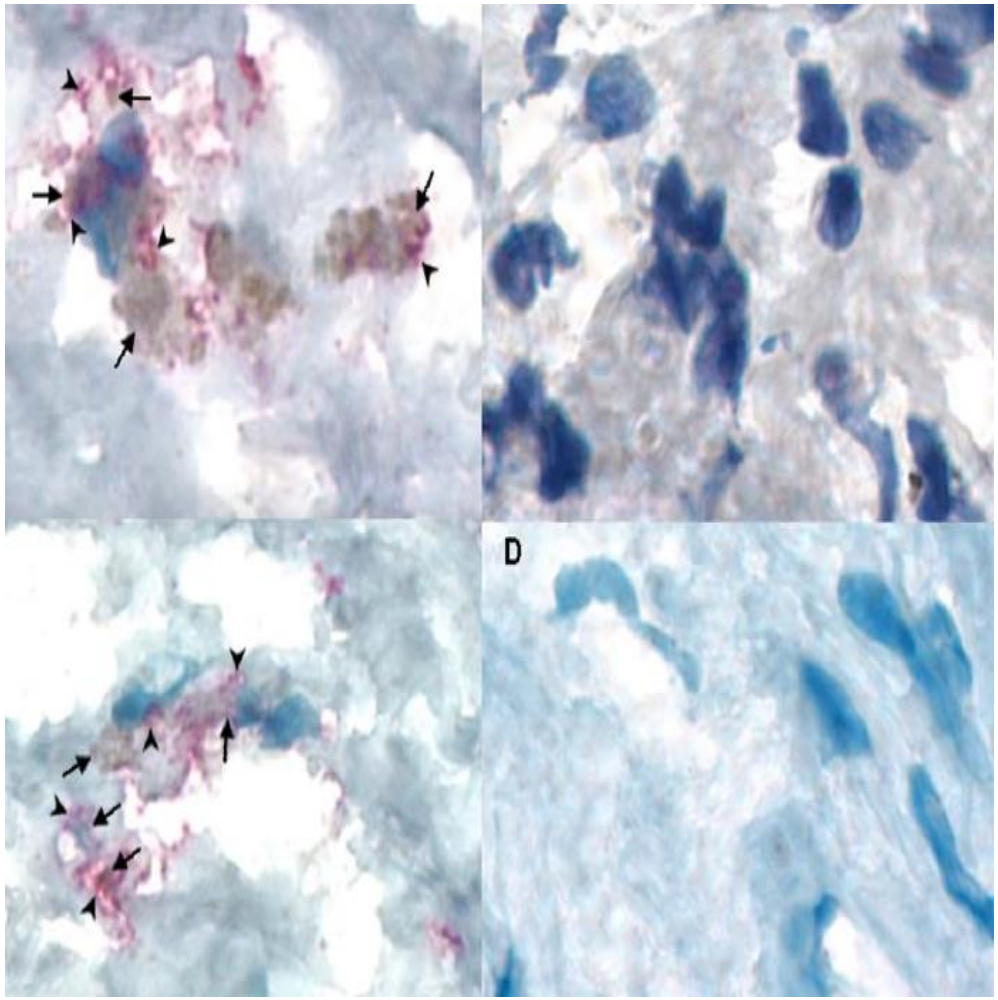
Njamnshi et al, Chronic Chlamydia pneumoniae infection and stroke in Cameroon: a case-control study. Stroke. (2006)

OPEN ACCESS Freely available online PLoS one

Association of Carotid Plaque Lp-PLA$_2$ with Macrophages and *Chlamydia pneumoniae* Infection among Patients at Risk for Stroke

Berna Atik[1], S. Claiborne Johnston[2], Deborah Dean[1,3,4,5]*

- 42 patients
- Elective carotid endarterectomy
- Plaque Lp-PLA2 correlated with:
  - serum homocysteine levels (p=0.013)
  - plaque macrophages (p,0.01)
  - plaque C. pneumoniae (p,0.001) (predominantly infected macrophages, co-localizing with Lp-PLA2)



Carotid plaque sections showing co-localization of Lp-PLA2 and C. pneumoniae, and macrophages and C. pneumoniae.

Atik et al, Association of Carotid Plaque Lp-PLA2 with Macrophages and Chlamydia pneumoniae Infection among Patients at Risk for PLoS ONE (2010)

Helicobacter pylori (HP)

- Gram-negative, spiral shaped bacterium
- Infection of H. pylori always occurs in childhood , persists throughout a lifetime
- Seroprevalence of HP-I :
  - **50%** of the world's population
  - Higher in developing countries
- HP and Stroke: **Conflicting** results++++

Wang et al, Helicobacter pylori infection contributes to high risk of ischemic stroke: evidence from a meta-analysis. J J Neurol. (2012)

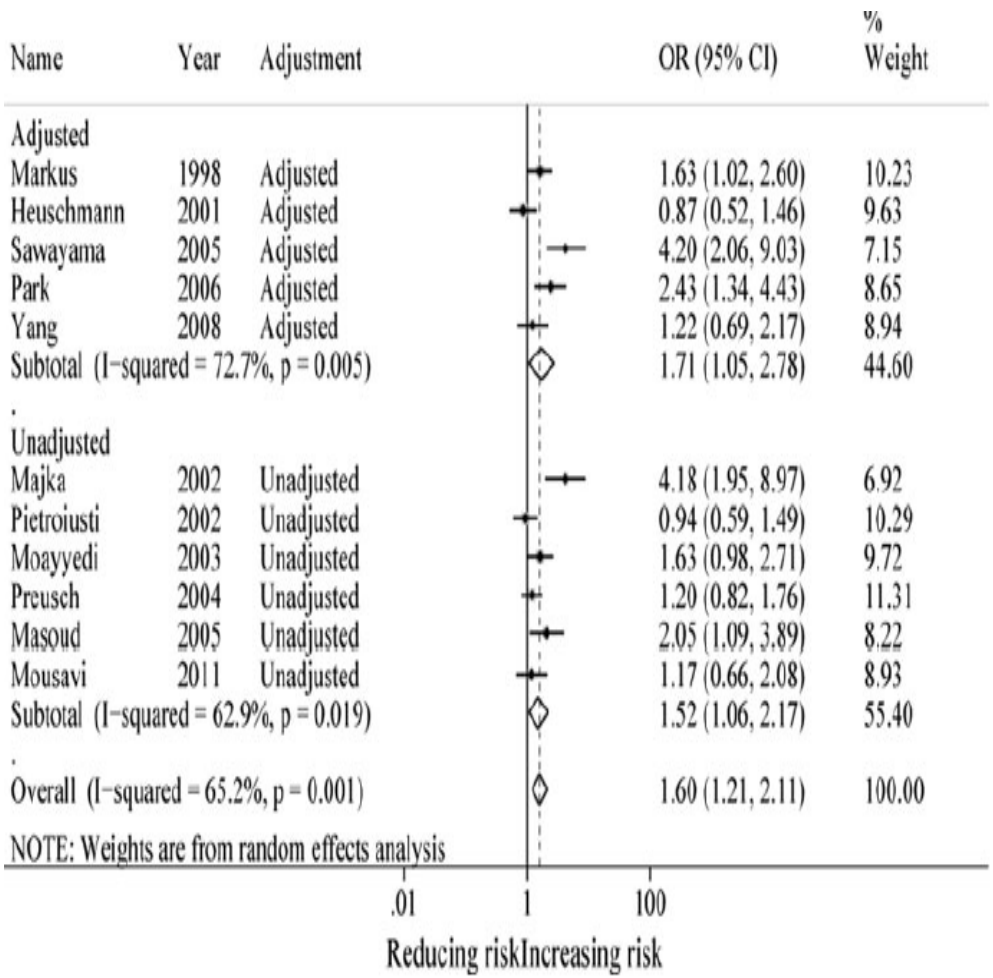
Yu et al, Association between Helicobacter pylori infection and stroke: a meta-analysis of prospectiveobservational studies.. J Stroke Cerebrovasc Dis. (2014)

J Neurol (2012) 259:2527–2537
DOI 10.1007/s00415-012-6558-7

REVIEW

Helicobacter pylori infection contributes to high risk of ischemic stroke: evidence from a meta-analysis

- Meta-analysis:13 studies; 4,041 participants
- ***chronic H. pylori infection: significantly associated with increased risk of IS***
- positive anti-H. pylori IgG :
  - associated with risk of IS caused by ***atherosclerosis and small artery disease***
  - but not for cardioembolic IS



Wang et al, Helicobacter pylori infection contributes to high risk of ischemic stroke: evidence from a meta-analysis. J J Neurol. (2012)

QJM Advance Access published June 16, 2014
Q J Med
doi:10.1093/qjmed/hcu117

Helicobacter pylori infection increases subsequent ischemic stroke risk: a nationwide population-based retrospective cohort study

- Chronic HP-I: significantly associated with ***increased*** risk of IS
- ***Nonembolic*** IS
- ***Anti-HP therapy***: beneficial to IS ***prevention***?

Table 2 The risk of IS compared to study subjects without *HP*-I in Cox proportional hazard regression

Variables	*HP*-I				Compared to non-HPI	
	No		Yes			
	Stroke Event	Stroke Rate#	Stroke Event	Stroke Rate#	Crude HR* (95% CI)	Adjusted HR† (95% CI)
All	2103	8.45	837	14.8	1.76(1.68, 1.83)***	1.52(1.40, 1.65)***
Subtype						
Embolic IS	35	0.14	10	0.18	1.26(1.18, 1.35)***	0.93(0.45, 1.91)
Nonembolic IS	2068	8.31	827	14.7	1.76(1.69, 1.84)***	1.53(1.41, 1.67)***

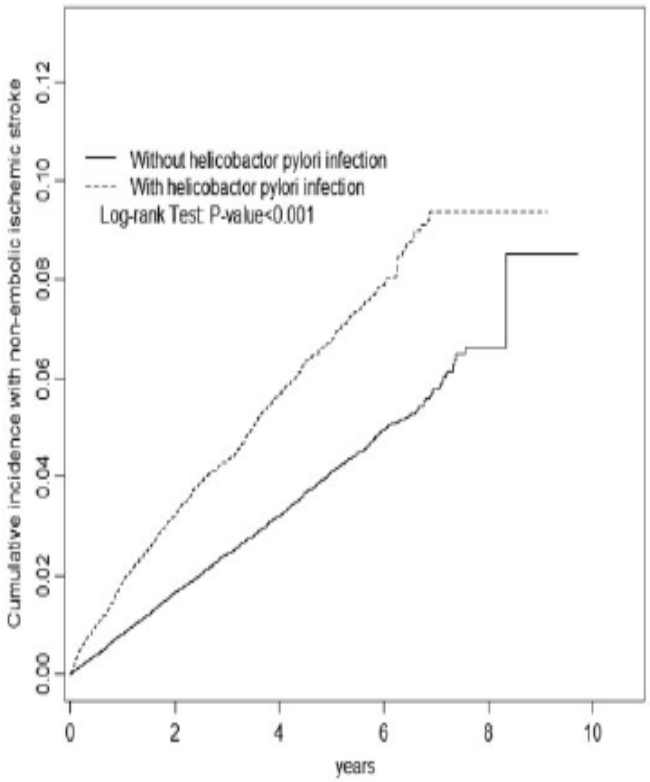


Figure 1. Cummulative incidence of nonembolic IS in patients with and without *HP*-I.

Huang et al, Helicobacter pylori infection increases subsequent ischemic stroke risk: a nationwidepopulation based retrospective cohort study. QJM. (2014)

Association between *Helicobacter pylori* Infection and Stroke: A Meta-analysis of Prospective Observational Studies

Min Yu, MS,* Yangbo Zhang, MS,† Zhen Yang, MD,* Jiangwu Ding, PhD,‡ Chuan Xie, MD,* and Nonghua Lu, PhD*

- 10 prospective observational studies
- Overall combined odds ratio for . infection and stroke =**0 .96** (95% confidence interval, .78-1.14).

No strong association between H. pylori infection and stroke neither in those with cytotoxin-associated gene-A–positive infection

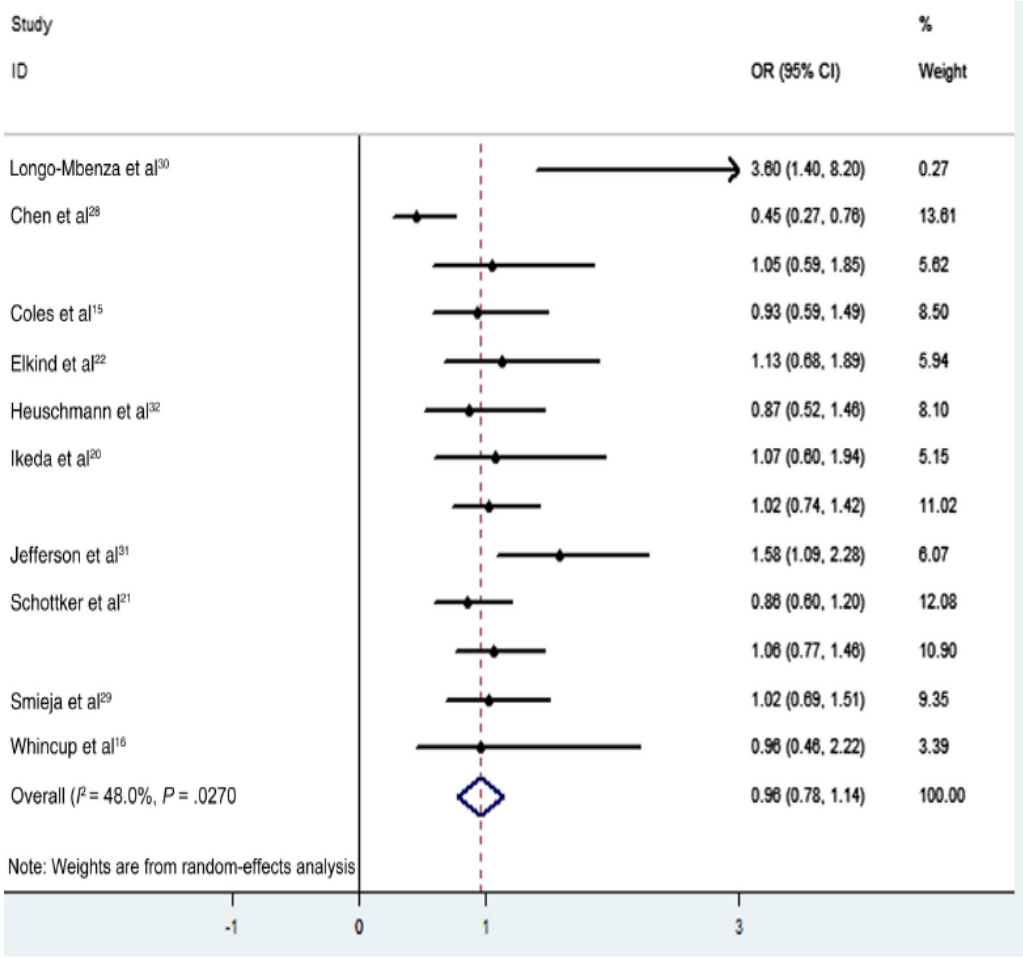


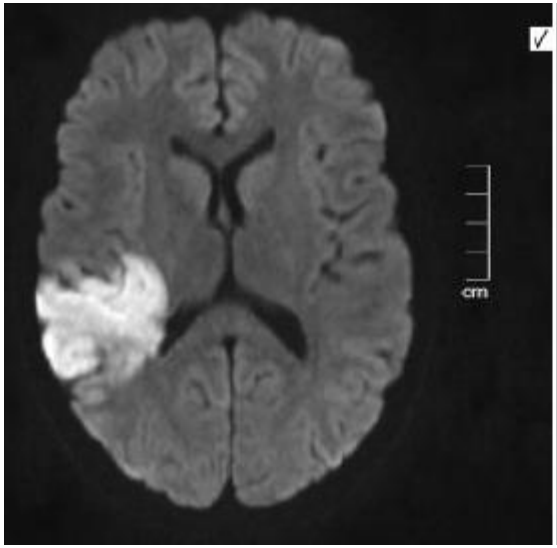
Figure 2. *Association between* Helicobacter pylori *and risk of stroke. Abbreviations: CI, confidence interval; OR, odds ratio.*

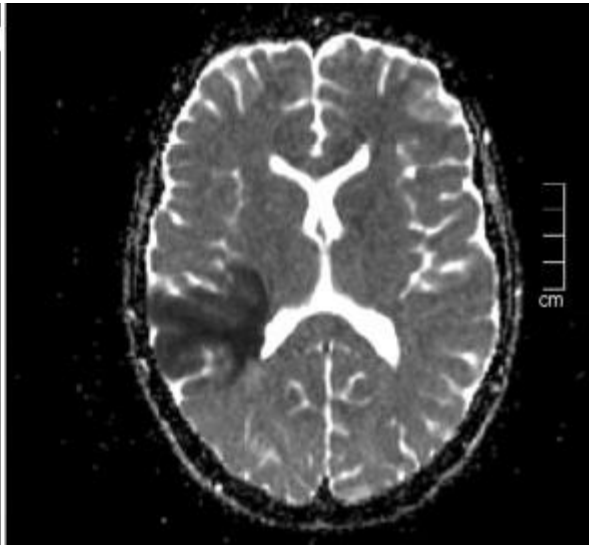
Yu et al, Association between Helicobacter pylori infection and stroke: a meta-analysis of prospectiveobservational studies.. J Stroke Cerebrovasc Dis. (2014)

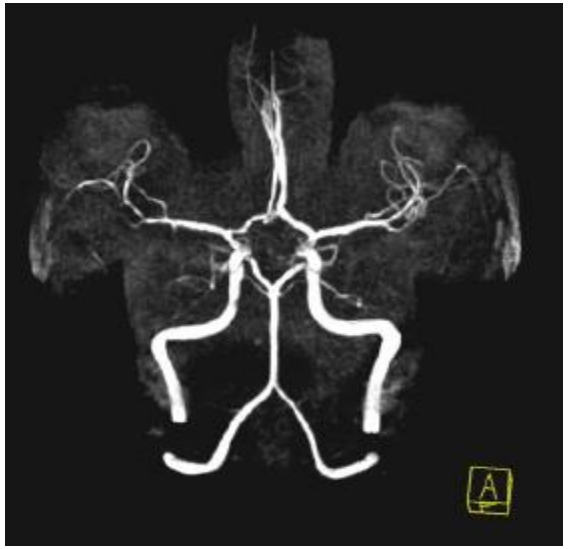
Arterial Ischemic Stroke As a Complication to Disseminated Infection with *Fusobacterium necrophorum*

Yamuna Ratnasingham[1] Lena Hagelskjaer Kristensen[2] Lise Gammelgaard[3] Thomas Balslev[1]

- Girl, 14 years old, previously healthy, 3-week history of antigen positive streptococcal tonsillitis, positive influenza A infection
- painful swelling of the right gluteal region➔ abcess: gram-negative pleomorphic rods➔ F. necrophorum +➔ penicillin + metronidazole
- Day4: sudden slurred speech + transient central, left-sided facial nerve palsy
- Lemierre syndrome (LS) (rare complication of oropharyngeal and odontogenic infections)+ stroke: 3 cases in the literature







Ratnasingham et al, Arterial ischemic stroke as a complication to disseminated infection with Fusobacteriumnecrophorum. Neuropediatrics. (2014)

Pediatr Infect Dis J. 2005 Sep;24(9):843-5.

Wolters Kluwer

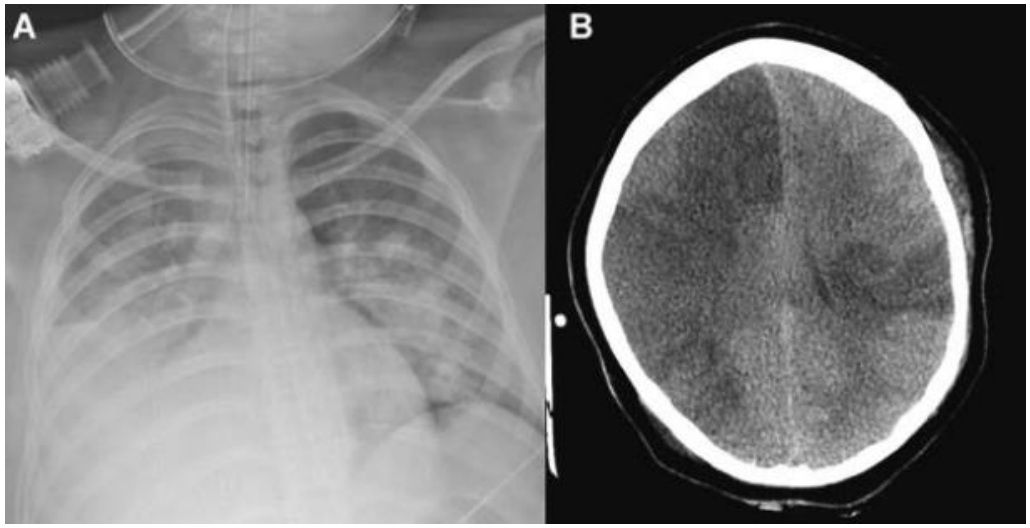
Stroke in two children with Mycoplasma pneumoniae infection. A causal or casual relationship?

Leonardi S[1], Pavone P, Rotolo N, La Rosa M.

Abstract

We report on 2 children who had a **stroke** biologically related to Mycoplasma pneumoniae **infection**. Invasion of the central nervous system and an immune mechanism represent 2 pathogenesis pathways. Prompt macrolide therapy does not prevent **stroke**, but immediate and aggressive immunosuppressive treatment seems to help recovery.

Severe *Mycoplasma pneumoniae* Infection Requiring Extracorporeal Membrane Oxygenation With Concomitant Ischemic Stroke in a Child

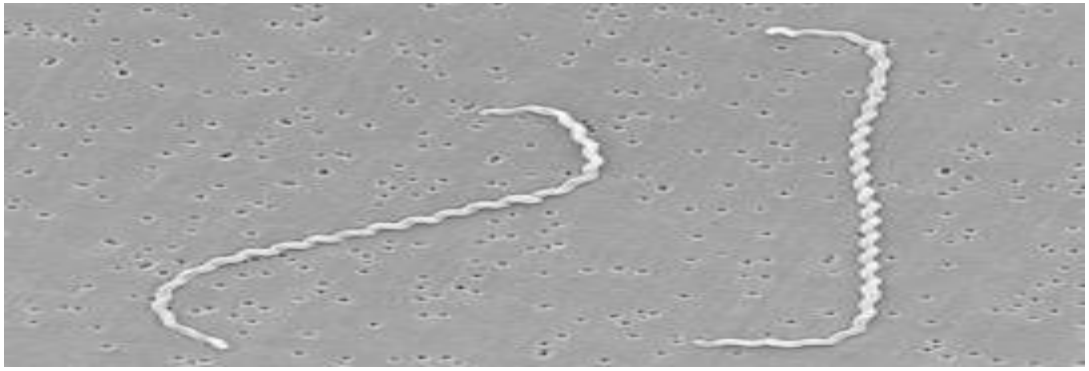


Leonardi et al, Stroke in two children with Mycoplasma pneumoniae infection. A causal or casual relationship? Pediatr Infect Dis J. (2005)

Garcia et al, Severe Mycoplasma pneumoniae infection requiring extracorporeal membrane oxygenation with concomitant ischemic stroke in a child. Pediatr Pulmonol. (2013)

Leptospira interrogans

- Progressive intracranial arteriopathy after Leptospira interrogans infection
- Involvement of large intracranial arteries



Carod-Artal FJ. Stroke in central nervous system infections. Ann Indian Acad Neurol (2008)

Viral Infections and Stroke

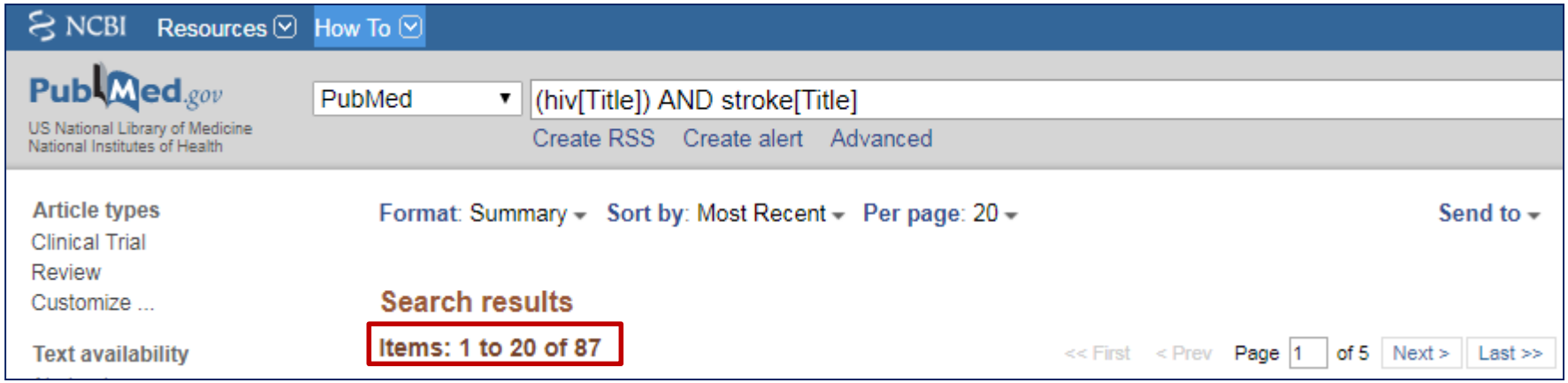
Viral infections implicated in stroke

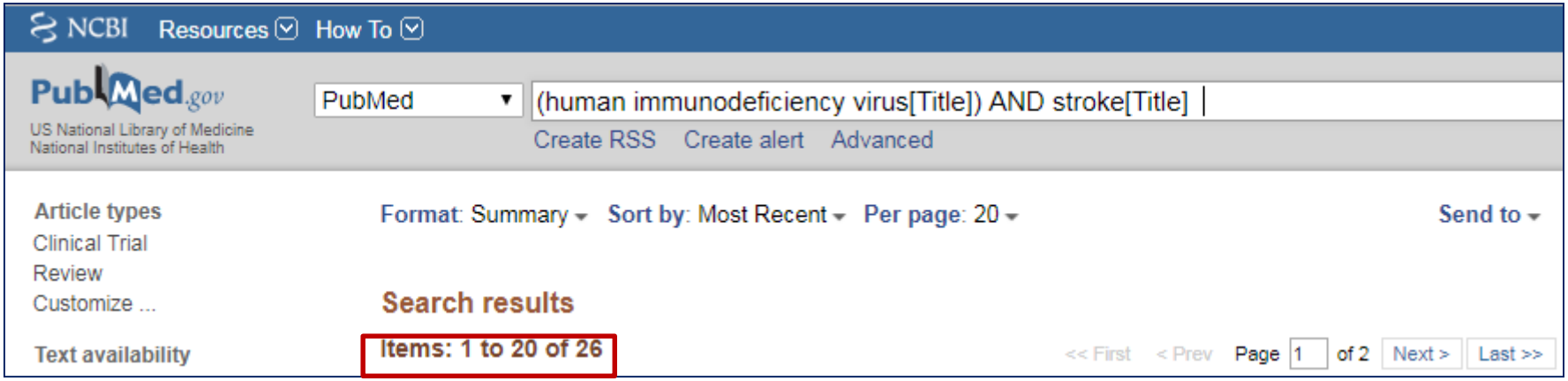
Viral infections		
Human immunodeficiency virus (HIV)	HIV disease/AIDS	Vasculopathy; susceptibility to opportunistic CNS infections
Cytomegalovirus	Often asymptomatic, latent; occasional mononucleosis-like syndrome	Inflammatory response with accelerated atherogenesis
Varicella zoster virus	Chickenpox, shingles	Vasculitis/vasculopathy
Herpes simplex virus (types 1 and 2)	Oral and genital infections	Vasculopathy; possible stroke trigger in young people
Parvovirus B19	"Fifth disease"	Possible arteriopathy

Miller et al, Infection and Stroke: an Update on Recent Progress. Curr Neurol Neurosci Rep (20015

Human Immunodeficiency Virus(HIV)

- HIV: the **most studied** infection in stroke+++





Pubmed

HIV and Stroke

- Prevalence of stroke:
  - In HIV patients: **1%**
  - In HIV-autopsy series (ischemic and hemorrhagic): **6 and 34%**
- Pathogenic mechanisms include:
  - HIV vasculopathy
  - Vasculitis
  - Cardioembolism
  - acquired hypercoagulability
  - effect of opportunistic infections

- Treatment with protease inhibitors: associated with **premature atherosclerotic** vascular disease

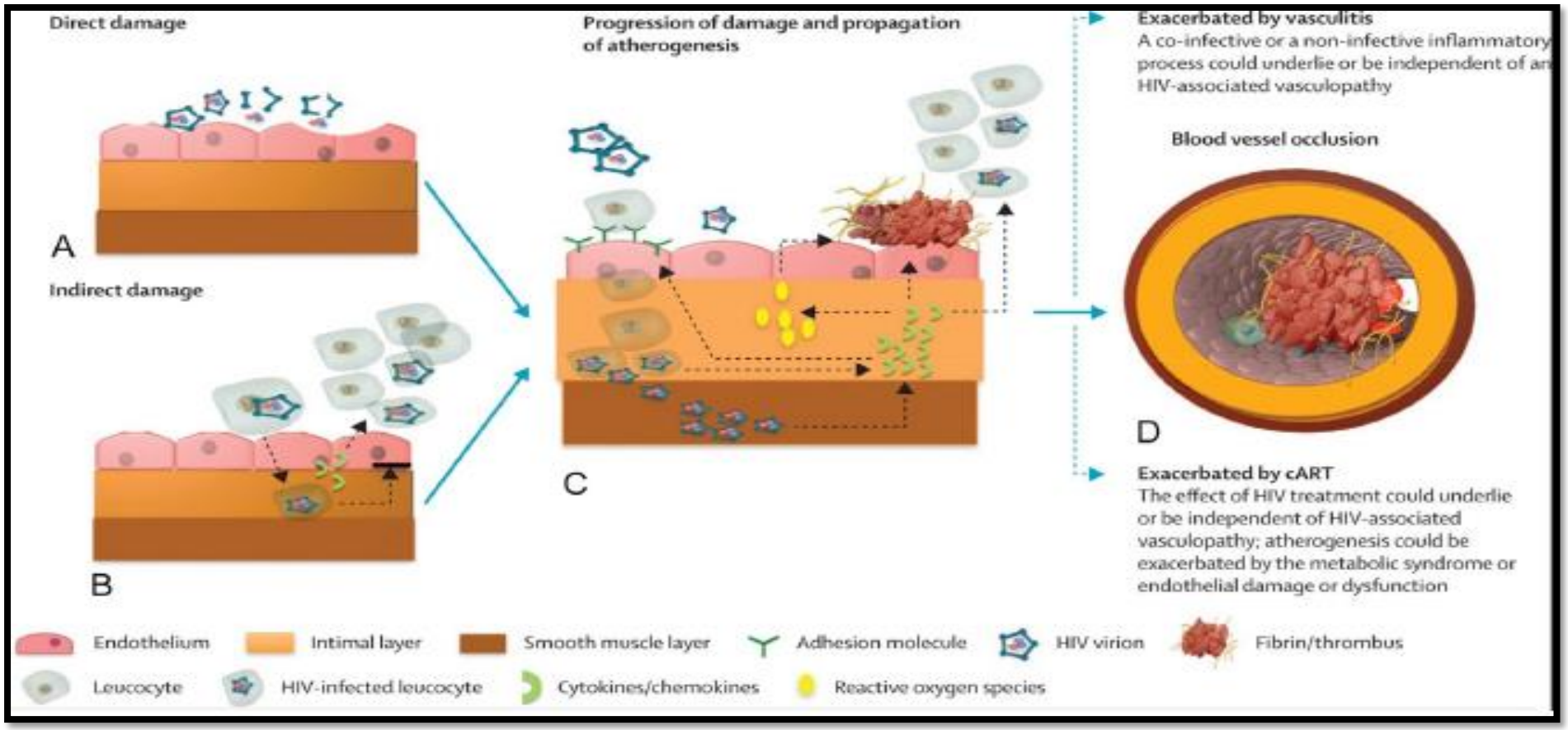
Carod-Artal FJ. Stroke in central nervous system infections. Ann Indian Acad Neurol (2008)

Potential Causes of Ischemic Stroke in AIDS/HIV Infected Patients

- Cardioembolic
  - Nonbacterial thrombotic endocarditis (with and without IVDA)
  - Infective endocarditis (IVDA)
  - HIV myocarditis with thrombus
  - Myxoid valvular degeneration
  - Mural thrombus
  - Dilated cardiomyopathy
- Cerebral opportunistic vasculitis/vasculopathy
  - Opportunistic infections
    - Cytomegalovirus
    - Mycobacterium tuberculosis
    - Varicella-Zoster virus
    - Syphilis
    - Cryptococcosis
    - Mucormycosis
    - Aspergillosis
    - *Candida albicans*
    - Toxoplasmosis
    - Coccidioidomycosis
    - Trypanosomiasis
  - Cerebral opportunistic neoplasm
    - Lymphoma
- Prothrombotic states
  - Protein S deficiency
  - Antiphospholipid antibodies
  - Disseminated intravascular coagulation
- Intravenous drug abuse
  - Cocaine
  - Heroin
- HIV-related vasculitis/vasculopathy
  - Impaired vasoreactivity
  - Impaired vascular bed-specific homeostasis
- Accelerated atherosclerosis with protease inhibitors
  - Dyslipidemia, insulin resistance
  - Endothelial dysfunction
- Cryptogenic

Nogueira Pinto et al, AIDS/HIV Infection and Cerebrovascular Disease. Semin Cerebrovasc Dis Stroke. (2005)

Mechanism of HIV-associated vasculopathy



(Reproduced from Benjamin LA, Bryer A, Emsley HC, et al. (2012) HIV infection and stroke: current perspectives and future directions. Lancet Neurol 11: 878–890)

BENJAMIN et al, HIV infection and stroke. Handbook of Clinical Neurology, Vol. 152 (3rd series) The Neurology of HIV Infection(2018)

Mechanism of HIV-associated vasculopathy

Different pathologic description of vasculopathy associated with HIV infection:

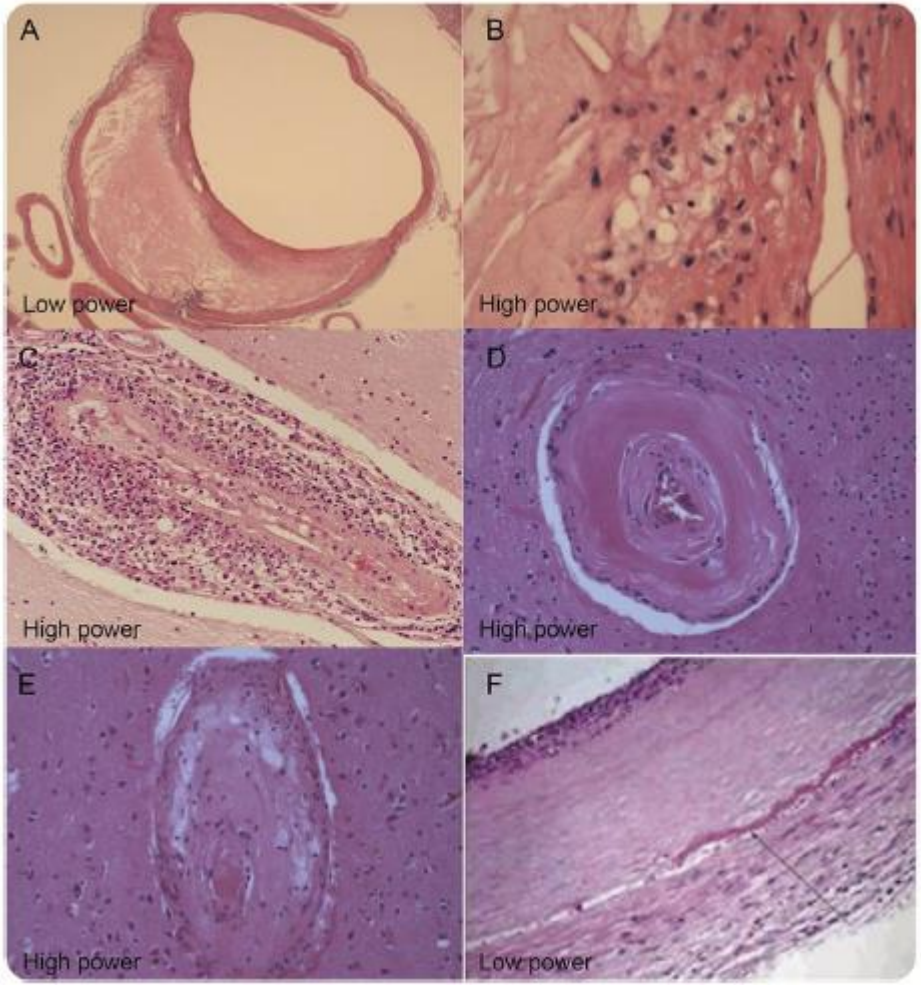
(A, B) ***Atherosclerotic*** vasculopathy

(C) HIV-associated ***vasculitis***

(D) ***Arteriolosclerosis***

(E) lipohyalinosis. ***Small-vessel*** disease

(F) ***Nonatherosclerotic*** vasculopathy



Reproduced from Benjamin LA, Bryer A, Lucas S, et al. (2016a) Arterial ischemic stroke in HIV: defining and classifying etiology for research studies Neurol Neuroimmunol Neuroinflamm 3: e254

BENJAMIN et al, HIV infection and stroke. Handbook of Clinical Neurology, Vol. 152 (3rd series) The Neurology of HIV Infection(2018)

Viewpoint

A new look at human immunodeficiency virus infection and stroke in Sub-Saharan Africa

Engelbert Bain Luchuo[1], Clovis Nkoke[2]

[1]Department of Military Health, Ministry of Defense, Yaounde, Cameroon; [2]Department of Internal Medicine and Specialties, Faculty of Medicine and Biomedical Sciences, University of Yaounde I, Yaounde, Cameroon

Correspondence to: Clovis Nkoke, MD. Department of Internal Medicine and Specialties, Faculty of Medicine and Biomedical Sciences, University of Yaounde I, Yaounde, Cameroon. Email: cnkoke@yahoo.com.

- SSA : greatest burden of HIV infection worldwide
- Study in Malawi: stroke patients with HIV infection:
  - 67% < 45 years (younger)
  - less traditional risk factors for stroke
- 90 % of stroke amongst HIV : ischemic ➔ systematic antiplateles? /Aspirin
- HIV infection +cART: worsen cardiovascular and metabolic profiles ➔ stroke-prone state➔ systematic statins

Luchuo et al, A new look at human immunodeficiency virus infection and stroke in Sub-Saharan Africa.. Ann Transl Med. (2016)

Stroke in Human Immunodeficiency Virus-infected Individuals in Sub-Saharan Africa (SSA): A Systematic Review

Amir Abdallah, MD,* Jonathan L. Chang, BS,† Cumara B. O'Carroll, MD,‡ Abdu Musubire, MBChB, MMED,§ Felicia C. Chow, MD,‖ Anthony L. Wilson, MD,* and Mark J. Siedner, MD, MPH*,¶

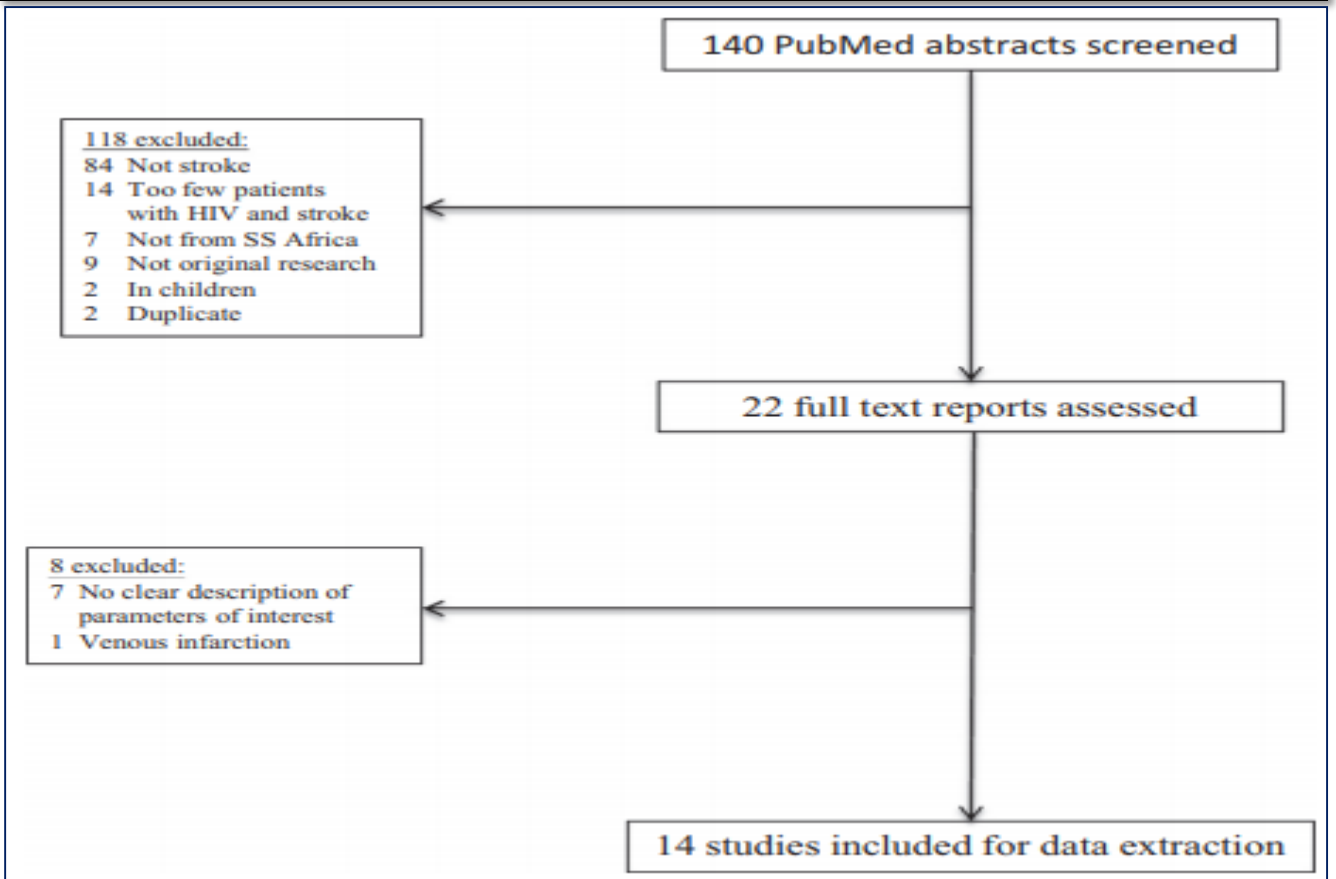


Figure 1. *Details of search and study inclusion from PubMed alone.*

Abdallah et al, Stroke in Human Immunodeficiency Virus-infected Individuals in Sub-Saharan Africa (SSA): A Systematic Review. J Stroke Cerebrovasc Dis.(2018)

Studies on HIV and Stroke in SSA

Table 1. *Characteristics of all studies included. A majority were case-control and cross-sectional studies. Three of the studies were case reports. All studies were hospital based and conducted in East, West, and South Africa.*

Year	First Author	Country	Ref	Sample size, n (HIV+)	Study design
2000	Hoffmann M.	South Africa	22	22	Case control
2003	Mochan A.	South Africa	10	35	Cross sectional
2004	Taylor A.	South Africa	23	3	Case series
2005	Lefeuvre D.	South Africa	24	1	Case report
2005	Patel V.	South Africa	25	56	Case control
2005	Cowppli-bony P.	Côte-d'Ivoire	26	1	Case report
2006	Corr P.D.	South Africa	27	1	Case report
2006	Tipping B.	South Africa	28	1	Case report
2007	Jowi J.O.	Kenya	29	19	Cross sectional
2007	Tipping B.	South Africa	11	67	Cohort
2011	Longo-Mbenza B.	Congo	30	17	Cross sectional
2012	Heikinheimo T.	Malawi	31	50	Cohort
2013	Gnonlonfoun D.	Benin	20	113	Cohort
2014	Van Rensburg J.	South Africa	32	21	Cohort
2015	Allie S.	South Africa	33	20	Case control
2015	Balarabe S.A.	Nigeria	34	20	Case control
2016	Benjamin L.A.	Malawi	7	31	Case control

Abdallah et al, Stroke in Human Immunodeficiency Virus-infected Individuals in Sub-Saharan Africa (SSA): A Systematic Review. J Stroke Cerebrovasc Dis.(2018)

Studies on HIV and Stroke in SSA

Table 2. *Clinical and radiological characteristics of patients with stroke and HIV-infection in sub-Saharan Africa. PLWH had a median age ranging from 32-43 years at the time of presentation, with low CD4 counts (median CD4 range of 108-225 cells/μl). Most patients were ART naïve and were presenting with an unknown HIV status. Ischemic stroke accounted for up to 96% of strokes, and most occurred in the anterior circulation territory. In the studies that graded stroke severity using the NIHSS scale, 63.1% and 71% of PLWH had a score of greater than 12 and greater than, 13 respectively.*

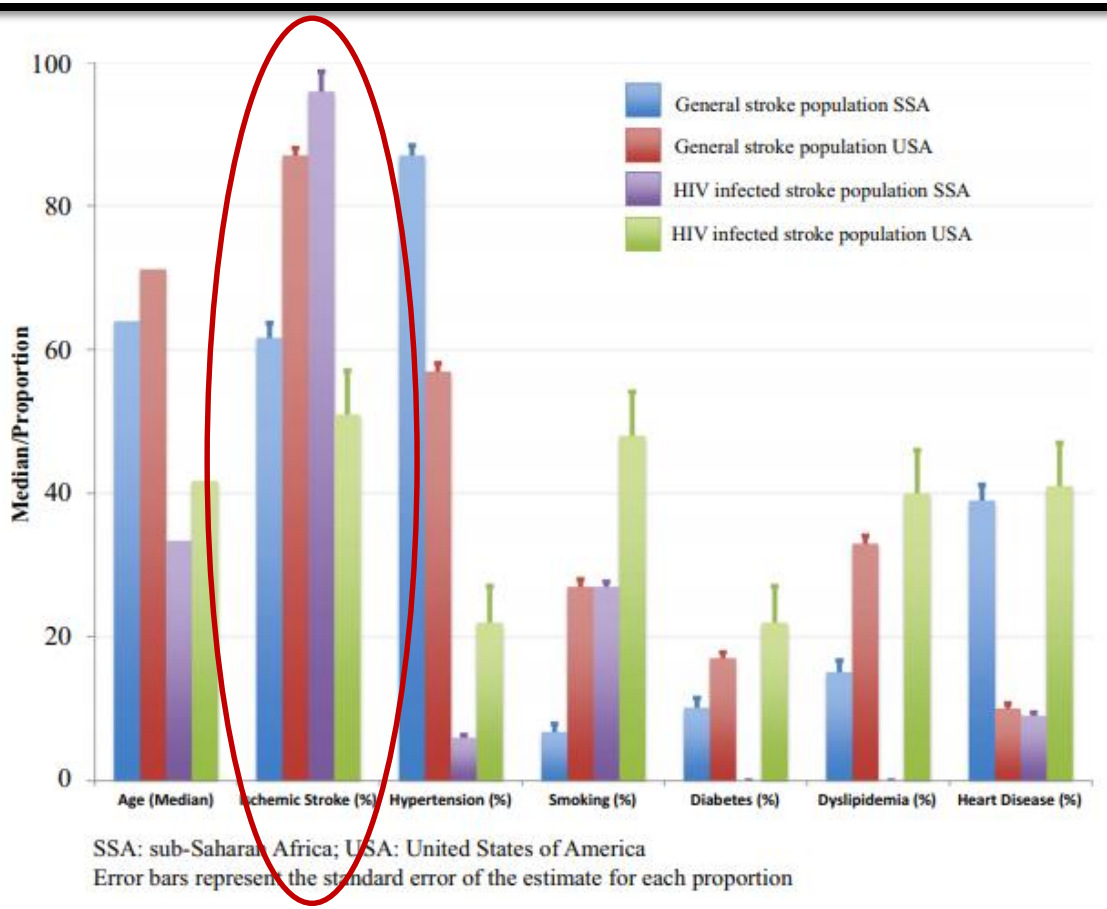
Year	Country	Ref	Mean Age (years)	Sex (M:F ratio)	Mean CD4 (cells/mm^3)	CD4 < 200 or <250$^+$ (cells/mm^3) (%)	On ART (%)	Unknown HIV status at stroke diagnosis (%)	Elevated NIHSS (%)	Ischemic Stroke (%)	Anterior circulation (ischemic, %)	Posterior circulation (ischemic, %)
2000	South Africa	22	NR	1.4:1.0	NR	NR	NR	NR	NR	100.0	81.0	10.0
2003	South Africa	10	32.1	1.5:1.0	NR	40.0	NR	57.0	NR	94.0	94.0	6.0
2007	Kenya	29	39.0	1.4:1.0	120.0	51.3	NR	NR	NR	96.0	NR	NR
2007	South Africa	11	33.4	.5:1.0	NR	46.0	11.9	42.0	NR	96.0	89.0	13.0
2011	Congo	30	NR	NR	107.6	NR	100.0	66.7	NR	94.0	82.4	17.6
2012	Malawi	31	39.8	.9:1.0	NR	62.8$^+$	22.0	NR	63.1 (>12)	80.0	94.0	6.0
2013	Benin	20	43.1	1.0:1.0	119.0	NR	.0	100.0	71.7 (>13)	67.3	NR	NR
2012015	Nigeria	34	36.4	1.4:1.0	224.9	69.0	NR	NR	NR	NR	NR	NR

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; PLWH, people living with HIV; NIHSS, National Institutes of Health Stroke Scale; NR, not reported.

Abdallah et al, Stroke in Human Immunodeficiency Virus-infected Individuals in Sub-Saharan Africa (SSA): A Systematic Review. J Stroke Cerebrovasc Dis.(2018)

Stroke in Human Immunodeficiency Virus-infected Individuals in Sub-Saharan Africa (SSA): A Systematic Review

Amir Abdallah, MD,* Jonathan L. Chang, BS,† Cumara B. O'Carroll, MD,‡ Abdu Musubire, MBChB, MMED,§ Felicia C. Chow, MD,‖ Anthony L. Wilson, MD,* and Mark J. Siedner, MD, MPH*,¶



SSA: sub-Saharan Africa; USA: United States of America
Error bars represent the standard error of the estimate for each proportion

Abdallah et al, Stroke in Human Immunodeficiency Virus-infected Individuals in Sub-Saharan Africa (SSA): A Systematic Review. J Stroke Cerebrovasc Dis.(2018)

Stroke in Human Immunodeficiency Virus-infected Individuals in Sub-Saharan Africa (SSA): A Systematic Review

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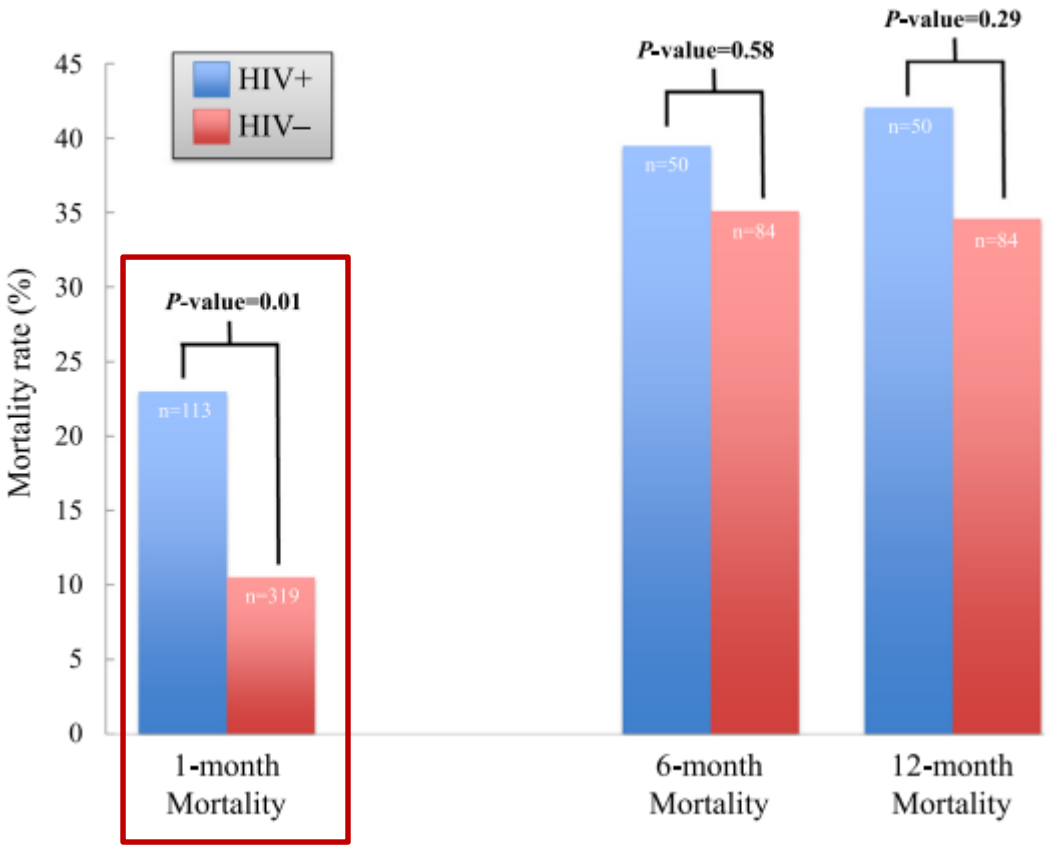

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Stroke in Human Immunodeficiency Virus-infected Individuals in Sub-Saharan Africa (SSA): A Systematic Review

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- Stroke + HIV in SSA occurs:
  - at a ***young age***
  - in those with ***advanced disease***
  - with ***worse*** outcomes

Abdallah et al, Stroke in Human Immunodeficiency Virus-infected Individuals in Sub-Saharan Africa (SSA): A Systematic Review. J Stroke Cerebrovasc Dis.(2018)

Varicella zoster virus (VZV)

- Highly neurotropic DNA virus
- >95% of the world population

- Increased stroke risk after **reactivation** of VZV: due to:
  - **Characteristic vasculopathy** caused by this pathogen:
    - Transaxonal migration (trigeminal nerves to cranial vasculature)
    - Transmural spread (through the tunica adventitia, media, and intima)
    - Inflammation and thickening of the intima, reduction of media, damage of inner elastic layer of vessels
    - Presence of VZV in intracerebral arteries
      - shortly after the acute infection ➔ 10 months after
      - ➔ risk of stroke : up to a year after initial infection
  - Inflammation associated with systemic infection

Marra et al, A meta-analysis of stroke risk following herpes zoster infection. BMC Infectious Diseases. (2017)

Marra et al. BMC Infectious Diseases (2017) 17:198
DOI 10.1186/s12879-017-2278-z

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

A meta-analysis of stroke risk following herpes zoster infection

Fawziah Marra[1*], Jeremy Ruckenstein[1] and Kathryn Richardson[2]

Results: Data were pooled from nine studies. Relative risk for stroke after zoster was 1.78 (95% CI 1.70–1.88) for the first month following herpes zoster, dropping progressively to 1.43 (95% CI 1.38–1.47) after 3 months, to 1.20 (95% CI 1.14–1.26) after 1 year. We found that stroke risk increases by a larger margin during the first month after a herpes zoster ophthalmicus episode: relative risk 2.05 (95% CI 1.82–2.31). The risk remains elevated one year after the acute episode.

Conclusions: Herpes zoster is an established risk factor for increasing the risk of stroke, especially shortly after infection. Vaccination should be encouraged in patients at high risk of cardiovascular disease.

Marra et al, A meta-analysis of stroke risk following herpes zoster infection. BMC Infectious Diseases. (2017)

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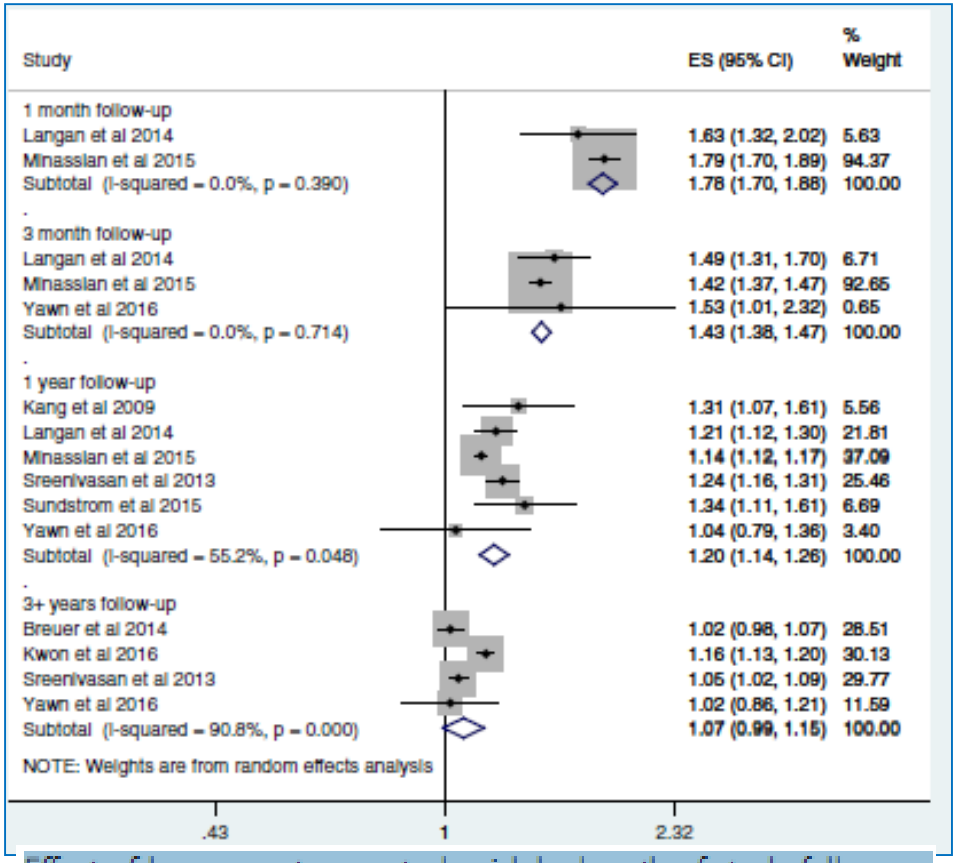
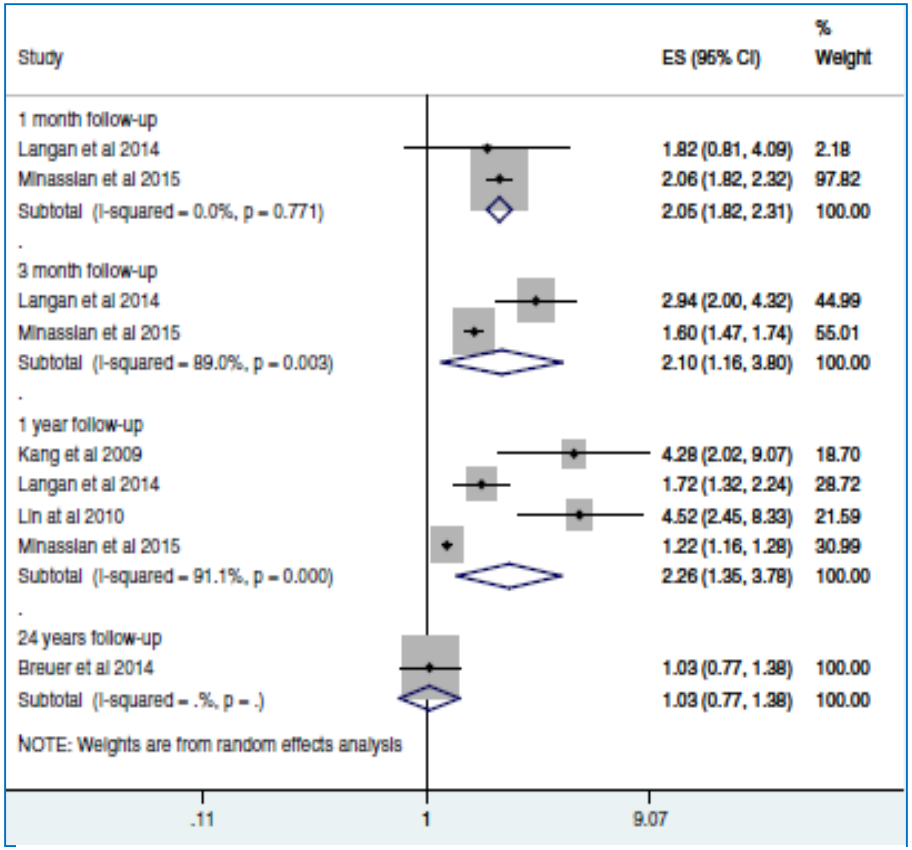


Effect of herpes zoster on stroke risk by length of study follow-up

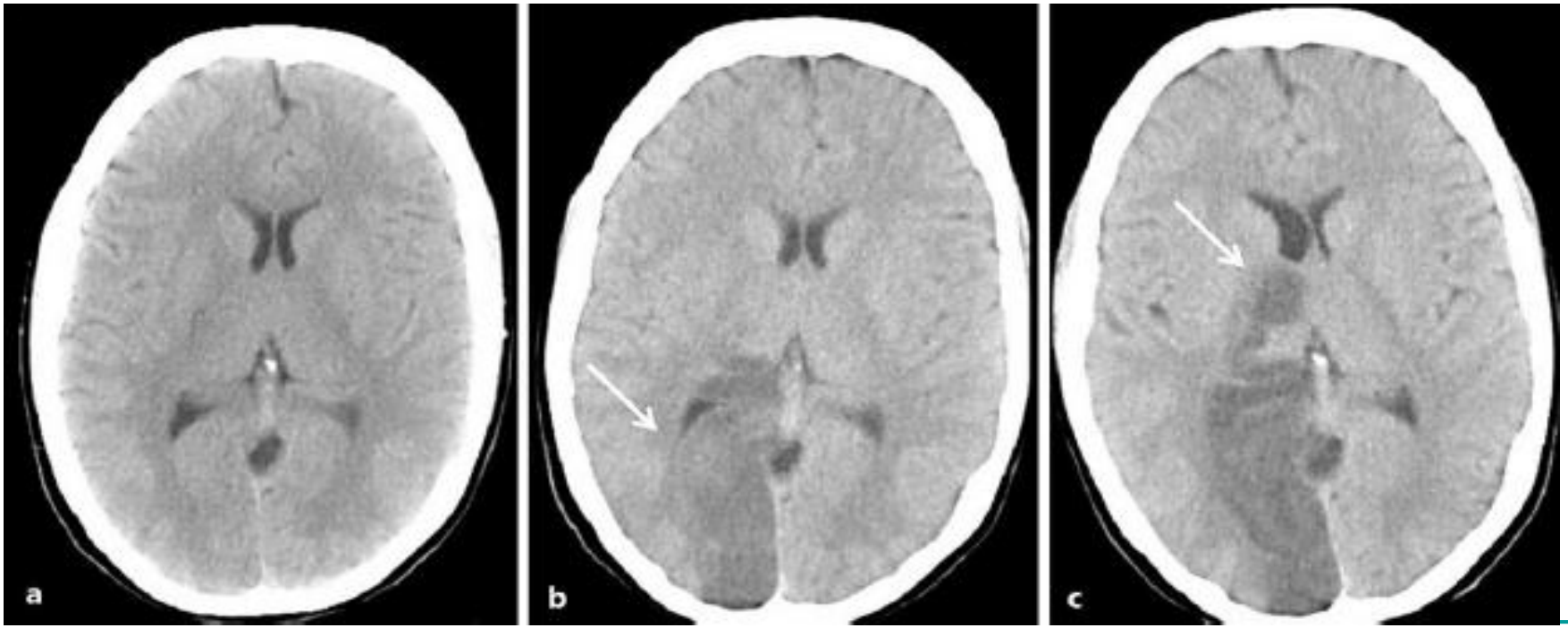


Effect of herpes zoster ophthalmicus on stroke risk by length of study follow-up

Marra et al, A meta-analysis of stroke risk following herpes zoster infection. BMC Infectious Diseases. (2017)

A Young Woman with Ischemic Stroke: Should We Pay More Attention to Varicella Zoster Infection?

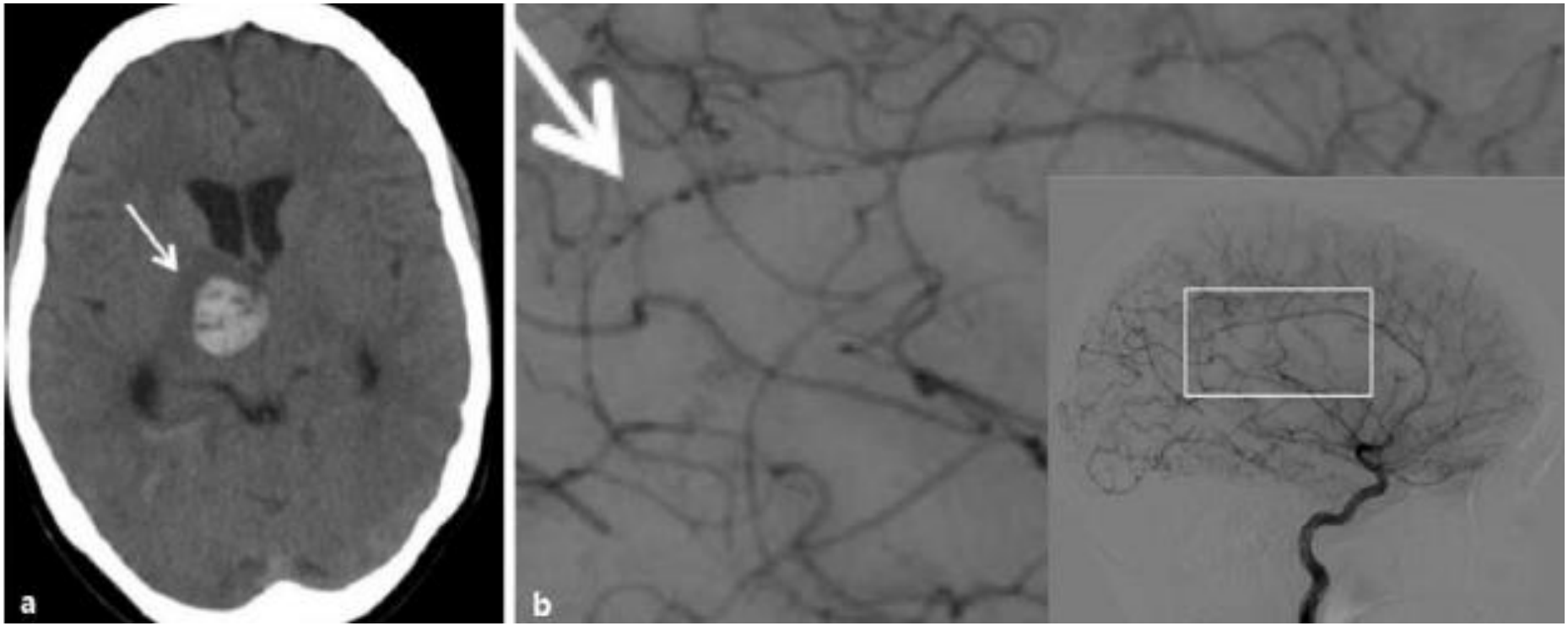
- F, 31 years old, thoracic rash < 1 month, acute ischemic stroke of the right posterior cerebral artery



Borbinha et al.: A Young Woman with Ischemic Stroke: Should We Pay More Attention to Varicella Zoster Infection?

Evolution

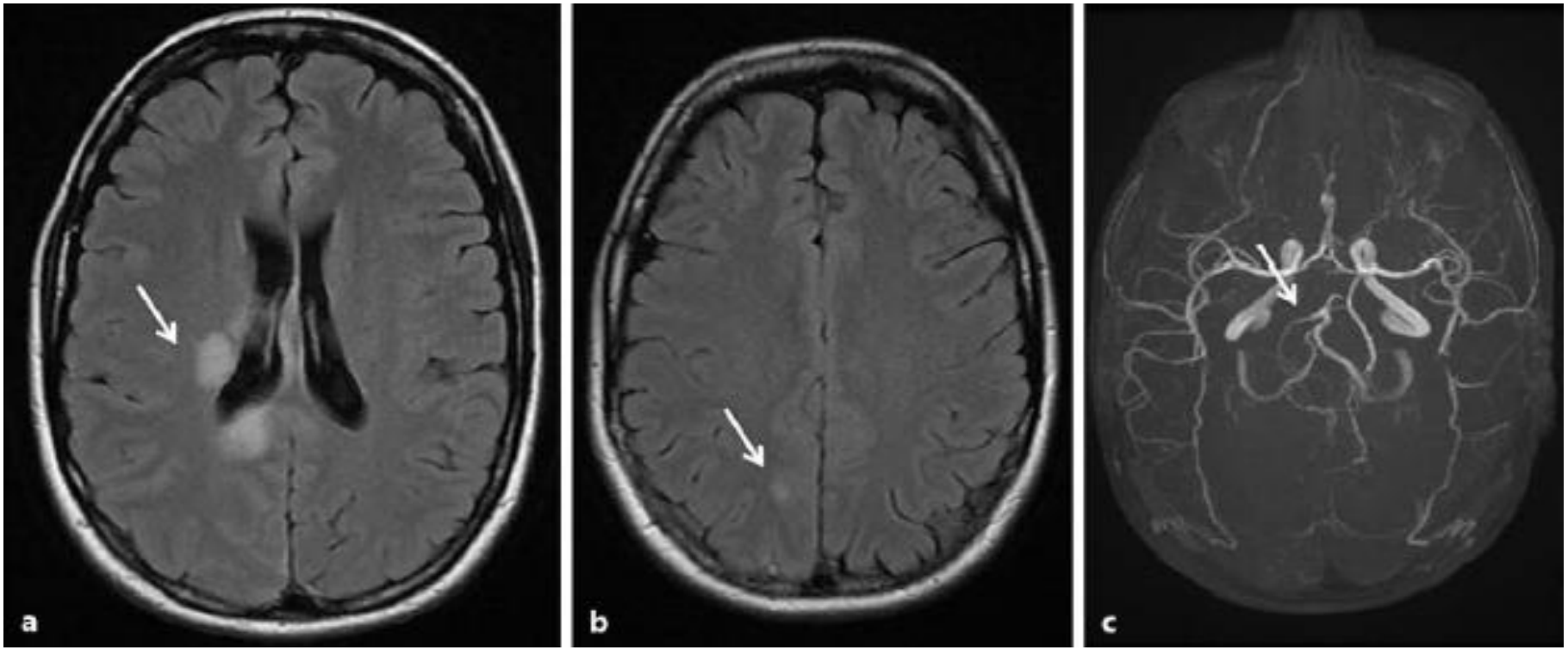
- Aspirin and simvastatin ➔ ***stepwise deterioration*** the following days+ new areas of infarction on brain imaging
- Anticoagulation (empirical) 6 days after stroke onset
- One week later: symptomatic ***hemorrhagic transformation***



Borbinha et al.: A Young Woman with Ischemic Stroke: Should We Pay More Attention to Varicella Zoster Infection?

VZV vasculopathy

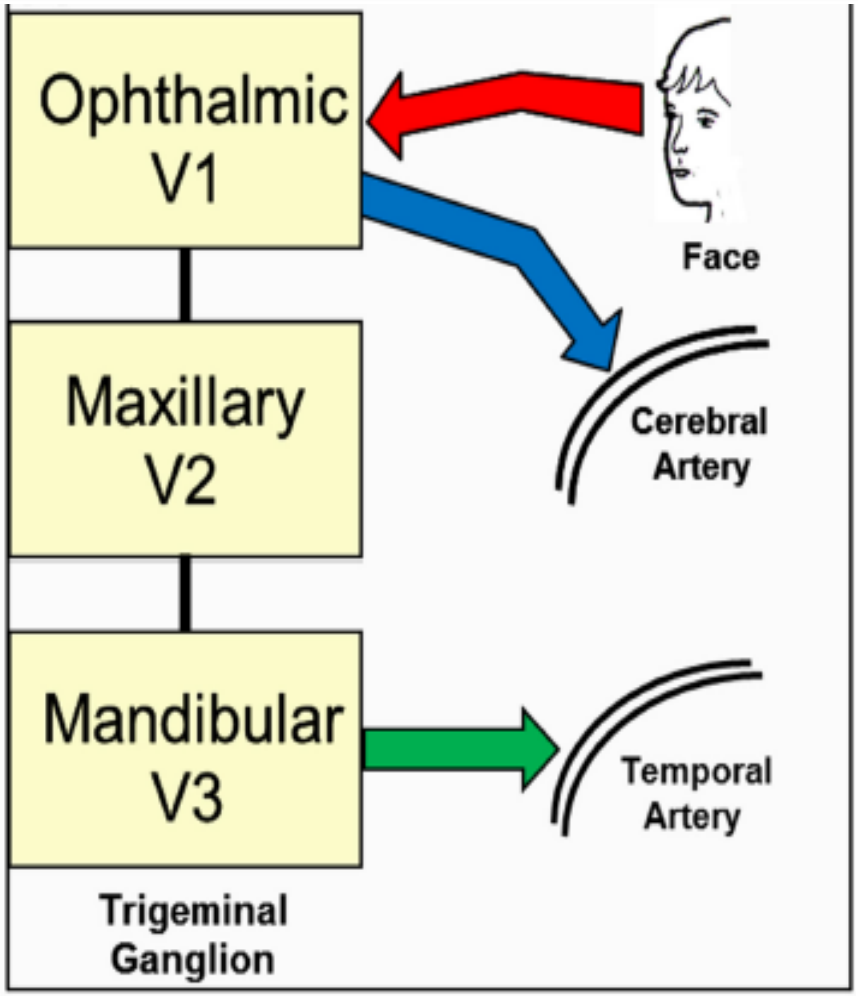
- CSF: +
- Digital subtraction angiography:+

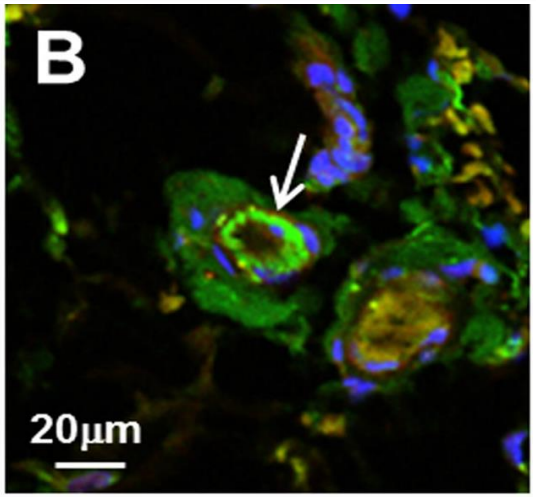


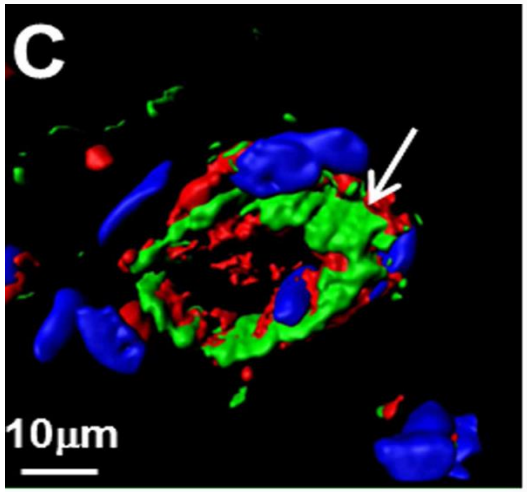
- Acyclovir + prednisolone ➔ no further vascular events

Borbinha et al.: A Young Woman with Ischemic Stroke: Should We Pay More Attention to Varicella Zoster Infection?

Biological Plausibility of a Link Between Arterial Ischemic Stroke and Infection with Varicella-Zoster Virus or Herpes Simplex Virus







Grose et al.: Biological Plausibility of a Link Between Arterial Ischemic Stroke and Infection With Varicella-Zoster Virus or Herpes Simplex Virus. Circulation. (2016)

Cytomegalovirus (CMV)

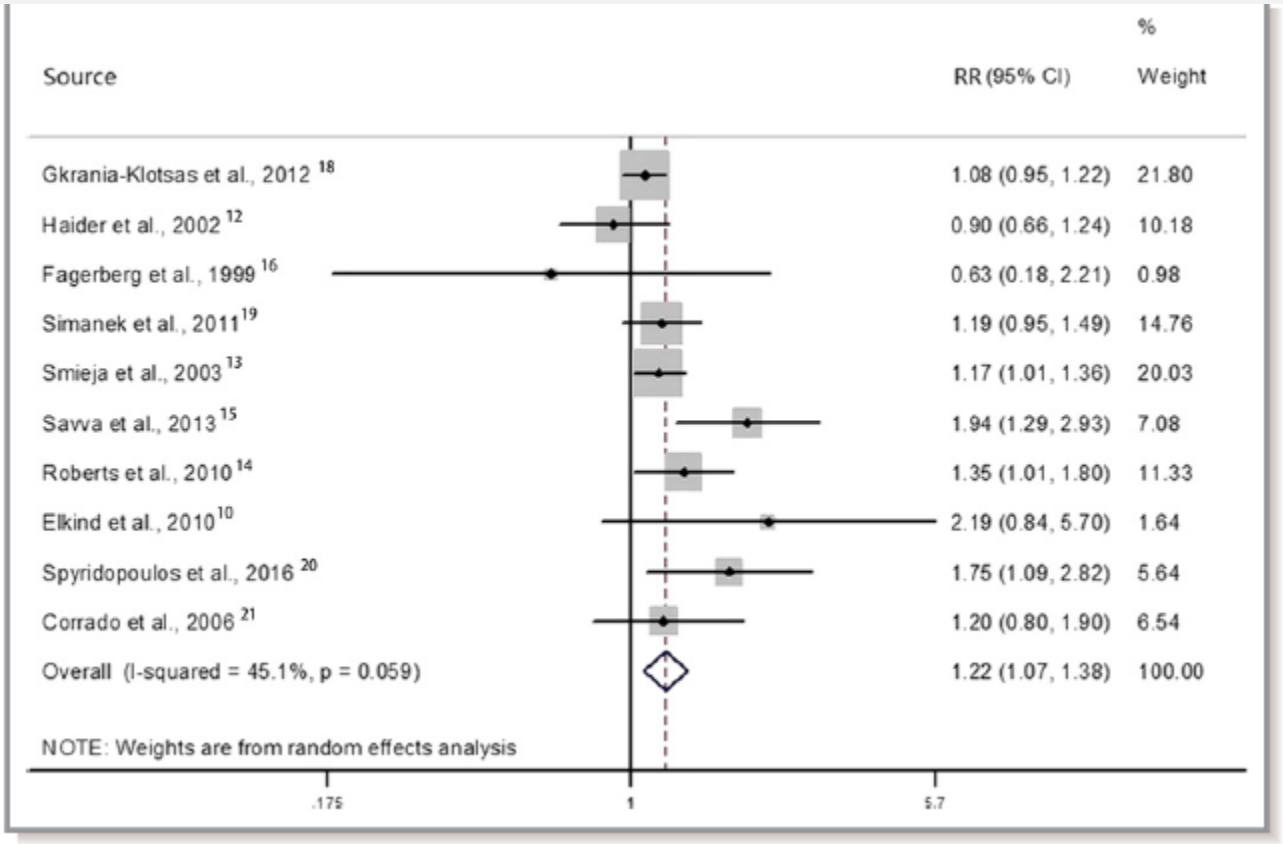
- Cytomegalovirus (CMV):
  - DNA virus
  - belongs to the herpes family of virus
  - widely distributed in population
  - role in the development of atherosclerosis

Wang et al.: **Cytomegalovirus Infection and Relative Risk of Cardiovascular Disease (Ischemic Heart Disease, Stroke, and Cardiovascular Death): A Meta-Analysis of Prospective Studies Up to 2016.** ***J Am Heart Assoc. (2017)***

Cytomegalovirus Infection and Relative Risk of Cardiovascular Disease (Ischemic Heart Disease, Stroke, and Cardiovascular Death): A Meta-Analysis of Prospective Studies Up to 2016

Haoran Wang, MD;* Geng Peng, MD;* Jing Bai, MD; Bing He, MD; Kecheng Huang, MD; Xinrong Hu, MD; Dongliang Liu, MD

Association between CMV infection and risk of CVDs.



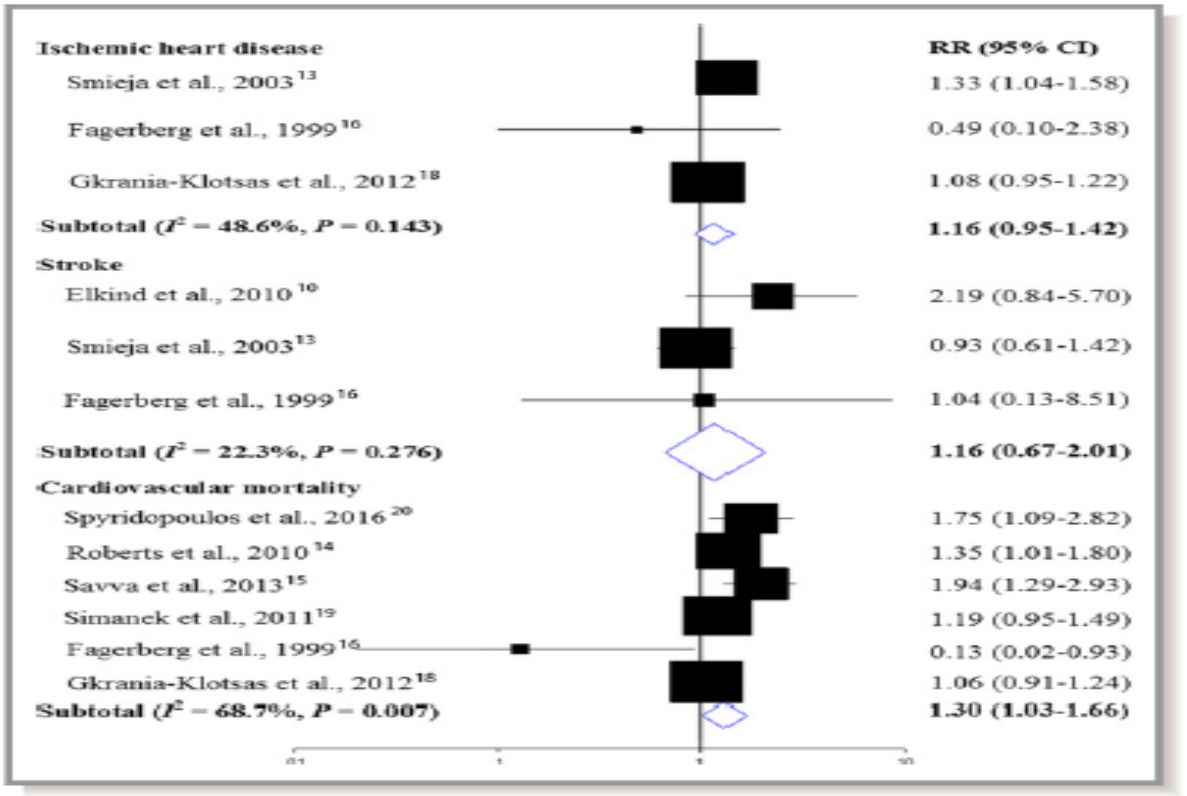
Wang et al.: **Cytomegalovirus Infection and Relative Risk of Cardiovascular Disease (Ischemic Heart Disease, Stroke, and Cardiovascular Death): A Meta-Analysis of Prospective Studies Up to 2016.** ***J Am Heart Assoc. (2017)***

American Heart Association | American Stroke Association.

Cytomegalovirus Infection and Relative Risk of Cardiovascular Disease (Ischemic Heart Disease, Stroke, and Cardiovascular Death): A Meta-Analysis of Prospective Studies Up to 2016

Haoran Wang, MD;* Geng Peng, MD;* Jing Bai, MD; Bing He, MD; Kecheng Huang, MD; Xinrong Hu, MD; Dongliang Liu, MD

Associations between CMV infection and relative risk of IHD, stroke, and cardiovascular mortality



Wang et al.: **Cytomegalovirus Infection and Relative Risk of Cardiovascular Disease (Ischemic Heart Disease, Stroke, and Cardiovascular Death): A Meta-Analysis of Prospective Studies Up to 2016.** ***J Am Heart Assoc. (2017)***

PLOS ONE

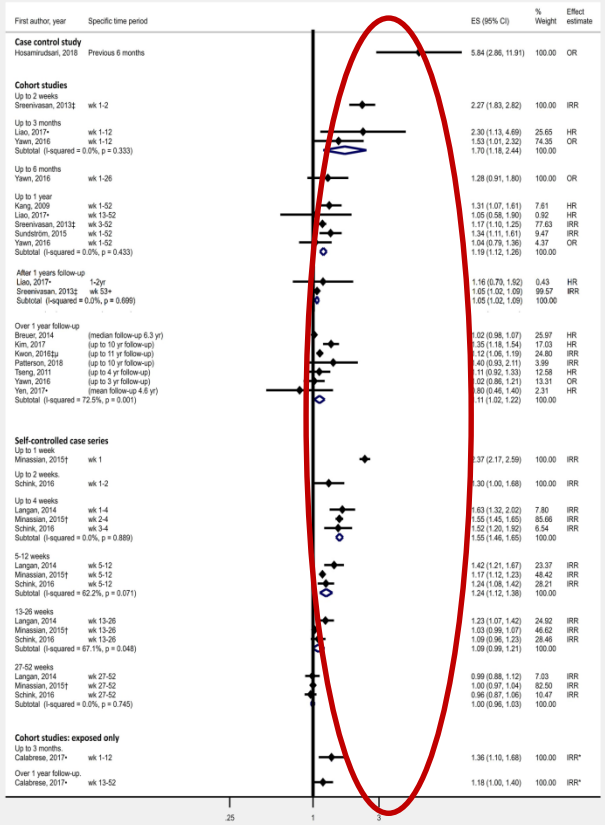
RESEARCH ARTICLE

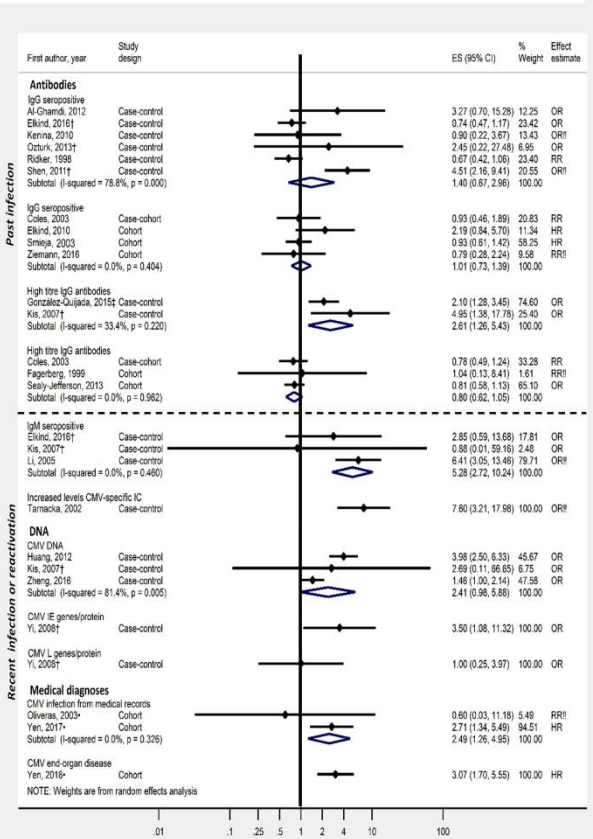
Association of herpesviruses and stroke: Systematic review and meta-analysis

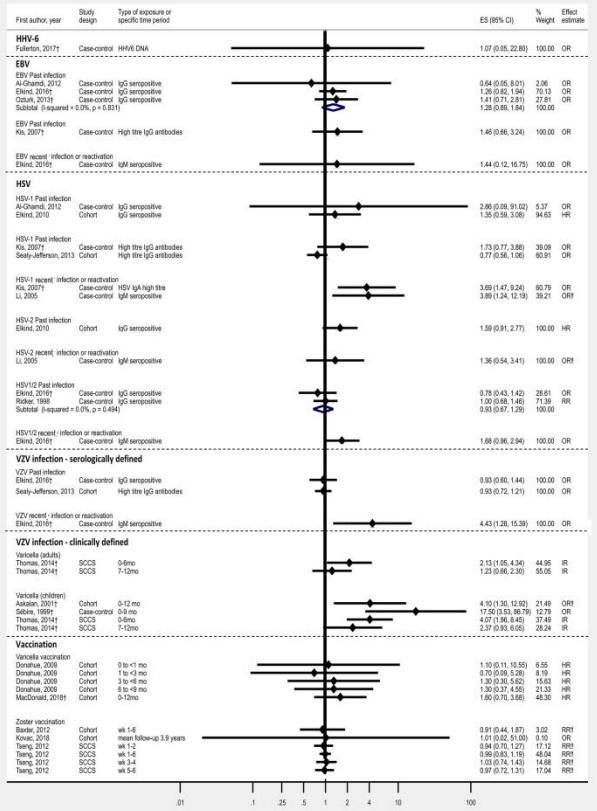
Harriet J. Forbes[1]*, Elizabeth Williamson[1], Laura Benjamin[2,3], Judith Breuer[4], Martin M. Brown[5], Sinéad M. Langan[1], Caroline Minassian[1], Liam Smeeth[1], Sara L. Thomas[1], Charlotte Warren-Gash[1]

- increased stroke risk following **zoster**
- **recent infection or reactivation of other herpes** viruses increases stroke risk

herpes zoster	CMV	EBV, HSV, VZV







Hepatitis C virus (HCV)

- 300 Million patients worldwide
- Increased cardiovascular disease related morbidity and mortality

- All types of stroke
  - Ischemic: Atherosclerosis+++ (chronic inflammatory stimuli)
  - Hemorrhagic: hypertension, older age, aticoagulants

Lin et al.: Antiviral therapy reduces risk of haemorrhagic stroke in patients with HCV infection: a nationwide cohort study. Antivir Ther. (2018)

Chronic HCV infection is a risk factor of ischemic stroke

- HCV infected patients :
  - At ***higher*** and ***earlier*** risk of stroke
  - ***Inflammation*** = key mediator

Variable	HCV positive $n = 33$ (26.8%)	HCV negative $n = 90$ (73.8%)	$p=$
Age, median (range)	73 (53–98)	76 (46–93)	0.017
Males	51.5%	58.9%	n.s.
Smokers	39%	37%	n.s.
ALT (IU/dl)	48 ± 29	33 ± 29	0.016
Platelets (10^3/mcL)	209 ± 66	214 ± 77	n.s.
Serum cholesterol mg/dL (mean ± s.d.)	167 ± 25	193 ± 39	0.001
Serum triglycerides mg/dL (mean ± s.d.)	111 ± 49	135 ± 75	0.045
Eritro-sedimentation rate (1st hour, mm)	46 ± 23	31 ± 18	0.001
CRP (mg/dl)	1.5 ± 1.5	0.72 ± 0.58	0.0001
Fibrinogen (mg/dl)	425 ± 141	337 ± 132	0.012
Diabetes	51.5%	48%	n.s.
Hypertension	50%	59%	0.012
Atrial fibrillation	32%	26%	n.s.
Past ischemic heart event	24%	6.6%	0.007

Variable	O.R.	95% CI	p
HCV	2.04	1.69–2.46	0.0001
Male sex	1.12	1.01–1.27	0.031
Hypertension	1.14	1.01–1.26	0.021

Adinolfi et al.: Chronic HCV infection is a risk factor of ischemic stroke. Atherosclerosis. (2013)

OPEN ACCESS Freely available online

PLoS one

Does Hepatitis C Virus Infection Increase Risk for Stroke? A Population-Based Cohort Study

Chien-Chang Liao[1,2], Ta-Chen Su[3], Fung-Chang Sung[4], Wan-Hsin Chou[1,2], Ta-Liang Chen[1,2]*

1 Health Policy Research Center, Taipei Medical University, Taipei, Taiwan, 2 Department of Anesthesiology, Taipei Medical University Hospital, Taipei, Taiwan, 3 Department of Cardiology, National Taiwan University Hospital, Taipei, Taiwan, 4 Department of Public Health, China Medical University, Taichung, Taiwan

- Taiwan; 4,094 newly diagnosed HCV adults; 16,376 controls
- During 96,752 person-years of follow-up, 1981 newly diagnosed stroke cases
- Risk of stroke HCV+= 2.5%, HCV-: 1.9% (p,0.0001)
- Adjusted HR of stroke in HCV+: 1.27 (95% CI 1.14 to 1.41)

Table 2. Incidences of stroke and Cox model measured hazard ratios of stroke associated with hepatitis C infection, demographic factors and comorbidities.

				Univariate	
	Person-years	Cases	Incidence rate[a]	HR	(95% CI)
Hepatitis C					
No	77686	1499	19.3	1.00	(reference)
Yes	19066	482	25.3	1.30	(1.17–1.44)

Table 3. Multivariable Cox model measured hazard ratios and 95% confidence intervals for stroke.

		Multivariate-adjusted	
		HR	(95% CI)
Hepatitis C	yes vs. no	1.22	(1.13–1.40)

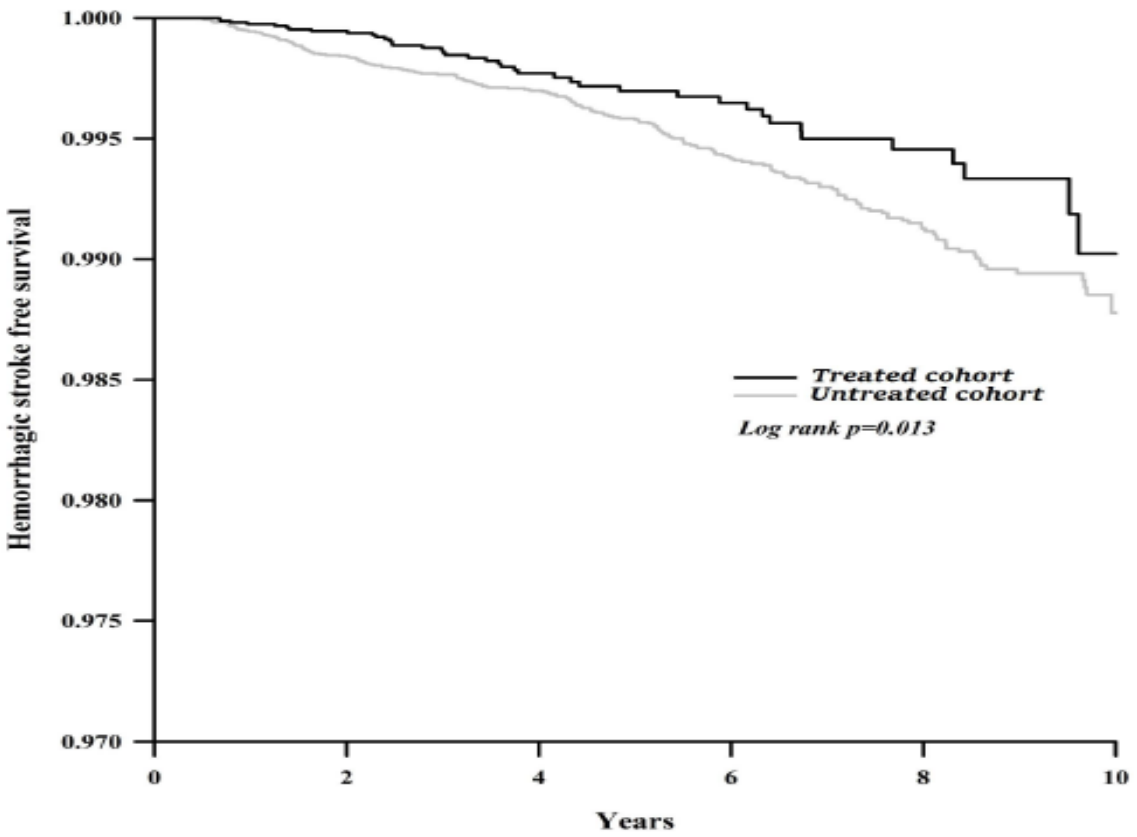
Liao et al.: **Does hepatitis C virus infection increase risk for stroke? A population-based cohort study. PLoS One.** *(2012)*

Antiviral therapy reduces risk of haemorrhagic stroke in patients with HCV infection: a nationwide cohort study

Ming-Shyan Lin, Chang-Min Chung, Wey-Yil Lin, Kuo-Liang Wei, Jui Wang, Ying-Ying Lee, Jing-Hong Hu, Tao-Hsin Tung, Yu-Sheng Lin

Antiviral Therapy 2017; 10.3851/IMP3172

- 11 year population-based study
- Taiwan
- ***97198*** HCV infected patients
- Higher Hemarrhagic stroke in untreated patients (p=0,0014)



Lin et al.: Antiviral therapy reduces risk of haemorrhagic stroke in patients with HCV infection: a nationwide cohort study. Antivir Ther. (2018)

Hepatitis B virus (HBV)

- 350 million people
- 5%–7% of the world's population
- Inverse relationship between HBV infection and metabolic syndrome
- HBV infection: independent factor associated with a lower risk of fatty liver
- HBV: decrease risk of stroke
- However: association=controversial

Lin et al.: Antiviral therapy reduces risk of haemorrhagic stroke in patients with HCV infection: a nationwide cohort study. Antivir Ther. (2018)

Acta Neurologica Scandinavica
Acta Neurol Scand DOI: 10.1111/ane.12548

ACTA NEUROLOGICA SCANDINAVICA

Association of hepatitis B virus infection with decreased ischemic stroke

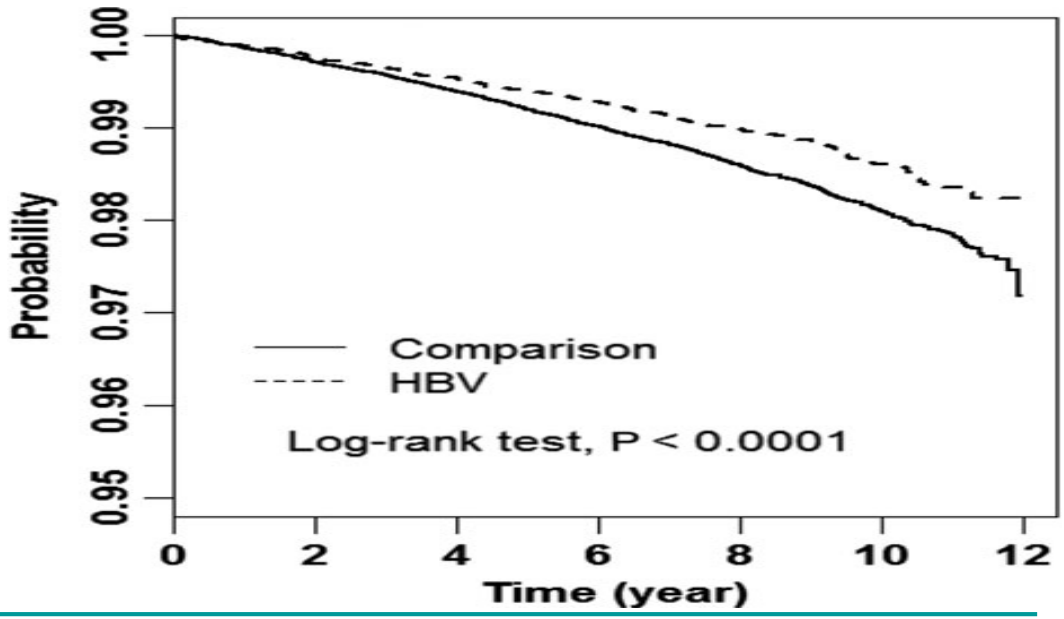
- Taiwan national insurance claims data
- 22,303 patients with HBV
- 89,212 randomly selected sex- and age-matched controls

- HBV group : lower AIS risk (adjusted hazard ratio [aHR] = 0.77, 95% confidence interval [CI]: 0.66–0.89)

Table 2 Incidence rate and hazard ratio for acute ischemic stroke and acute ischemic stroke-associated risk factor

	Event	P-Y	IR	Crude HR (95% CI)	Adjusted HR# (95% CI)
HBV infection					
No	1258	688,596	1.83	1.00	1.00
Yes	232	172,483	1.34	0.73 (0.64–0.84)***	0.77 (0.66–0.89)***

****P* < 0.001.



Tseng et al.: Association of hepatitis B virus infection with decreased ischemic stroke. Acta Neurol Scand.(2016)

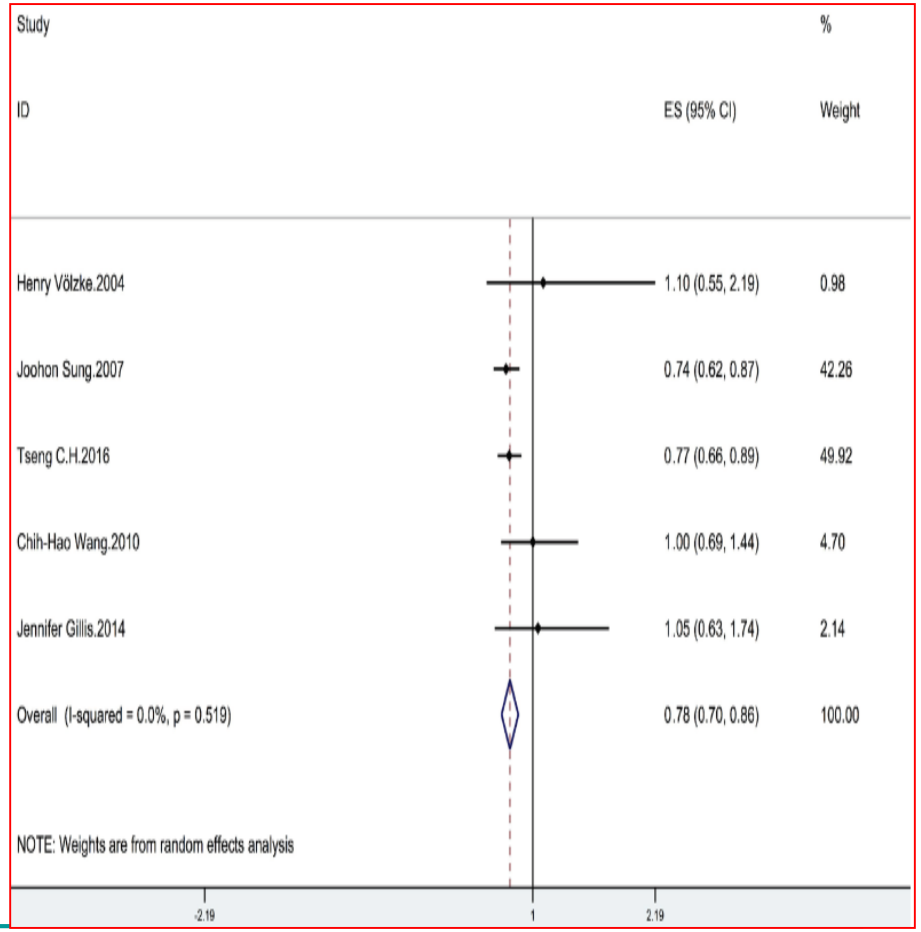
www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 35), pp: 59658-59665

Meta-Analysis

Hepatitis B virus infection and decreased risk of stroke: a meta-analysis

- Meta-analysis:5 articles
- *834,75* HBV-infected patients
- *593,949* uninfected controls
- Risk of stroke :
- Significantly lower in HBV+ (summary OR = 0.78; 95% CI = 0.70–0.86; I2 = 0%).
- However, this inverse relationship:
  - only observed in cohort studies (OR = 0.77; 95% CI = 0.69–0.86)
  - rather than cross-sectional study (OR = 1.10; 95% CI = 0.55–2.19)

HBV infection= associated with lower risk of developing stroke

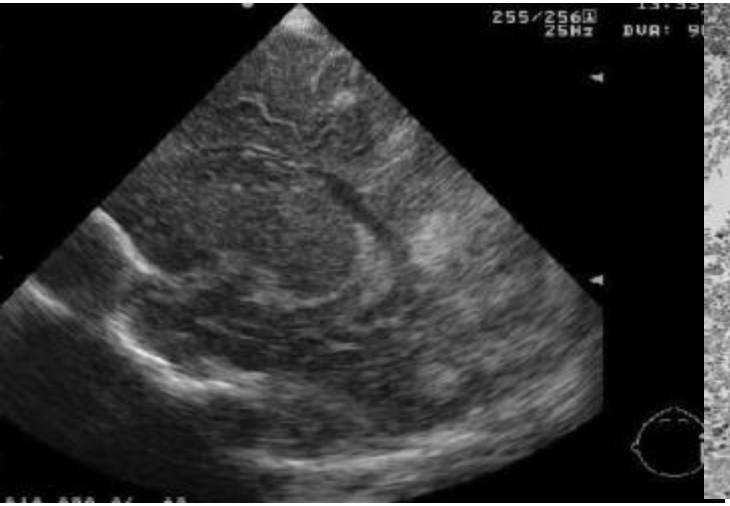


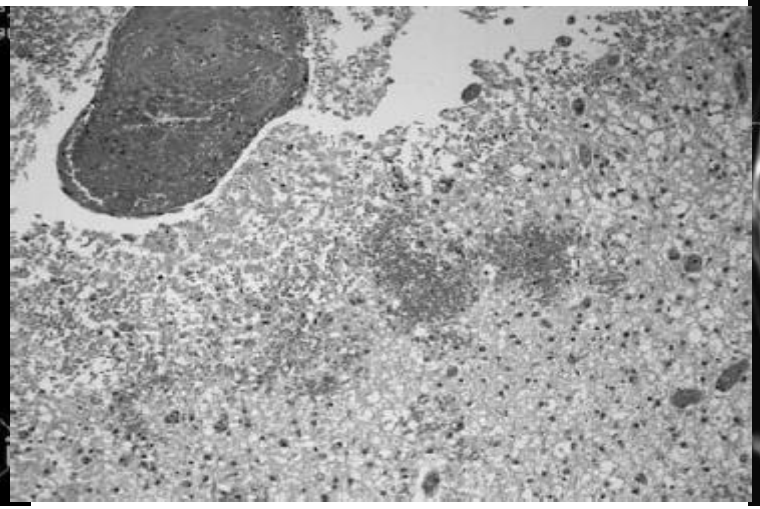
Wang et al.: **Hepatitis B virus infection and decreased risk of stroke: a meta-analysis.** ***Oncotarget. 2017)***

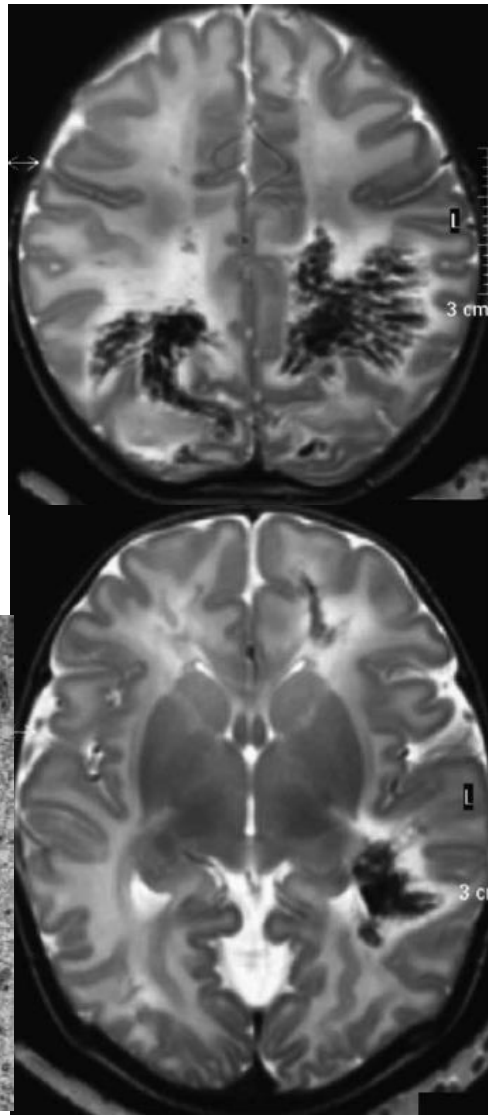
Fetal stroke and congenital parvovirus B19 infection complicated by activated protein C resistance

Newborn infant, parvovirus B19+factor V Leiden mutation

- Human parvovirus B19 (B19V) is a small, single stranded DNA virus
- 35- 45% of women in reproductive age: susceptible to infection
- 3rd trimester: severe complications, i.e. fetal death
- associated with vasculitis+ pathological changes in CNS ➔ stroke
  - ***Inflammatory cytokines*** IL-6, TNF-a, IFN-g, MCP-1 and GM-CSF
  - Cerebral ***vasculitis***
  - ***narrowing of cerebral arteries*** on MR angiography







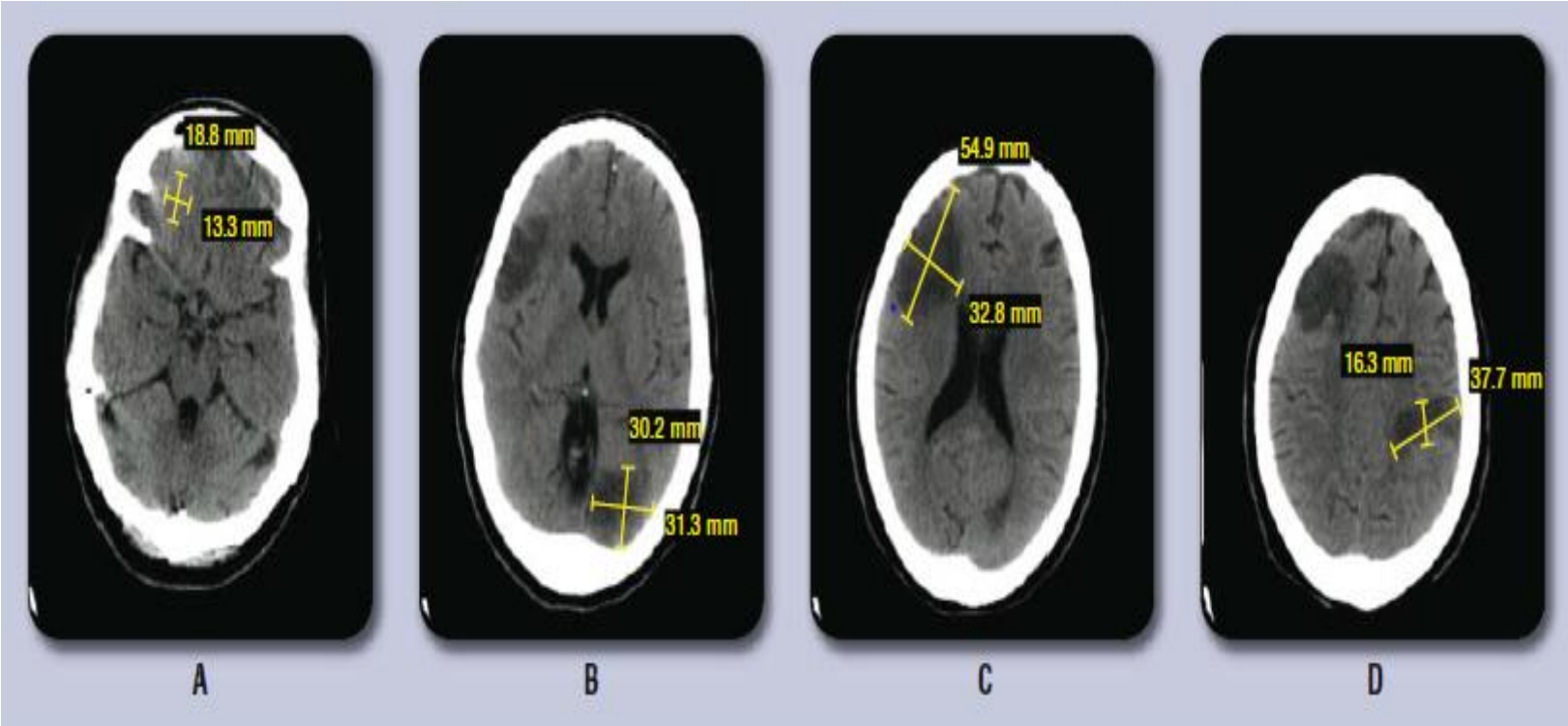
De Haan et al.: **Fetal stroke and congenital parvovirus B19 infection complicated by activated protein Cresistance.** ***Acta Paediatr. (2006)***

Feature

Stroke as a Complication of H1N1 Influenza Infection: A Case Study

Kirsten Krummel-McCracken, RN, MSN, CNRN

- This case study describes the clinical course of a patient who had multiple strokes due to disseminated intravascular coagulation triggered by H1N1 infection



Krummel-McCracken et al.: **Stroke as a complication of H1N1 influenza infection: a case study. Crit Care Nurse.** ***(2011)***

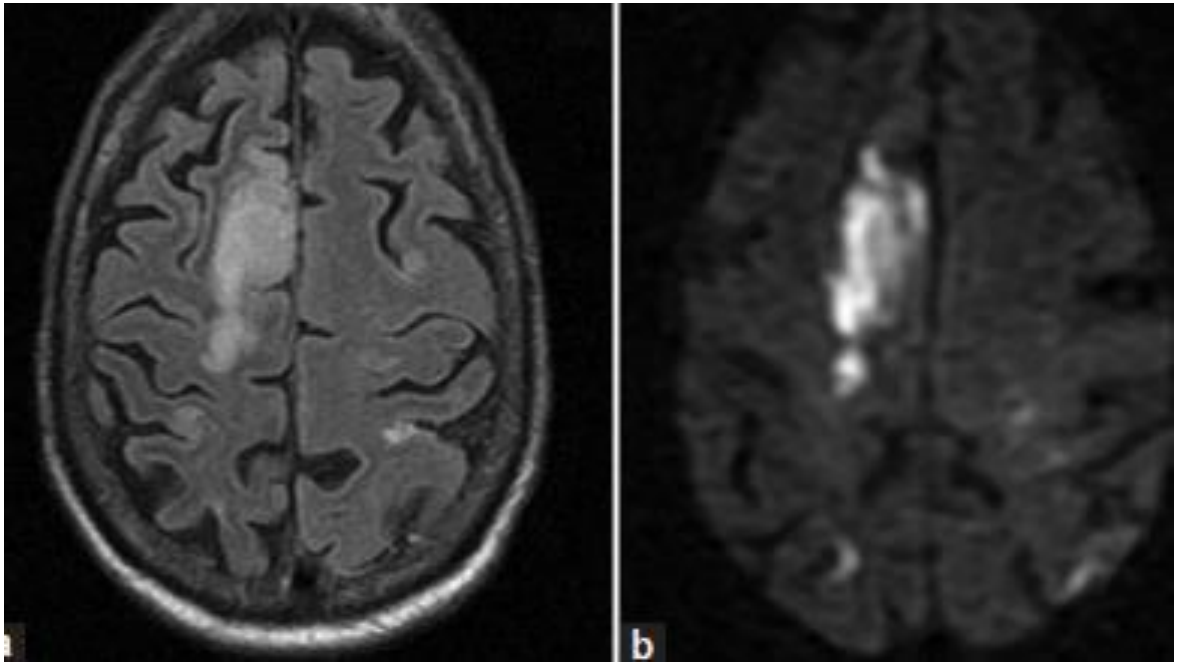
Emerging viral infections associated with stroke

- Viral hemorrhagic fevers
- Japanese encephalitis
- Dengue
- West Nile virus

Carod-Artal FJ. Stroke in central nervous system infections. Ann Indian Acad Neurol (2008)

Dengue infection presenting as ischemic stroke: An uncommon neurological manifestation

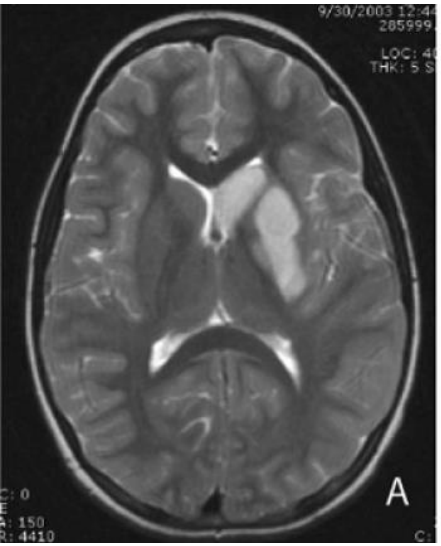
- 68-year-old man; no personal history, moderate grade, continuous fever of 15 days duration; sudden onset weakness of left half of body with facial asymmetry
- Hemogram: leukocytosis + thrombocytopenia
- Non-structural protein 1 antigen for dengue was positive in blood.
- CSF: 15 cells (all lymphocytes) + ELISA test was positive for dengue specific immunoglobulin M antibody
- Stroke + Dengue: 3 case reports: meningovasculitis; transient hypercoagulable state

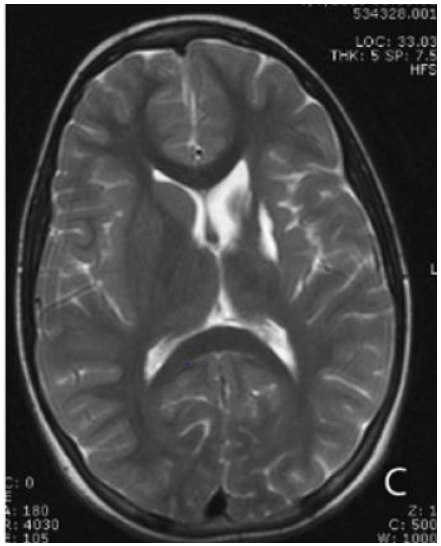


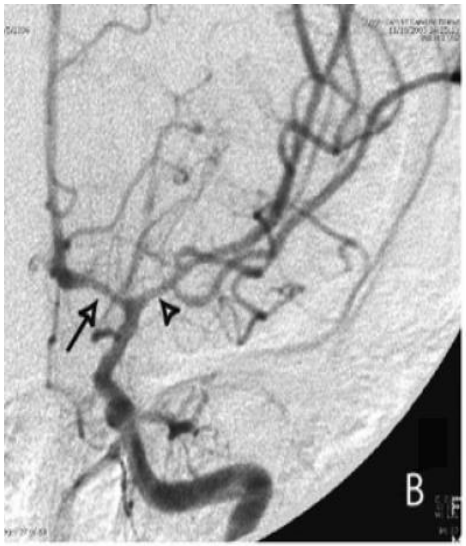
Terma et al.: **Dengue infection presenting as ischemic stroke: An uncommon neurological manifestation*. Neurol India. (2013)***

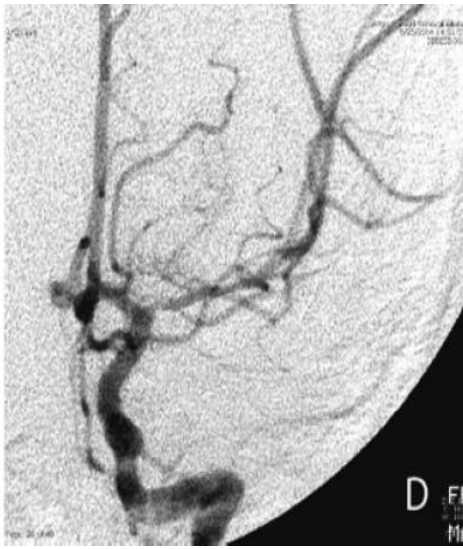
Stroke Associated With Central Nervous System Vasculitis After West Nile Virus Infection

- 9-year-old girl , intermittent right arm and leg weakness over 3 days in early autumn, On the day of hospital admission, she fell from her bicycle and developed transient aphasia
- Pertinent social history included environmental exposure to mosquitoes and the diagnosis of mild West Nile virus infection in her grandfather 2 weeks prior to her illness.









West Nile Virus vasculitis

Alexander et al.: **Stroke associated with central nervous system vasculitis after West Nile virus infection.** ***J Child Neurol. (2006)***

West Nile Virus (WNV) vasculitis and stroke

- Isolated vasculitis and chronic perivascular inflammation involving the parenchymal vessels in the autopsies of fatal WNVdisease in humans
- Occlusive retinal vasculitis in a single human with WNV infection
- Severe renal lymphoplasmacytic vasculitis with focal cerebral cortex gliosis in the autopsy of an arctic wolf with WNVdisease
- Viral antigens in perivascular tissue in patients with other forms of viral central nervous system vasculitis, such as varicella-zoster virus–associated vasculitis

Carod-Artal FJ. Stroke in central nervous system infections. Ann Indian Acad Neurol (2008)

Parasitic Infections and Stroke

Parasitic infections implicated in stroke

Parasitic infections		
Trypanosoma cruzi	Chagas disease, Heart failure	Cardioembolism
Taenia solium	Neurocysticercosis	Arachnoiditis/small artery vasculitis; direct compression of large arteries by cysts
Plasmodium falciparum	Cerebral malaria	Occlusion of cerebral arteries by infected erythrocytes
Echinococcus granulosis	Cardiac hydatidosis; cerebral cystic echinococcosis	Cardioembolism; arterial compression from cerebral cysts
Schistosoma mansoni	Schistosomiasis	Microembolic borderzone infarction
Toxocara canis	Toxocariasis	Arachnoiditis; vasculitis
Spirometra species (tapeworm)	Cerebral sparganosis	Vasculitis
Trichinella spiralis	Neurotrichinelliasis	Microinfarction due to direct obstruction of small vessels with larvae; vasculitis

Miller et al, Infection and Stroke: an Update on Recent Progress. Curr Neurol Neurosci Rep (20015

Cerebral malaria

- Malaria:
  - 400 to 500 million cases of malaria around the world:
    - 30% are located in Asia
    - Major remainder in Africa
  - 0.5 to 2.5 million deaths each year

- Cerebral malaria (CM):
  - Most severe complication of malaria
  - Acute and diffuse encephalopathy associated with Plasmodium falciparum infection
  - ***10% of strokes in endemic regions***

Moghtaderi A.. Infective Causes of Stroke in Tropical Regions. Iran J Med Sci September (2012)

Cerebral malaria

- Pathological findings of cerebral malaria include:
  - Diffuse cerebral ***edema***
  - Perivascular ring ***hemorrhages***
  - ***White matter*** necrosis
  - Parenchyma ***petechial*** hemorrhages
  - ***Occlusion*** of brain vessels
  - ***Sequestration of infected erythrocytes*** in cortical and perforating arteries

Carod-Artal FJ. Stroke in central nervous system infections. Ann Indian Acad Neurol (2008)

Cerebral malaria

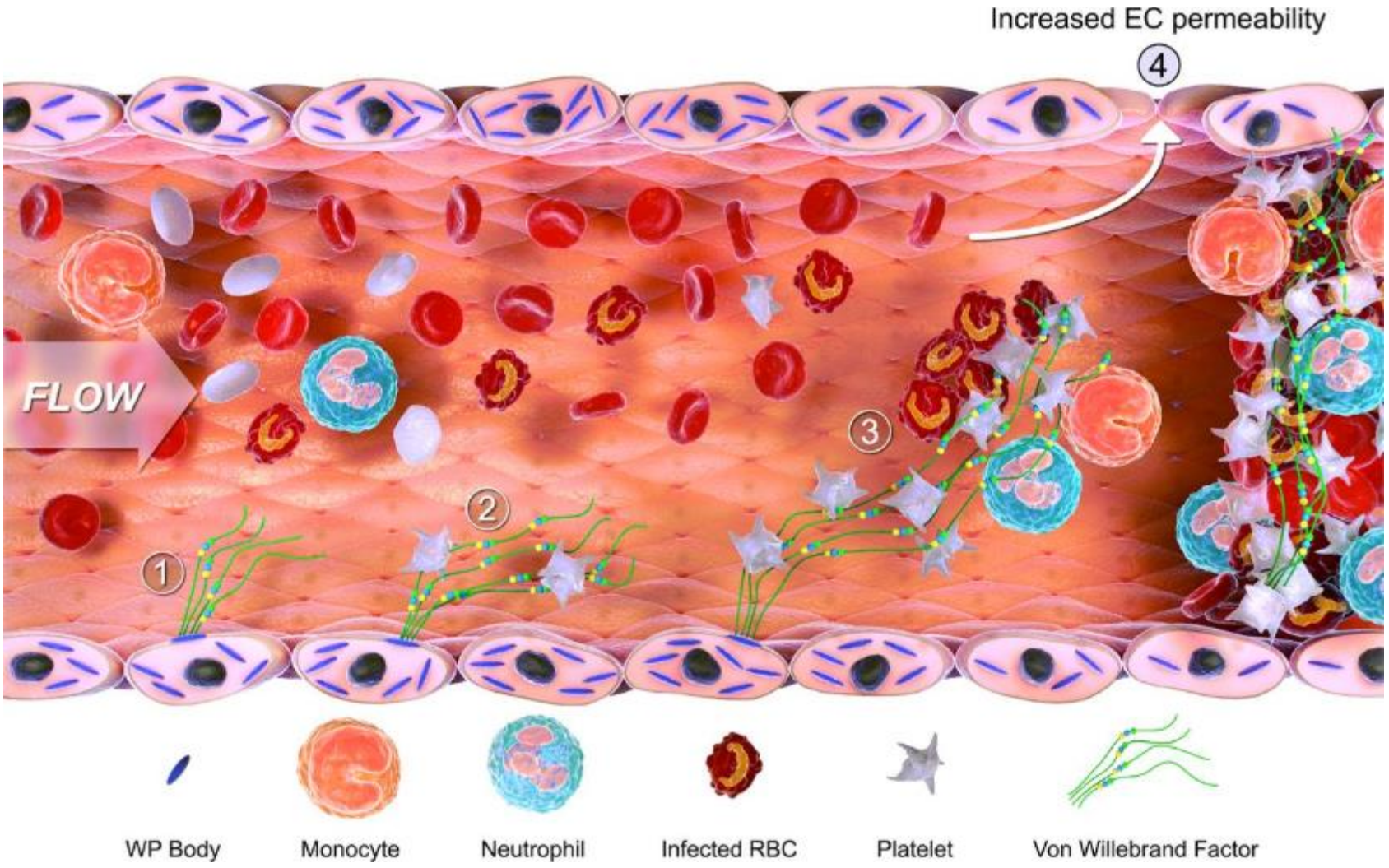


Image from: O'Regan N et al. A novel role for von Willebrand factor in the pathogenesis of experimental cerebral malaria. Blood (2016)

Cerebral malaria

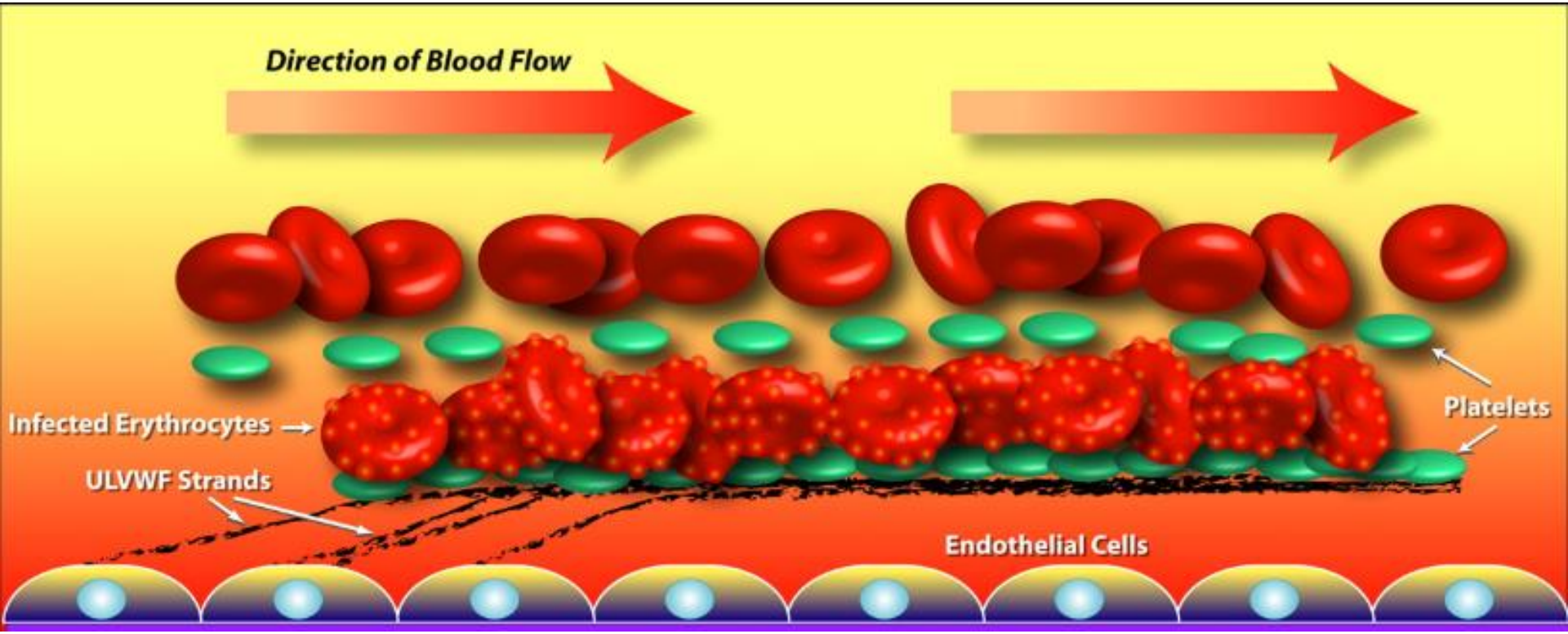


Image from: López JA et al. Malignant malaria and microangiopathies: merging mechanisms. Blood (2010)

Cerebral malaria

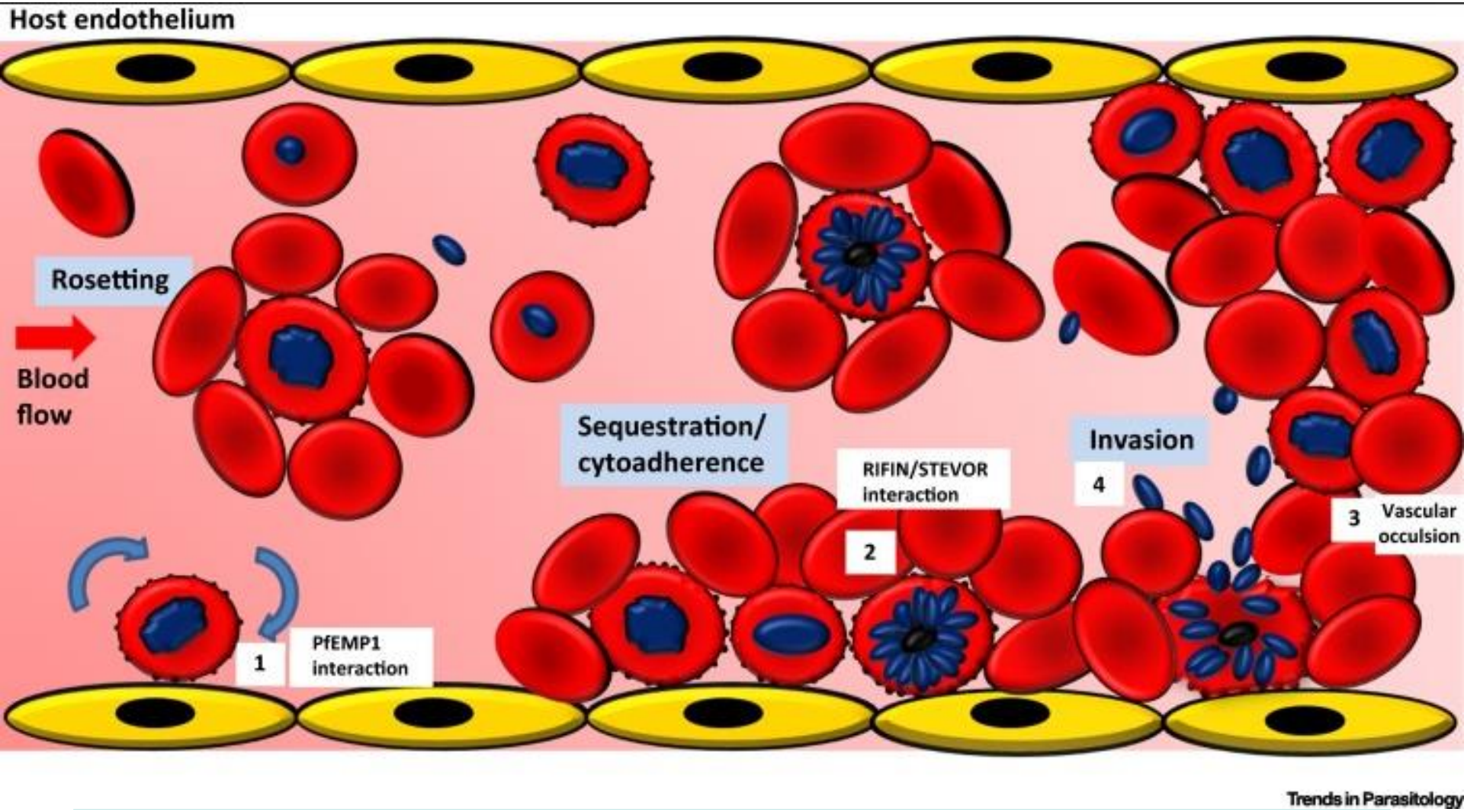
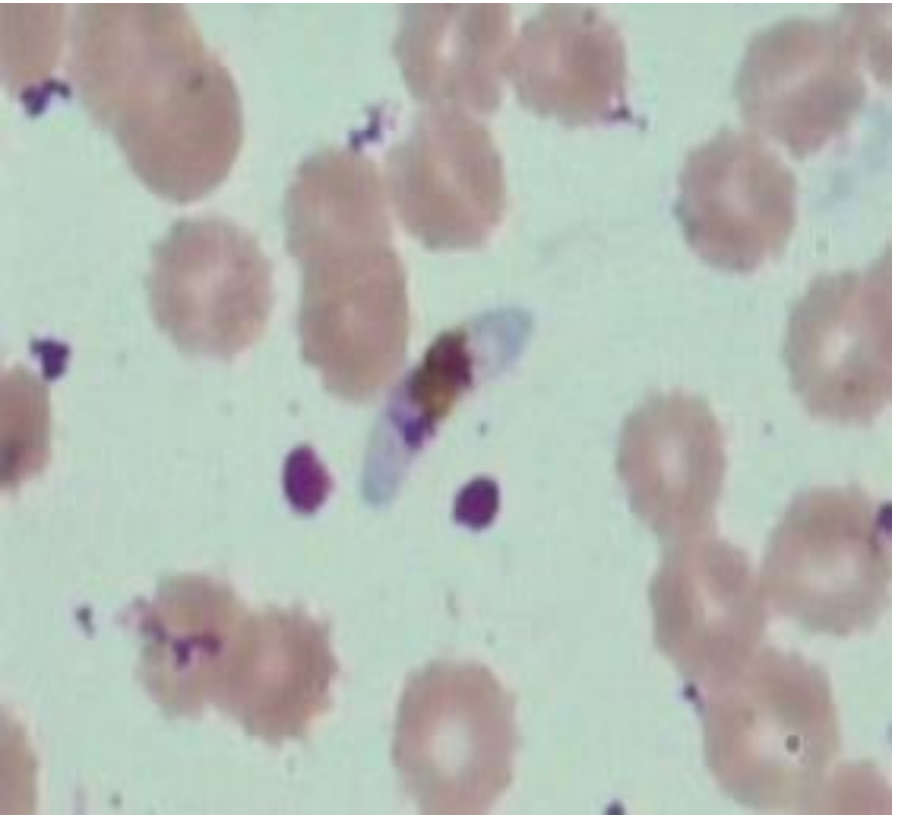
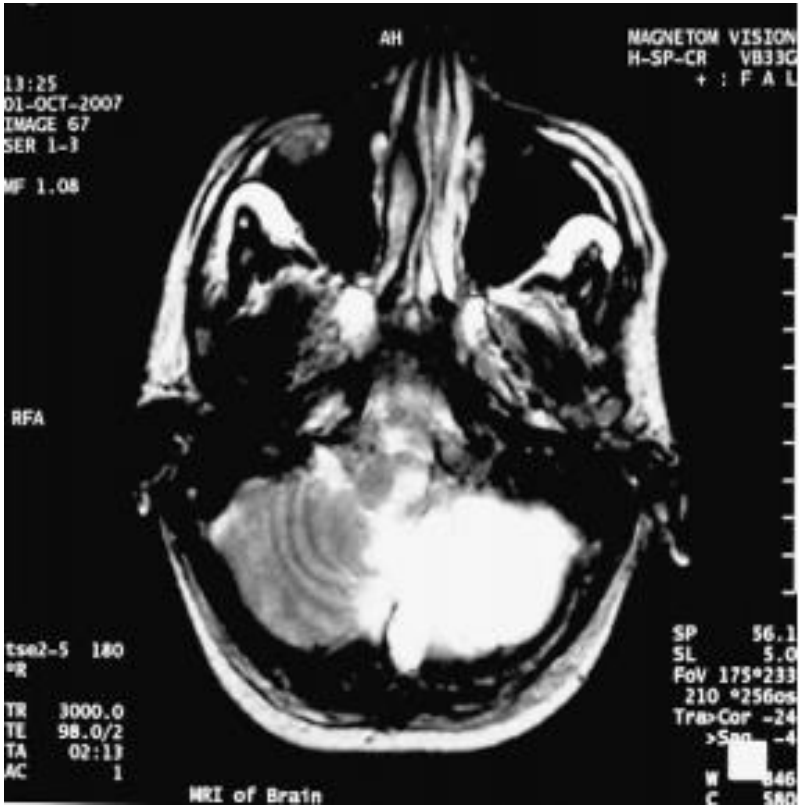


Image from: Yam XY et al. Three Is a Crowd – New Insights into Rosetting in Plasmodium falciparum. Trends Parasitol.(2017)

CASE REPORT

Plasmodium falciparum malaria presenting with vertebrobasilar stroke





Kaushik et al. Plasmodium falciparum malaria presenting with vertebrobasilar stroke. Int J Infect Dis. (2009)

Child's Nerv Syst (1998) 14:697–699

BRIEF COMMUNICATION

Mehmet Turgut
Kemal Bayülkem

Cerebrovascular occlusive disease: hydatidosis

Table 1 Summary of six patients with multiple metastatic hydatid cysts caused by embolization from the rupture of a fertile intracardiac hydatid cyst (*NS* not stated, *CT* computed tomography, *MRI* magnetic resonance imaging, *IICP* increased intracranial pressure, *EC* echocardiography)

Reference	Code of country	Year	Age of patient (years)	Sex	Type of rupture	No. of cysts	Presenting symptoms	No. of operations	Diagnostic procedures	Side of cysts	Outcome
19	ES	1982	37	Male	Surgical	19	Left hemiparesis	2	CT	Right	NS
15	BG	1987	18	Male	Spontaneous	NS	Epileptic seizure	NS	CT, EC	NS	Normal in 6 month
9	SU	1990	11	Female	Spontaneous	8	Right hemiparesis	4	MRI	Left	NS
1	AUS	1991	7	Male	Traumatic	NS	Epileptic seizure	0	Necropsy	Right and left	Exitus
18	TR	1994	19	Female	Spontaneous	1	Right hemiparesis and speech disorder	NS	CT, EC	Left	NS
7	TR	1997	7	Female	Spontaneous	32	IICP	9	MRI, EC	Right and left during a 2-years follow-up	No recurrence

Turgut et al. Cerebrovascular occlusive disease: hydatidosis. Childs Nerv Syst. (1998)

Neurocysticercosis

- Stroke can occur in subarachnoid neurocysticercosis:
  - endarteritis of small penetrating arteries

  - deep lacunar infarctions

Carod-Artal FJ. Stroke in central nervous system infections. Ann Indian Acad Neurol (2008)

Trypanosomosis

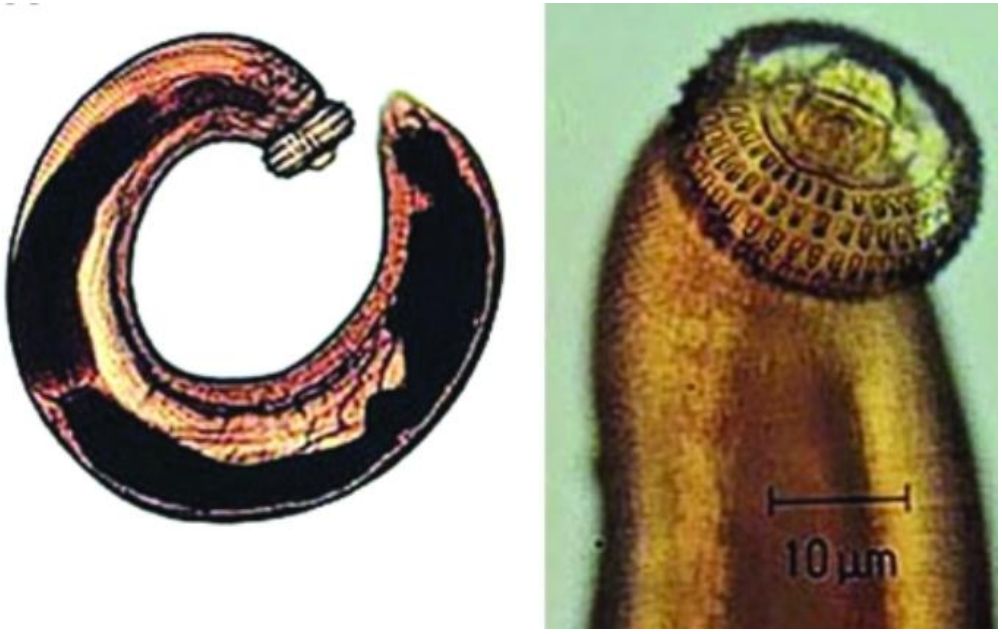
- Several diseases in vertebrates caused by parasitic protozoan trypanosomes of the genus Trypanosoma

- American trypanosomiasis: predisposition to cardioembolism due to:
  - Cardiac arrhythmias
  - Congestive heart failure
  - Apical aneurysm
  - Mural thrombus

Carod-Artal FJ. Stroke in central nervous system infections. Ann Indian Acad Neurol (2008)

Gnathostomiasis

- Due to Gnathostoma spinigerum infestation
- Parasitic nematode
- Cause of **hemorrhagic stroke** in Asia



Reproduced with the permission of Pichart Uparanukraw, Department of Parasitology, Faculty of Medicine, Chiang Mai University, Thailand.

Moore et al. Gnathostomiasis: an emerging imported disease. Ann Indian Emerg Infect Dis. (2003)

Carod-Artal FJ. Stroke in central nervous system infections. Ann Indian Acad Neurol (2008)

Fungal Infections and Stroke

Fungal infections implicated in stroke

Fungal infections		
Cryptococcus	Systemic and CNS infections (usually immunocompromised)	Meningitis; vasculitis
Aspergillus	Systemic and CNS infections	Arteritis, vasculopathy
Mucorales (including *Rhizopus*, *Mucor*, etc.)	Mucormycosis	Vascular invasion of fungus, aneurysmal dilatation, vascular necrosis

Miller et al, Infection and Stroke: an Update on Recent Progress. Curr Neurol Neurosci Rep (20015

Cerebrovascular complications of mycosis

- Large vessel ***vasculitis***
- Direct vessel ***damage*** by invasion or ***embolization***
- Subarachnoid hemorrhage due to ***mycotic aneurysm rupture***

Carod-Artal FJ. Stroke in central nervous system infections. Ann Indian Acad Neurol (2008)

Acta Neurol Taiwan. 2009 Mar;18(1):30-3.

A flow chart proposed for early diagnosis of cryptococcal infection as a cause of stroke.

Kao CD[1], Liao KK.

An 82-year-old woman had a transient ischemic attack and **stroke** of the left middle cerebral artery syndrome that turned out to be attributed to cryptococcal meningoencephalitis (CM). An initial presentation of central nervous system **infection**, such as fever and headache, was absent. It was masked by chronic use of corticosteroids and immunosuppressants for her rheumatoid arthritis. The diagnosis was made by the clinical setting of **stroke**-in-evolution and progression of hydrocephalus on the second brain imaging study. In this case, we discuss the atypical presentation of CM in an immunosuppressed patient and offer a flow chart for early diagnosis, thus improving outcome and survival rates.

Kao et al, A flow chart proposed for early diagnosis of cryptococcal infection as a cause of stroke. Acta Neurol Taiwan. (2009)

Stroke+Fever?
First diagnosis?

Infective endocarditis (IE) +++++

Diagnostic and therapeutic EMERGENCY++++++

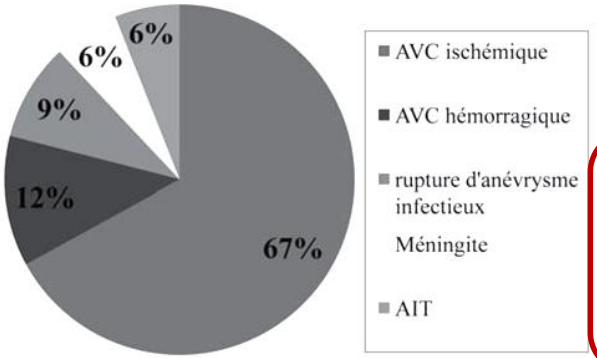
Derex L. Impact of stroke on therapeutic decision making in infective endocarditis. J Neurol. (2010)

Stroke and infective endocarditis

Neurological complications of infective endocarditis
[Frequency: 30-50%; Ushering: 40%; Mortality x3 (60%)]

Stroke

- **Ischemic**
- **Hemorrhagic**
- **Transient**
- **Silent**



Infectious complications

- **Infectious aneurysm**
- **Cerebral abcess**
- **Meningitis**

- Cerebral embolic Complications : **10-65%**

- ***Ischemic stroke due to septic embols***: Most frequent cerebral complications of infective endocarditis

Chirurgie Thoracique Cardio-Vasculaire - 2010 ; 15 : 97-103

E. Novy et al. / Médecine et maladies infectieuses 43 (2013) 443–450

Stroke and infective endocarditis

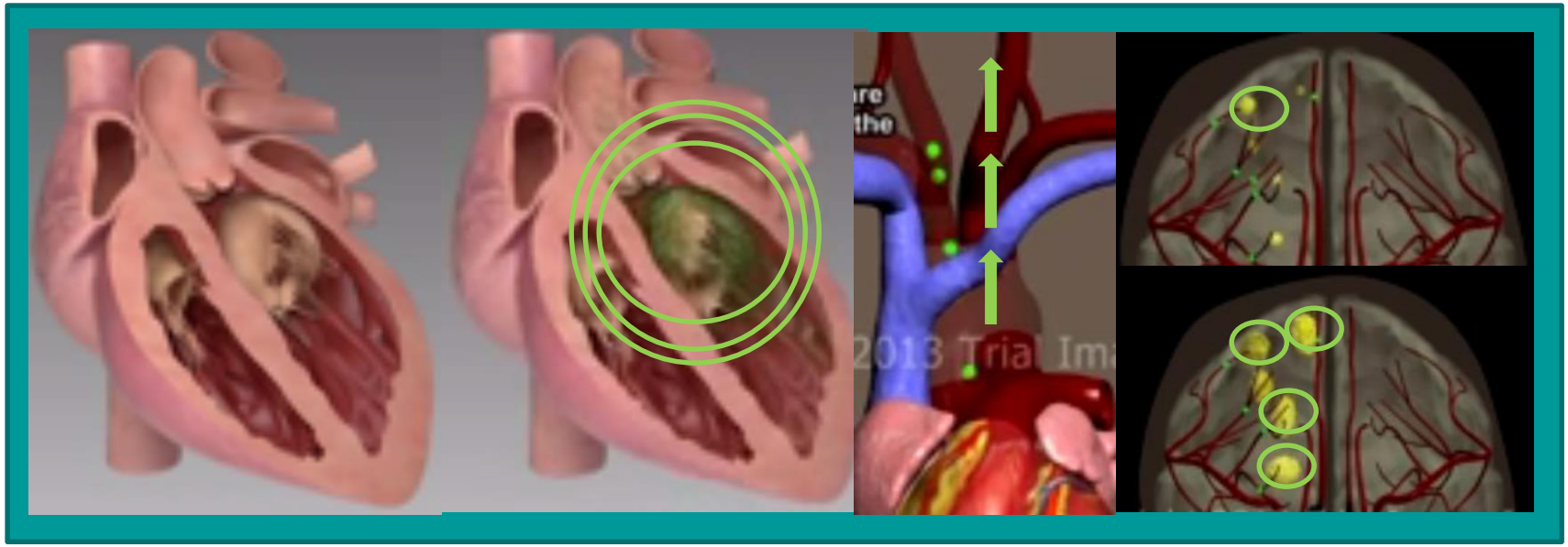
- Stroke complicates the outcome of left-sided IE in **20–40%** of cases, ushering: 47%
- Ischemic :2/3 (cardio-embolic: 100%)
- Associated with **poor outcome**
- Risk of stroke in IE:
  - Before initiation of antibiotherapy: **76%**
  - ↓↓↓ rapidly after initiation of effective **antimicrobial therapy**

Journal of Stroke and Cerebrovascular Diseases, Vol. 20, No. 1 (January-February), 2011: pp 1-9

Derex L. Impact of stroke on therapeutic decision making in infective endocarditis. J Neurol. (2010)

Mechanisme of Stroke in IE

- ***Embolisation*** of CNS by unstable valvular vegetations (Left+++)➔ Occlusion of cerebral arteries



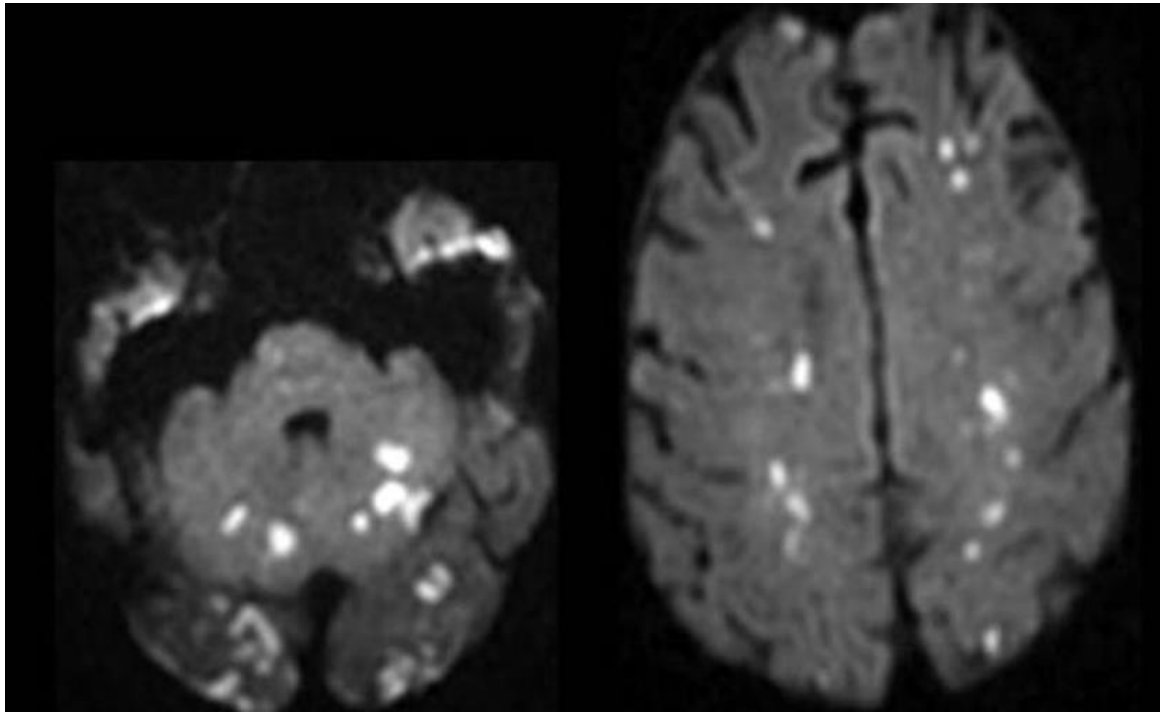
E. Novy et al. / Médecine et maladies infectieuses 43 (2013) 443–450
Journal of Stroke and Cerebrovascular Diseases, Vol. 20, No. 1 (January-February), 2011: pp 1-9

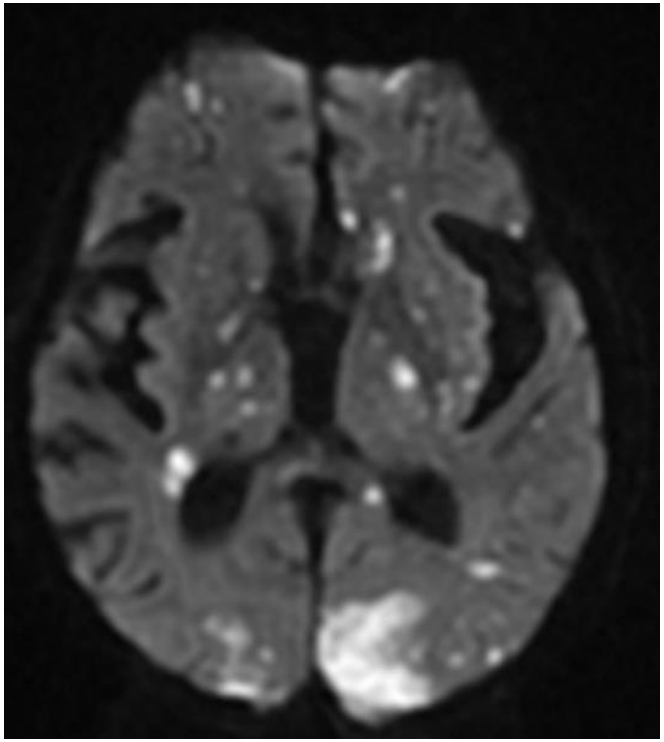
Imaging of Stroke in IE

- Infracts: (MRI> CT scan)
  - ***Multiple***, bilateral
  - ***Small*** size
  - ***Different Age***
  - Régions corticales et sous-corticales (Territoires jonctionnels)
  - Territoiry: ***Middle cerebral artery***+++
  - Association ***other neurological complications*** (cerebral hemrrhage, mycotic aneurysm, cerebral abcess)

  T2, Diffusion*

E. Novy et al. / Médecine et maladies infectieuses 43 (2013) 443–450



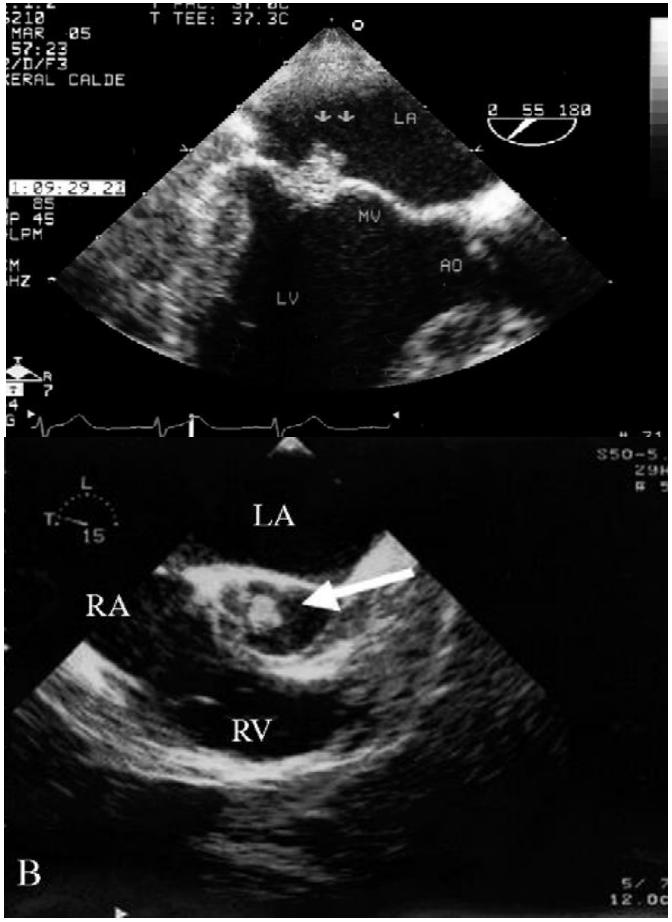


Sonneville *et al. Annals of Intensive Care* 2011, **1**:10

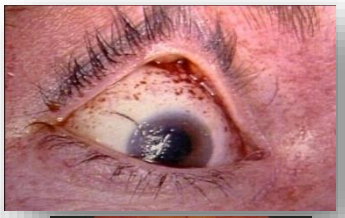
E. Novy et al. / Médecine et maladies infectieuses 43 (2013) 443–450

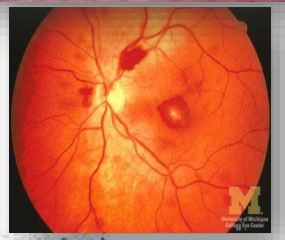
Cardiac manifestations of IE

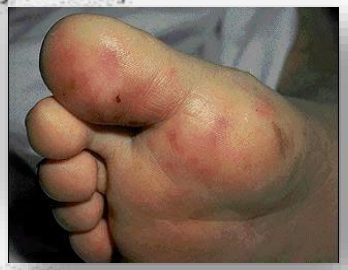
- Heart murmur+++++
- Systematic heart ausculatation + ECG
- If normal: diagnosis NOT excluded
- TTE and TOE++++
- Vegetations (TOE>>>TTE)

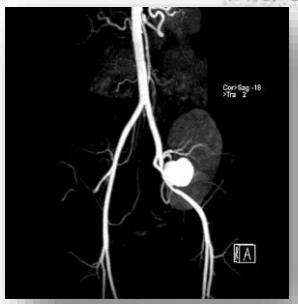


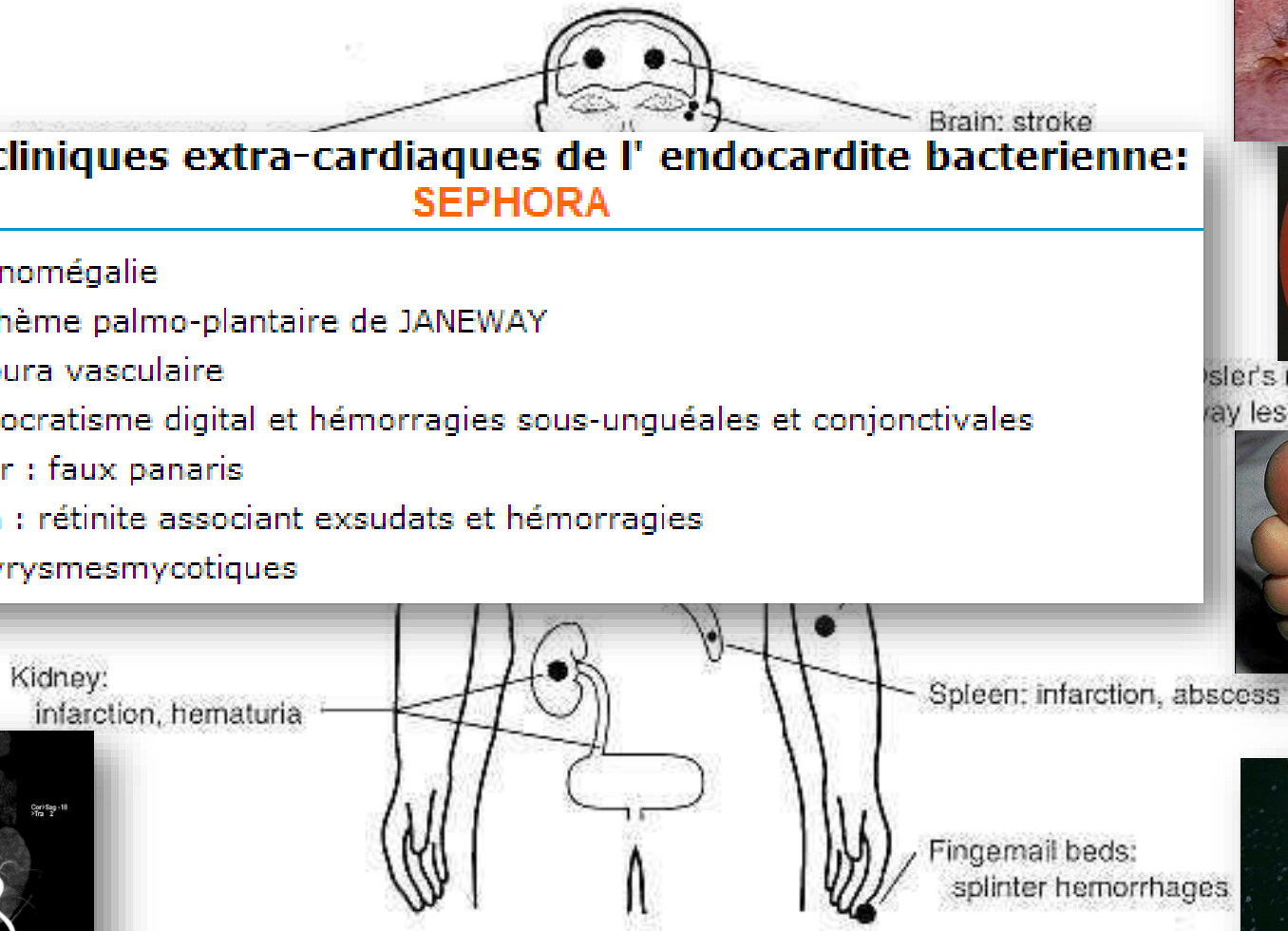
Systemic manifestations of IE









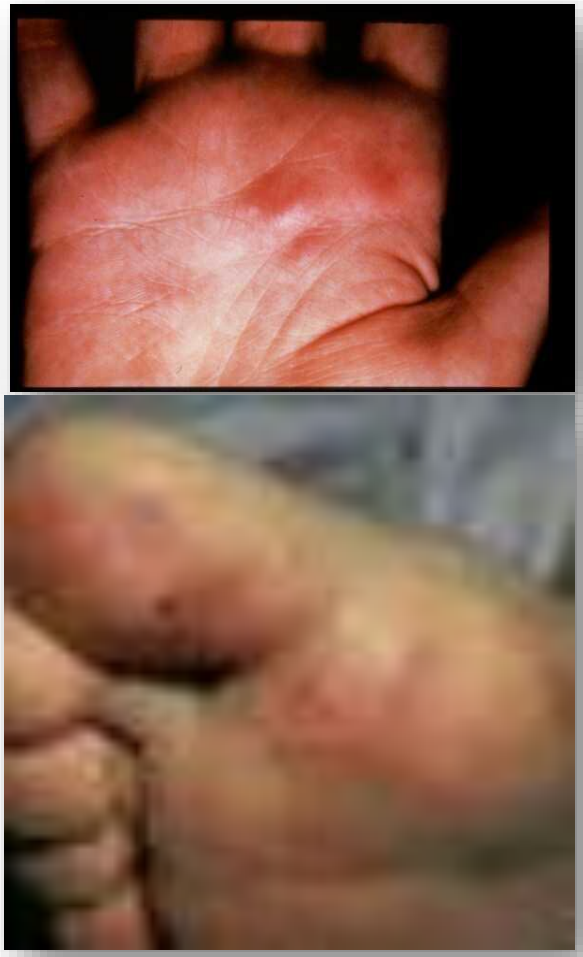


Signes cliniques extra-cardiaques de l' endocardite bacterienne:
SEPHORA

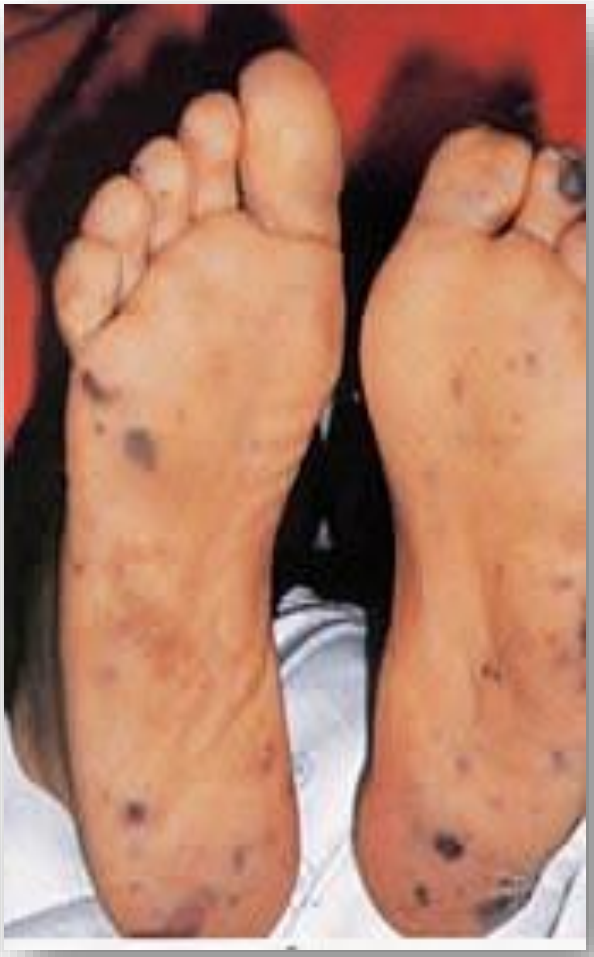
- **S**plénomégalie
- **E**rythème palmo-plantaire de JANEWAY
- **P**urpura vasculaire
- **H**ippocratisme digital et hémorragies sous-unguéales et conjonctivales
- **O**sler : faux panaris
- **R**oth : rétinite associant exsudats et hémorragies
- **A**névrysmesmycotiques

)sler's nodes)
vay lesions)

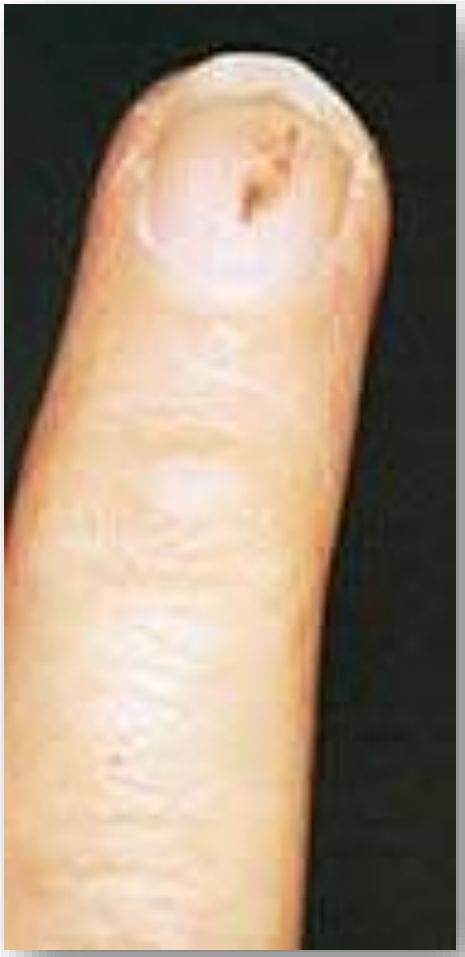
Stroke and infective endocarditis



Osler's Nodes



Janeway Lesions



Splinter Hemorrhages

When the heart rules the head: ischaemic stroke and intracerebral haemorrhage complicating infective endocarditis

Table 1 Clinical and laboratory findings and their prevalence in 2781 patients fulfilling the Duke criteria for infective endocarditis (modified from Klein *et al*[4])

Finding	Per cent of patients
Fever above 38°C	96
Splinter haemorrhages	8
Osler nodes	3
Janeway lesions	5
Roth spots	2
Vascular embolic event	17
Conjunctival haemorrhage	5
Splenomegaly	11
New cardiac murmur	48
Worsening of old cardiac murmur	20
Elevated erythrocyte sedimentation rate	61
Elevated serum C reactive protein	62
Elevated rheumatoid factor	5
Haematuria	26

Journal of Stroke and Cerebrovascular Diseases, Vol. 20, No. 1 (January-February), 2011: pp 1-9

Jiad E et al. When the heart rules the head: ischaemic stroke and intracerebral haemorrhage complicating infective endocarditis. Pract Neurol. (2017)

Stroke and infective endocarditis

- Hemoculture+++
- Biological inflammatory tests
- Imaging

Journal of Stroke and Cerebrovascular Diseases, Vol. 20, No. 1 (January-February), 2011: pp 1-9

Derex L. Impact of stroke on therapeutic decision making in infective endocarditis. J Neurol. (2010)

Stroke and IE: Prognosis

- Stroke in IE: independent predective factor of mortality
- Death:
  - 35% during hospitalization
  - 52% at 1 year
- Other predective independent factors of mortality:
  - Symptomatic stroke
  - Consciousness disorders
  - mechanical valvular prosthesis

Journal of Stroke and Cerebrovascular Diseases, Vol. 20, No. 1 (January-February), 2011: pp 1-9

Derex L. Impact of stroke on therapeutic decision making in infective endocarditis. J Neurol. (2010)

Septic cerebral venous thrombosis

Review Article

Infection related cerebral venous thrombosis

Suleiman Kojan, Mohammed Al-Jumah
Medicine department, King Abdulaziz Medical City of National Guard, Riyadh, Saudi Arabia.

- Septic sinus thrombosis:
  - potentially fatal disorder if unrecognized
  - In the past:
    - infection= main cause of cerebral venous thrombosis (CVT)
    - associated with a very high rate of morbidity and mortality
  - since introduction + widespread use of antibiotics
    - ➔ ↓↓↓incidence of septic sinus thrombosis (including cavernous sinuses)
  - Nowadays: septic thrombosis
    - extremely rare
    - often misdiagnosed
    - Delayed treatment
  - High suspicion: essential in early recognition and treatment

Kojan S et al. Infection related cerebral venous thrombosis. J Pak Med Assoc.(2006)

A Multicenter Study of 1144 Patients with Cerebral Venous Thrombosis: The VENOST Study

	Age group						
	18-36		37-50		51+		
	n	%	n	%	n	%	*P*
Gynecological causes							
Oral contraceptive use	50	13.8	49	17.1	9	7.0	.022
Pregnancy	55	15.2	19	6.6	0	.0	<.001
Puerperium	108	29.8	31	10.8	3	2.3	<.001
Infections							
Paracranial (focal)	27	5.1	23	6.1	20	8.7	.830
Systemic	10	1.9	9	2.4	4	1.7	.165

Table 5. *Etiological comparisons among studies*

	VENOST study	Dentali et al[14]	Ferro et al[7]	Wasay et al[11]	Algahtani et al[19]	Khealani et al[8]	English et al[27]	Terazzi et al[20]	Sidhom et al[17]	Souirti et al[15]
Number of cases	1144	706	624	182	111	109	78	48	41.0	30
Gynecological causes							68			
Oral contraceptive	13.9	39.4	54.3	NA	20	12	45	47.4	11.0	NA
Pregnancy	9.5	7.8	6.3	7	12.6	NA	NA	NA	9.0	NA
Puerperium	18.3		13.8		NA	31	23	5.3	29.0	33
Infections	8.1	8.3	12.3	NA	9.9	18	16	6.3	34.0	26
History of VTE	5.9	7.6	NA	NA	NA	NA	5	16.7	NA	NA
Malignancy	5.2	7.4	7.4	7	9.9	4.6	13	6.3	7.0	NA
Prothrombotic conditions	26.4	41.1	34.1	21	19.8	5	29	38.5	56.0	NA
Behçet's disease	9.4	NA	1	1	.9	.9	NA	NA	5.0	7
Iron deficiency	3.2	NA	9.2	NA	NA	NA	NA	NA	10.0	NA
Idiopathic	24.6	44.2	12.5	43	NA	NA	16	17	NA	23
SLE	1.4	NA	1	4	NA	NA	NA	NA	5.0	NA

Abbreviations: NA, not available; SLE, systemic lupus erythematosus; VTE, venous thromboembolism.

Duman T et al. Infection related cerebral venous thrombosis. A Multicenter Study of 1144 Patients with Cerebral Venous Thrombosis: The VENOST Study. J Stroke Cerebrovasc Dis. (2017)

Pathophysiology of septic CVT

- No valves in dural sinuses+ cerebral and emissary veins blood flows in either direction according to pressure gradients in the vascular system

- ➔ vulnerability of venous systems to septic thrombosis resulting from **spreading of infection from adjacent locations**

- All cerebral venous system can be affected but the most vulnerable:
  - cavernous sinus > lateral sinus > sagital sinus

Kojan S et al. Infection related cerebral venous thrombosis. J Pak Med Assoc.(2006)

Spreading of infection in septic CVT

- Spreading from adjacent structures:
  - In cavernous sinus thrombophlebitis:
    - From sphenoid sinuses
    - From ethmoid sinuses
  - In lateral sinus thrombophlebitis:
    - From mastoid

- Spreading from other sites:
  - Face, nose, tonsils, soft palate, teeth and ears ➔ thrombophlebitis in the cavernous and lateral sinuses +other sinuses
  - Orbital infection➔ cavernous sinus thrombosis (rarely)

Kojan S et al. Infection related cerebral venous thrombosis. J Pak Med Assoc.(2006)

Pathophysiology of septic CVT

- Infection= trigger of thrombosis
  - Directly by causing septic thrombosis
  - Indirectly by precipitating thrombosis in people with prothrombotic illness
    - CVT in children = multifactorial disease (prothrombotic risk factors + underlying clinical condition (infection))
    - Systemic infection+ prothrombotic conditions ➔ CVT

Kojan S et al. Infection related cerebral venous thrombosis. J Pak Med Assoc.(2006)

Septic sinus thrombosis and meningitis

- **Pneumococcal** meningitis++++
- Other causes:
  - Coccidioidomycosis
  - Cytomegalovirus
  - Herpes simplex
  - Measles

Kojan S et al. Infection related cerebral venous thrombosis. J Pak Med Assoc.(2006)

Clinical presentations of septic CVT

- Patients with septic CVT: generally, ***much sicker*** than those with non-septic CVT:
  - Very sick/toxic/***febrile***
  - Focal symptoms and signs (depending on site of CVT)
  - High intracranial pressure syndrome

Kojan S et al. Infection related cerebral venous thrombosis. J Pak Med Assoc.(2006)

Initial work up in septic CVT

- Complete blood count
- Blood cultures
- X-ray films of paranasal sinuses
- Enhanced brain MRI and/or Head CT scanning
- Cerebrospinal fluid (CSF) analysis +culture (often abnormal: high granulocyte count + elevated protein)

Kojan S et al. Infection related cerebral venous thrombosis. J Pak Med Assoc.(2006)

Management of septic CVT

- Early management:
  - **IV antibiotics**
  - Early **surgical drainage** of the primary site of infection (usually air sinuses /mastoid regions)

Improvement of mortality and morbidity

- **Anticoagulation**: IV heparin infusion
- **Corticosteroids**

uncertain benefit/ favorable response

Kojan S et al. Infection related cerebral venous thrombosis. J Pak Med Assoc.(2006)

Arq Neuropsiquiatr 2005;63(3-B):852-854

TUBERCULOSIS

An uncommon cause of cerebral venous thrombosis?

- A 38 years old man
- Abrupt right hemiparestesis, and hemiparesis

- Same period: diagnosis of *pulmonary tuberculosis* (chronic cough, fever, weight loss and acidfast bacilli on smear of sputum) + *testicle tuberculosis* (scrotal ultrasound that showed an inflammatory m a s s of testicle and epididymis)

- CSF study:
  - 178cells (81% lymphocytes, 11% monocytes, 8% neutrophils)
  - Protein 132 mg/dl
  - Glucose 30 mg/dl
  - Adenosine deaminase (ADA) 11.1

  ➔*tuberculous meningitis*

Fiorot Júnior JA et al. Tuberculosis: an uncommon cause of cerebral venous thrombosis? Arq Neuropsiquiatr.(2005)

Arq Neuropsiquiatr 2005;63(3-B):852-854

TUBERCULOSIS

An uncommon cause of cerebral venous thrombosis?

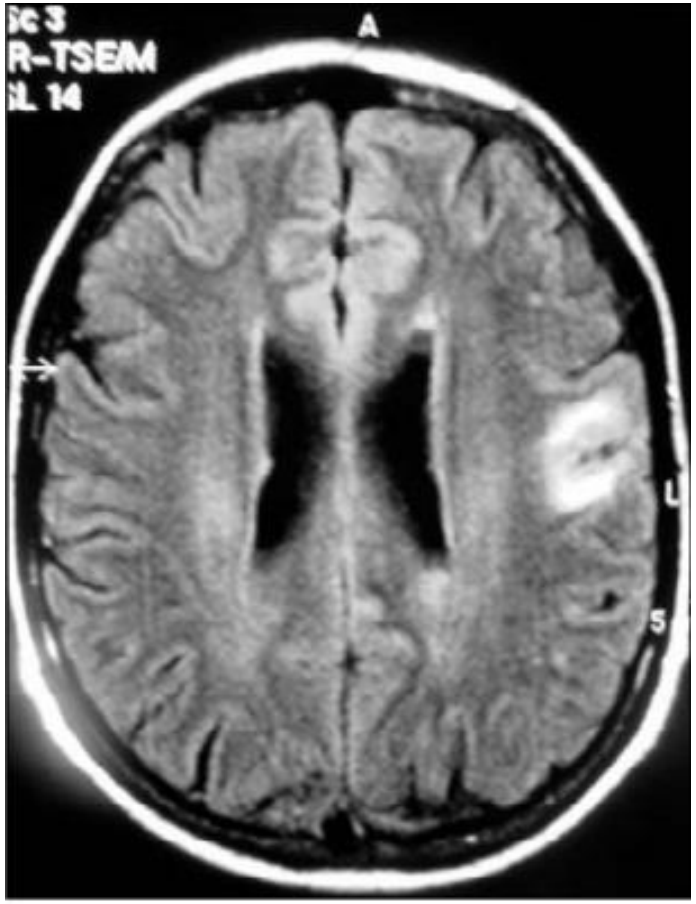


Fig 1. FLAIR axial image with hypersignal in the left parietal area.

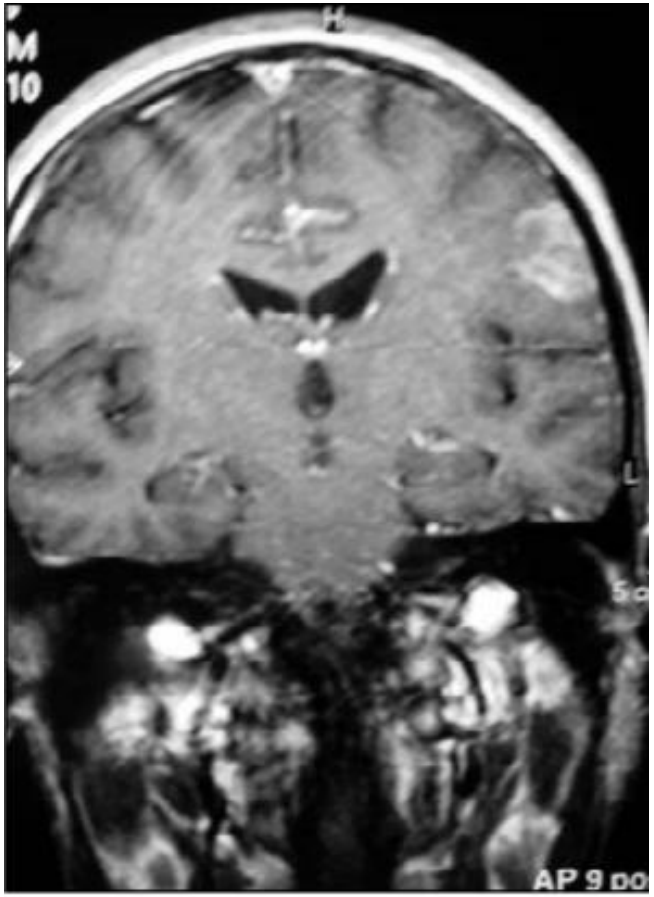


Fig 2. T1- weighted coronal image with enhanced left pariet area after contrast administration.

Fiorot Júnior JA et al. Tuberculosis: an uncommon cause of cerebral venous thrombosis? Arq Neuropsiquiatr.(2005

Arq Neuropsiquiatr 2005;63(3-B):852-854

TUBERCULOSIS

An uncommon cause of cerebral venous thrombosis?

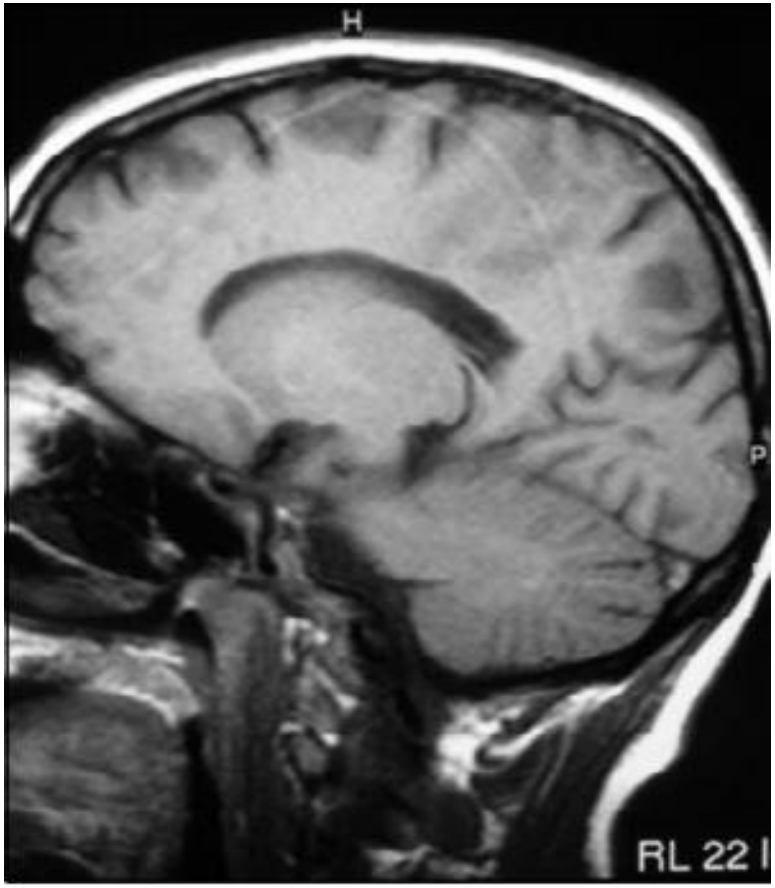


Fig 3. T1-weighted sagital image with irregular signals in th sagitals sinus.

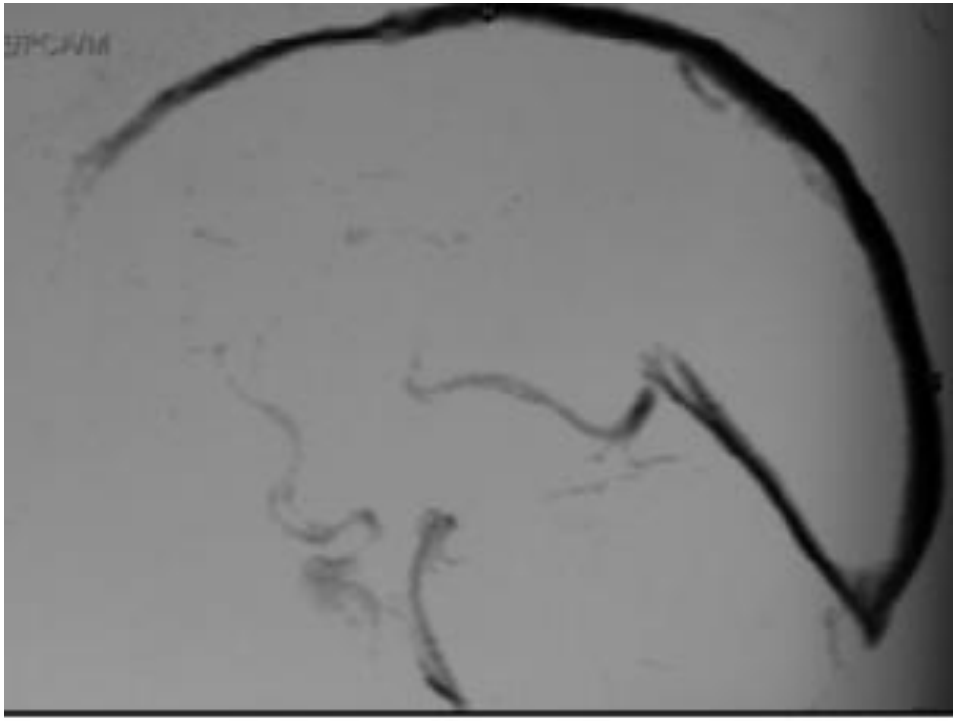


Fig 4. Venous phase of an angiogram shows irregular signals in the sagitals sinus.

Fiorot Júnior JA et al. Tuberculosis: an uncommon cause of cerebral venous thrombosis? Arq Neuropsiquiatr.(2005

Arq Neuropsiquiatr 2005;63(3-B):852-854

TUBERCULOSIS

An uncommon cause of cerebral venous thrombosis?

- Other etiologies of CVT: negative
- Treatment:
  - isoniazid, rifampicin (7 months), and pyrazinamide (2 months)
  - Corticosteroids: usual doses
  - 6 months anticoagulation (warfarin)
- Outcome: favorable confirmed by an Angio-MRI performed after 6 months: complete resolution of thrombosis in sagitals sinus

Fiorot Júnior JA et al. Tuberculosis: an uncommon cause of cerebral venous thrombosis? Arq Neuropsiquiatr.(2005)

CVT in Tuberculosis (TB)

- Few cases reported in the literature
- Mechanisms:
  - ***Injury to endothelium***: obliterative endarterites+ inflammatory infiltrates in their walls+marked intimal thickening
  - ***Alterations in normal blood flow***: Blood stasis (intracranial sinus = low-pressure system without valve)
  - ***Alterations in the blood coagulability***: increased platelet aggregability in TB (88% of patients)

Fiorot Júnior JA et al. Tuberculosis: an uncommon cause of cerebral venous thrombosis? Arq Neuropsiquiatr.(2005)

ELSEVIER MASSON

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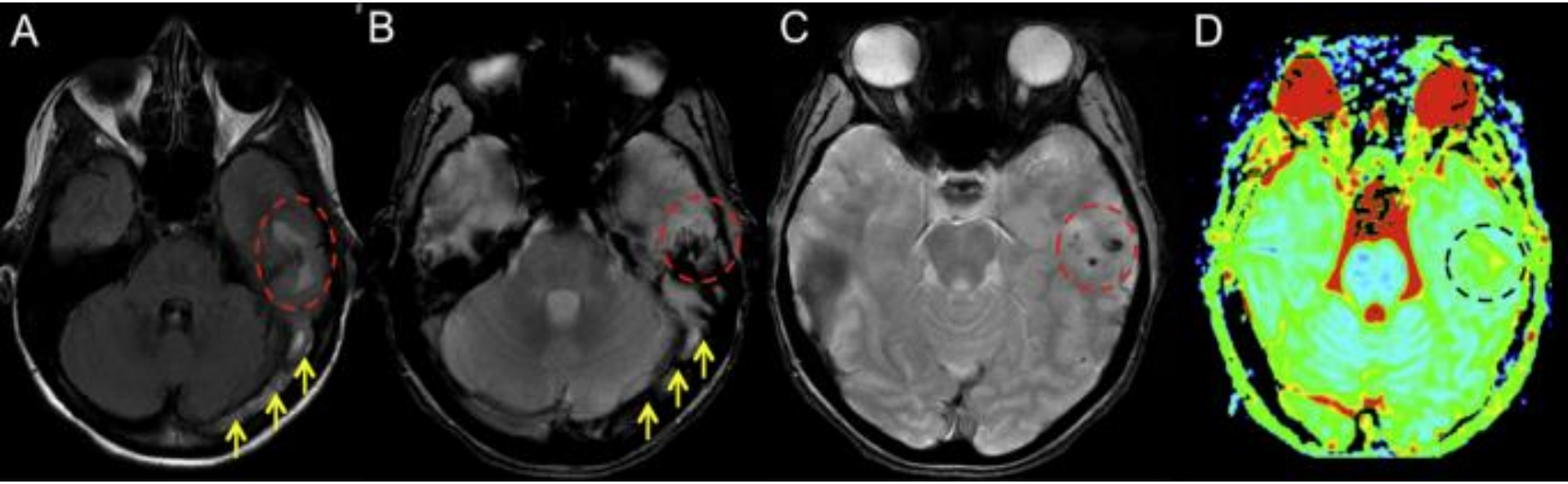
Communication brève

Thrombophlébite cérébrale : une complication rare de l'infection aiguë à cytomégalovirus

Cerebral venous thrombosis: An unusual complication of acute cytomegalovirus infection

Introduction. – Acute cytomegalovirus (CMV) infection increases the risk of vascular thrombosis but reports of cerebral venous thrombosis are rare.
Case report. – We report a 36-year-old woman who presented with a cerebral venous thrombosis and acute CMV infection heralded by a cytolytic hepatitis. Heterozygous factor V Leiden mutation was also identified. The patient was treated with anticoagulation for 1 year with favourable outcome.
Conclusion. – Serologic tests for CMV infection should be performed in case of cerebral venous thrombosis with liver cytolysis or flu-like symptoms. CMV infection often triggers thrombosis in combination with other inherited or genetic predisposing risk factors that should always be searched.

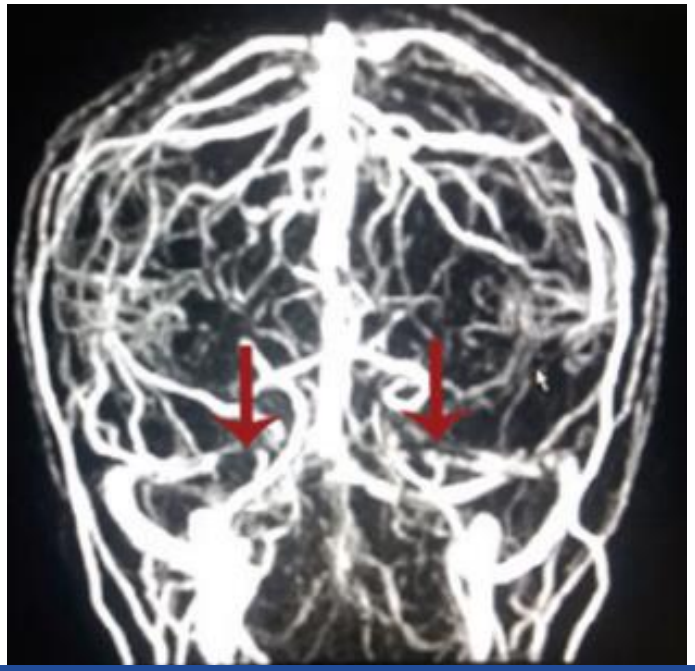


Périsse A et al. Cerebral venous thrombosis: an unusual complication of acute cytomegalovirus infection. Rev Med Interne. (2014)

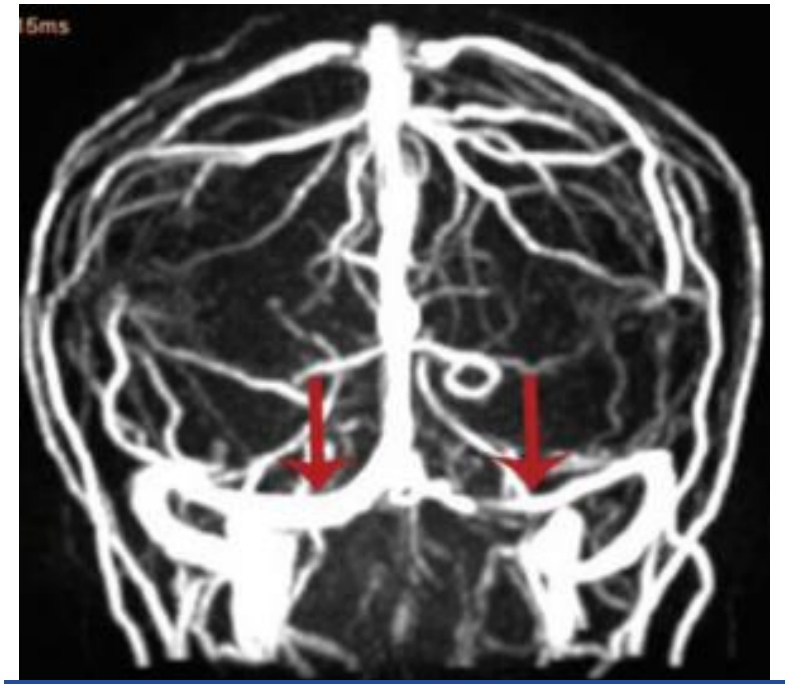
Case Report

Unusual Presentation of Dengue Fever-Cerebral Venous Thrombosis

A 16-year-old boy presented with fever for two week duration, headache and double vision involving left eye for two days. He had multiple erythematous rashes all over the body on 3rd day and treated conservatively. On examination he had bilateral papilloedema, left eye restricted abduction. His investigation revealed thrombocytopenia and positive dengue serology. His MRI brain with venogram showed bilateral transverse sinus thrombosis. Hence he was diagnosed as cerebral venous thrombosis due to dehydration with underlying dengue infection. He was hydrated and managed conservatively. On 3rd day his double vision started improving. His repeat MR Venogram was done after two week duration, which revealed recanalisation of bilateral transverse sinus.



MRI brain venogram showing bilateral thrombosis of transverse sinus



[Table/Fig-2]: Repeat - MRI brain venogram showing complete recanalisation of left transverse sinus

Vasanthi N et al. Unusual Presentation of Dengue Fever-Cerebral Venous Thrombosis. J Clin Diagn Res. (2015)

Journal of the Neurological Sciences 378 (2017) 69–74

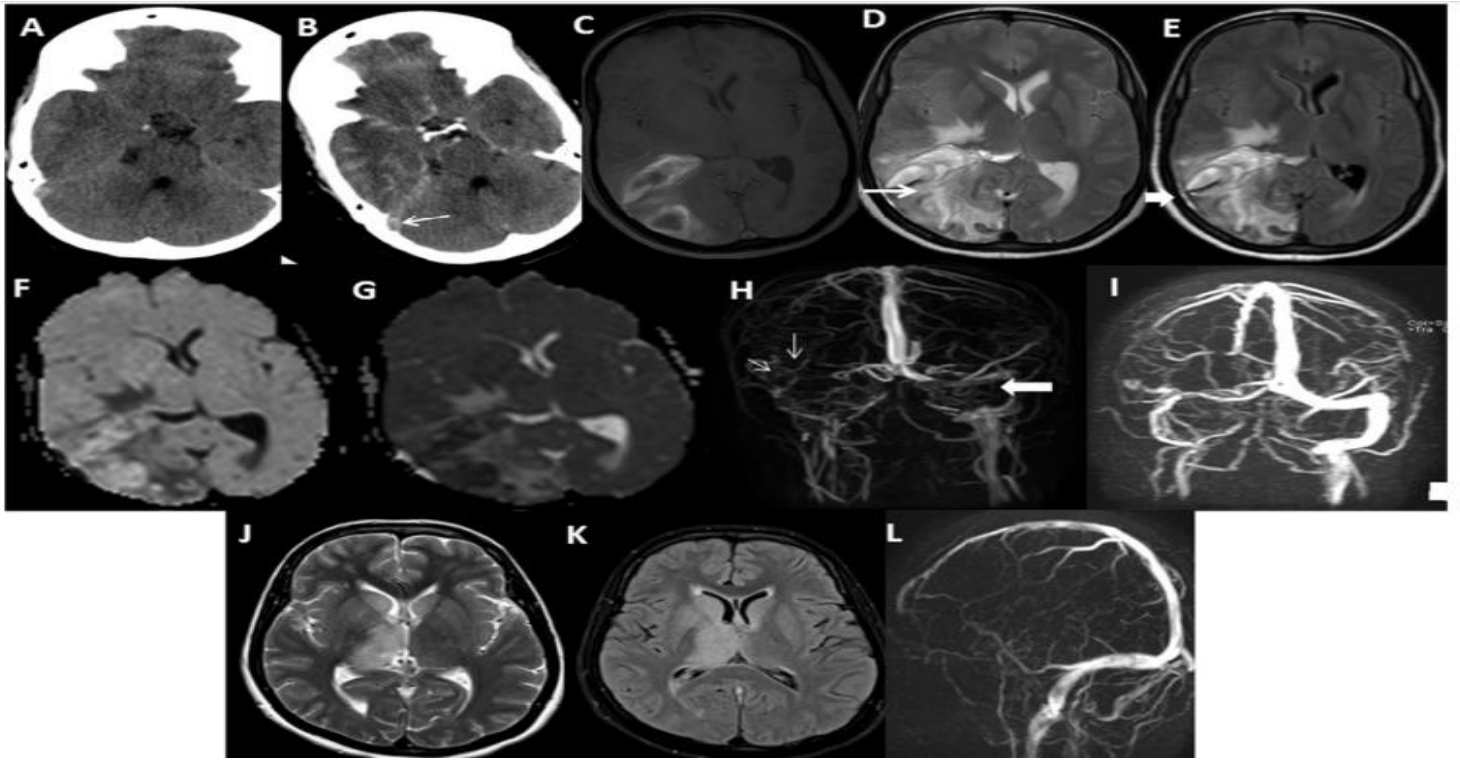
Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Profile of 26 HIV Seropositive individuals with Cerebral Venous Thrombosis

Conclusion: This study represents the largest series of CVT in HIV seropositive individuals. There is increased risk of thrombosis due to elevated homocysteine and low Vitamin B12. They have better sensorium inspite of exte sive radiological involvement.



M N et al. Profile of 26 HIV Seropositive individuals with Cerebral Venous Thrombosis. J Neurol Sci. (2017)

Journal of the Neurological Sciences 378 (2017) 69–74

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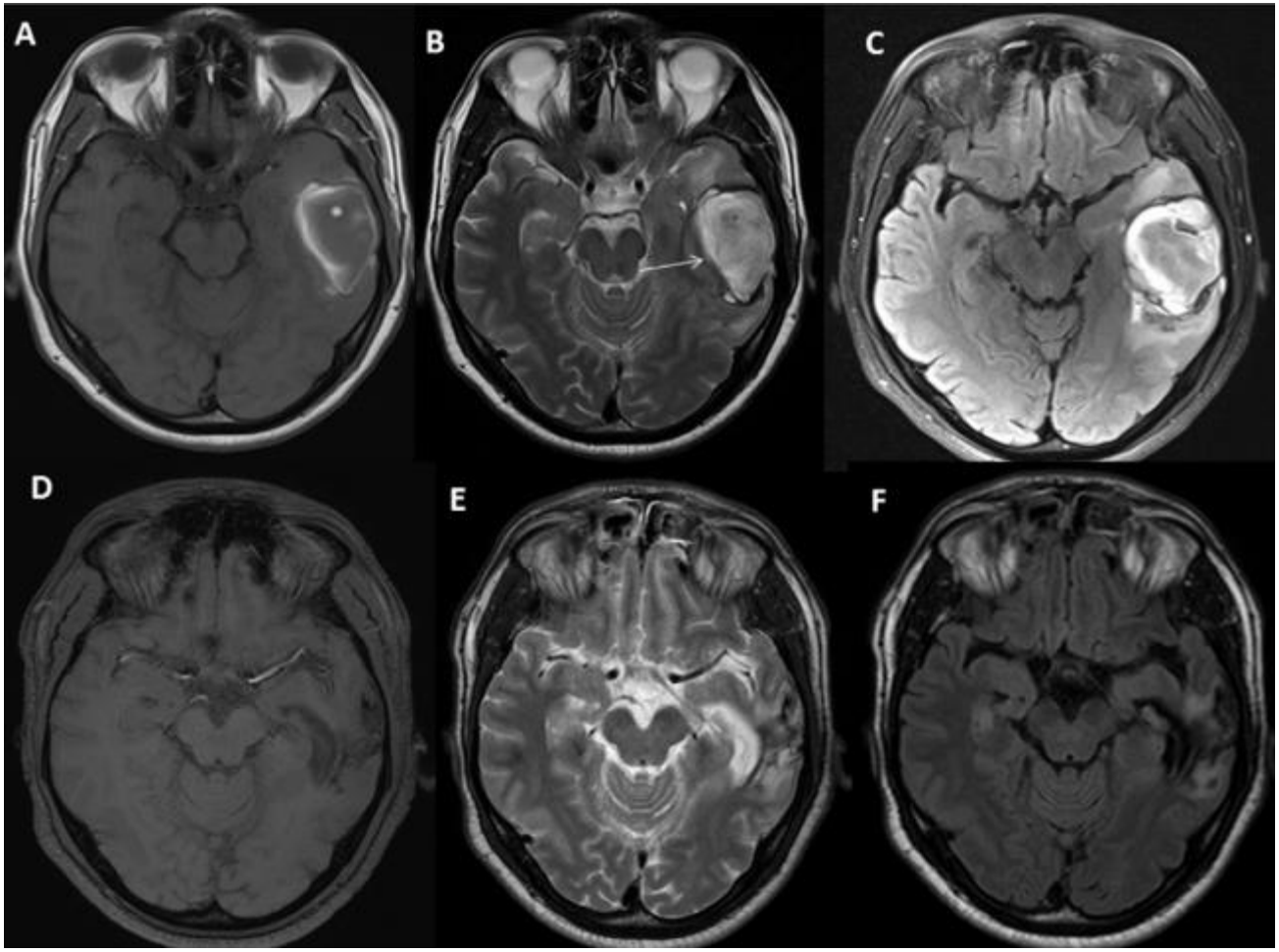
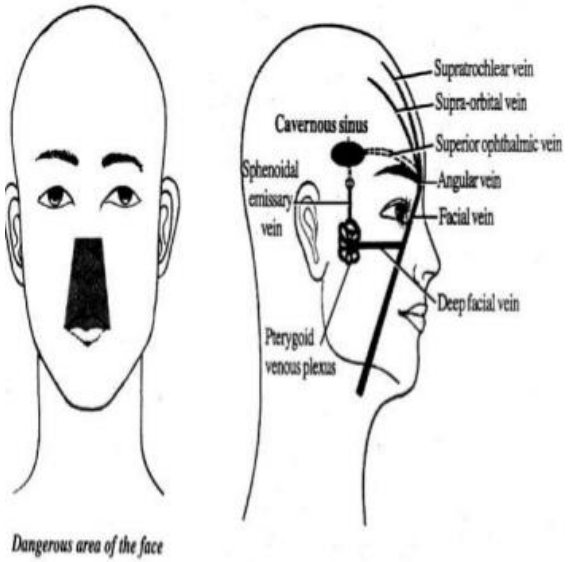


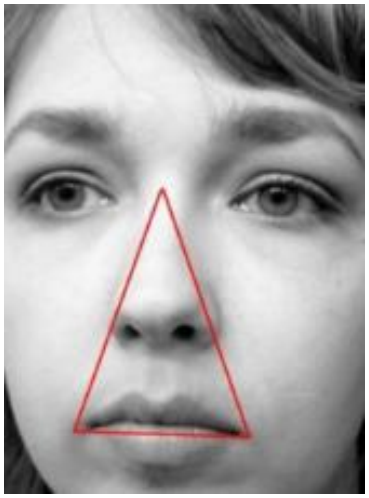
M N et al. Profile of 26 HIV Seropositive individuals with Cerebral Venous Thrombosis. J Neurol Sci. (2017)

Septic Cavernous-Sinus Thrombosis

- **Most common** site of septic thrombosis in the CNS

- Rare complication of infection in:
  - Face and/or paranasal sinuses (sphenoid, ethmoid, middle third of the face, mostly at ***the dangerous triangle*** (nose and upper lip)
  - Less often:
    - Orbit
    - Middle ear
    - Pharynx or teeth





Kojan S et al. Infection related cerebral venous thrombosis. J Pak Med Assoc.(2006)

Septic Cavernous-Sinus Thrombosis

- Infection reaches cavernous sinus: through **venous spreading**
- **Bilateral**+++> unilateral
- Coagulase+ **staphylococcus (aureus)** ++ (**60-70%)**

  > haemophilus influenzae and anaerobic organisms

  > gram-negative rods

  > aspergillus, mucormycosis, Eikenella corrodens, Pseudomonas aeruginosa, mixed flora

Kojan S et al. Infection related cerebral venous thrombosis. J Pak Med Assoc.(2006)

Septic Cavernous-Sinus Thrombosis

- Patients: septic, toxic features of facial infection

- Acute onset of:
  - Headache: inconstant
  - Fever: constant
  - Vomiting
  - Facial redness, pain and eyelid edema: orbital symptoms:
    - constant
    - Unilateral then bilateral (within 24- 48 hours)

Kojan S et al. Infection related cerebral venous thrombosis. J Pak Med Assoc.(2006)

Septic Cavernous-Sinus Thrombosis

- Triad of:
  - **Chemosis**
  - **Proptosis** (due to orbital venous congestion)
  - **Painful ophthalmoplegia** (due to involvement of the III, IV and VI cranial nerves)

- Occasional ophthalmic branch of trigeminal cranial nerve involvement
- Papilledema
  - some patients
  - usually mild and late in the course
- Decreased visual acuity < 50% of the times
- Pupils can be dilated (parasympathetic involvement) or smaller and immobile (both parasympathetic and sympathetic dysfunction).

Kojan S et al. Infection related cerebral venous thrombosis. J Pak Med Assoc.(2006)

IMAGING IN INTENSIVE CARE MEDICINE

Septic cavernous sinus thrombosis: potentially fatal conjunctival hyperemia

Tatsuya Fujikawa[1*] and Yuka Sogabe[2]

A 54-year-old man, several-week history of left ophthalmalgia. He was previously healthy apart from a 6-month history of gingivalgia. He presented with left-sided periorbital edema, injection, chemosis, proptosis, and decreased ocular movement (Fig. 1) following high fever, chills, and impaired consciousness.

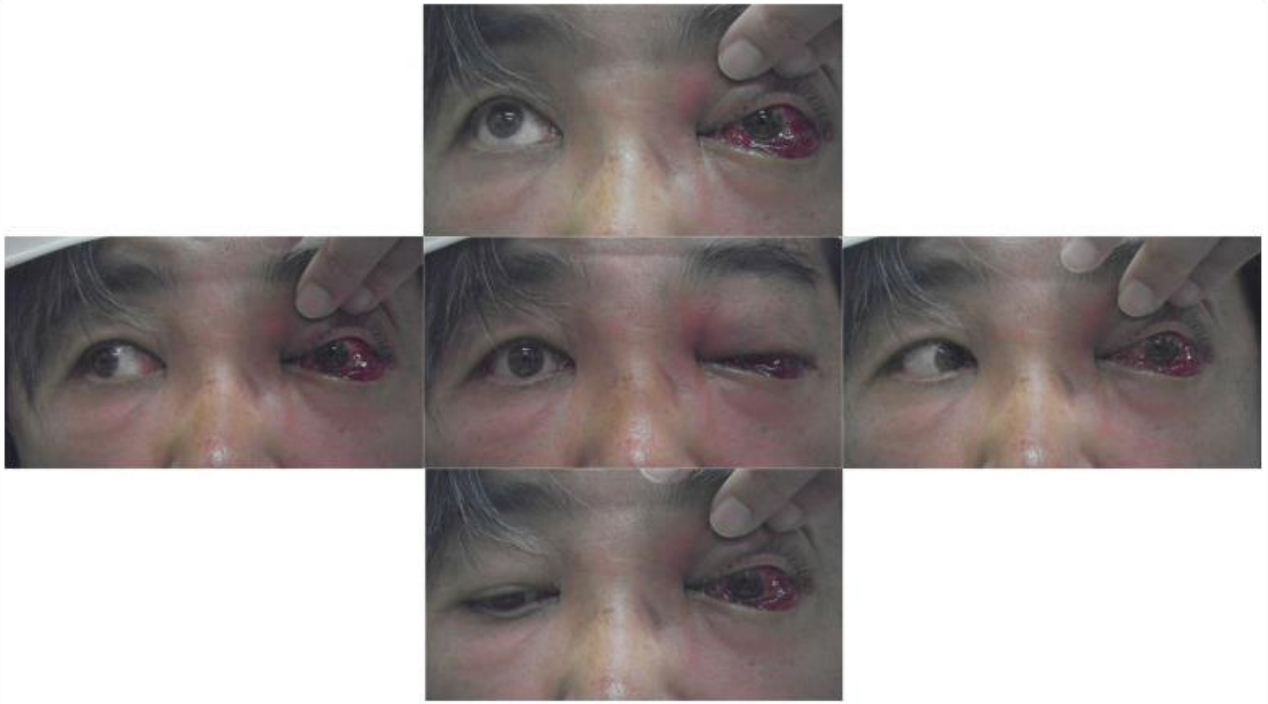


Fig. 1 Photographs of the patient with septic cavernous sinus thrombosis. The patient presented with periorbital edema, injection, chemosis, proptosis, and decreased ocular movement in his left eye

Fujikawa T et al. Septic cavernous sinus thrombosis: potentially fatal conjunctival hyperemia. Intensive Care Med.(2018)

IMAGING IN INTENSIVE CARE MEDICINE

Septic cavernous sinus thrombosis: potentially fatal conjunctival hyperemia

Tatsuya Fujikawa[1*] and Yuka Sogabe[2]

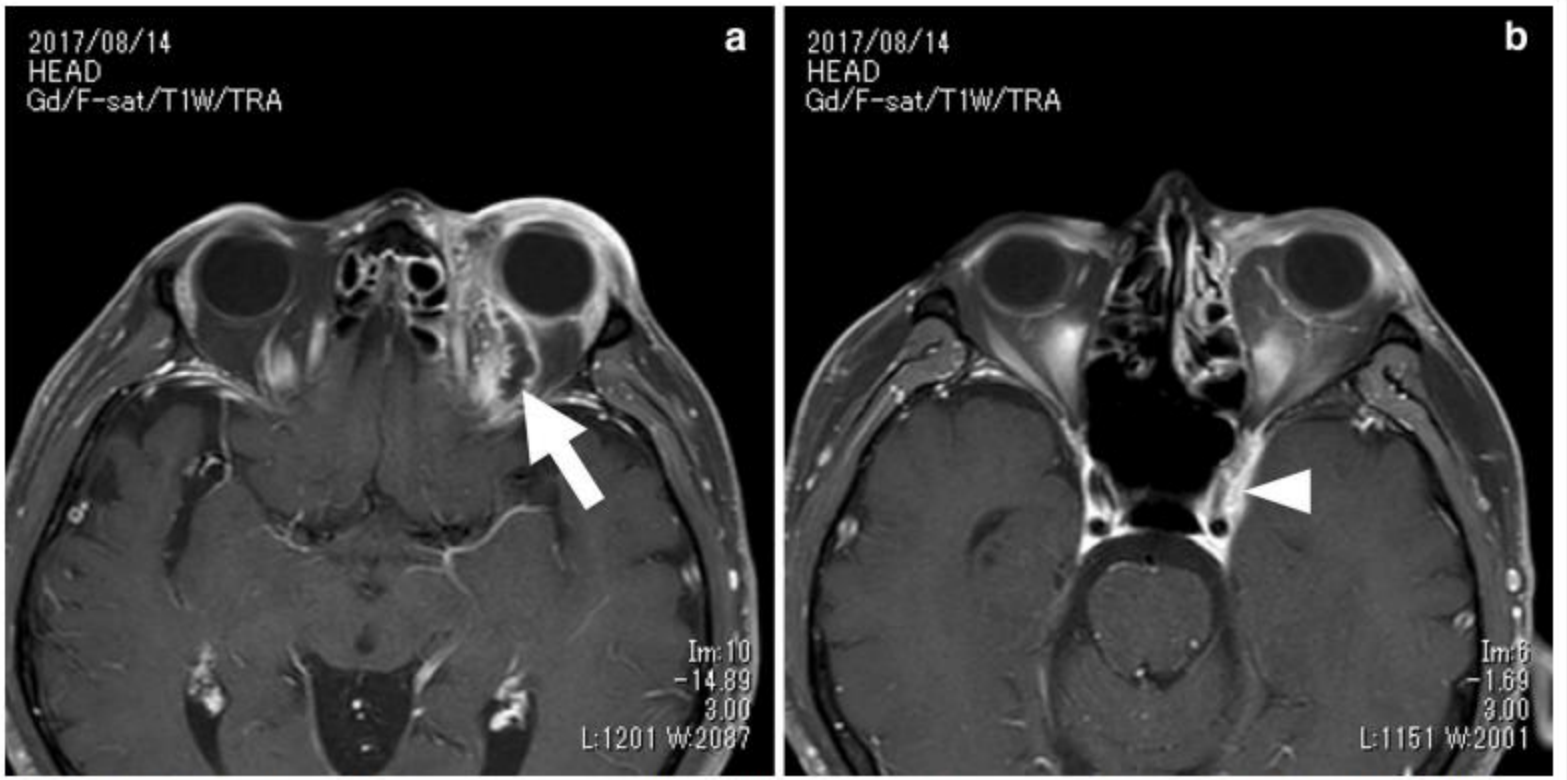


Fig. 2 Contrast-enhanced magnetic resonance images showing **a** poor contrast enhancement in the dilated left superior ophthalmic vein (arrow) and **b** heterogeneous enhancement in the cavernous sinus (arrowhead)

Fujikawa T et al. Septic cavernous sinus thrombosis: potentially fatal conjunctival hyperemia. Intensive Care Med.(2018)

DANGER TRIANGLE OF FACE AND SEPTIC CAVERNOUS SINUS THROMBOSIS

Ashok Kumar Pannu, MD, Atul Saroch, MD, and Navneet Sharma, MD

A 52-year-old man was admitted due to high-grade fever with chills and cranial nerve deficits. Fifteen days prior to hospitalization, a furuncle had developed over the tip of the nose and had extended to involve the surrounding area and upper lip. He was prescribed oral antibiotics, after which the lesion had started healing. However, fever persisted, and 1 day prior to admission he noticed pain in his right eye and forehead, with drooping of the eyelid and diplopia (Figure 1). On examination, complete right ophthalmoplegia due to right lateral and medial rectus palsy was found (Figure 2A and 2B).

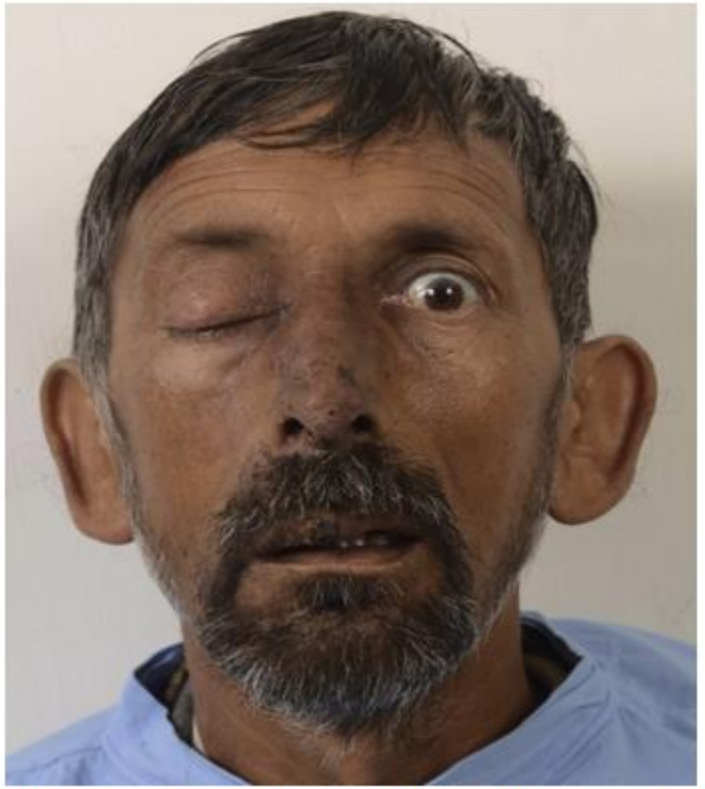


Figure 1. A lesion in the danger triangle of the face, and ptosis of the right eye.

Pannu AK et al. Danger Triangle of Face and Septic Cavernous Sinus Thrombosis. J Emerg Med. (2017)

DANGER TRIANGLE OF FACE AND SEPTIC CAVERNOUS SINUS THROMBOSIS

Ashok Kumar Pannu, MD, Atul Saroch, MD, and Navneet Sharma, MD

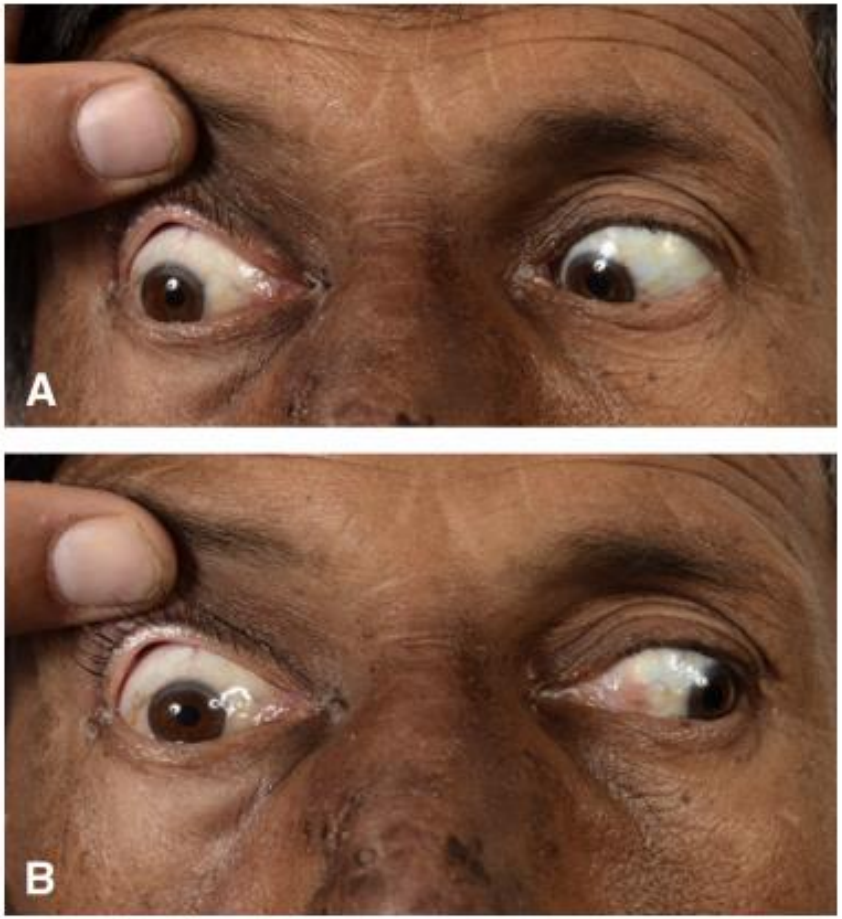


Figure 2. (A) Right lateral rectus palsy. (B) Right medial rectus palsy.

Pannu AK et al. Danger Triangle of Face and Septic Cavernous Sinus Thrombosis. J Emerg Med. (2017)

DANGER TRIANGLE OF FACE AND SEPTIC CAVERNOUS SINUS THROMBOSIS

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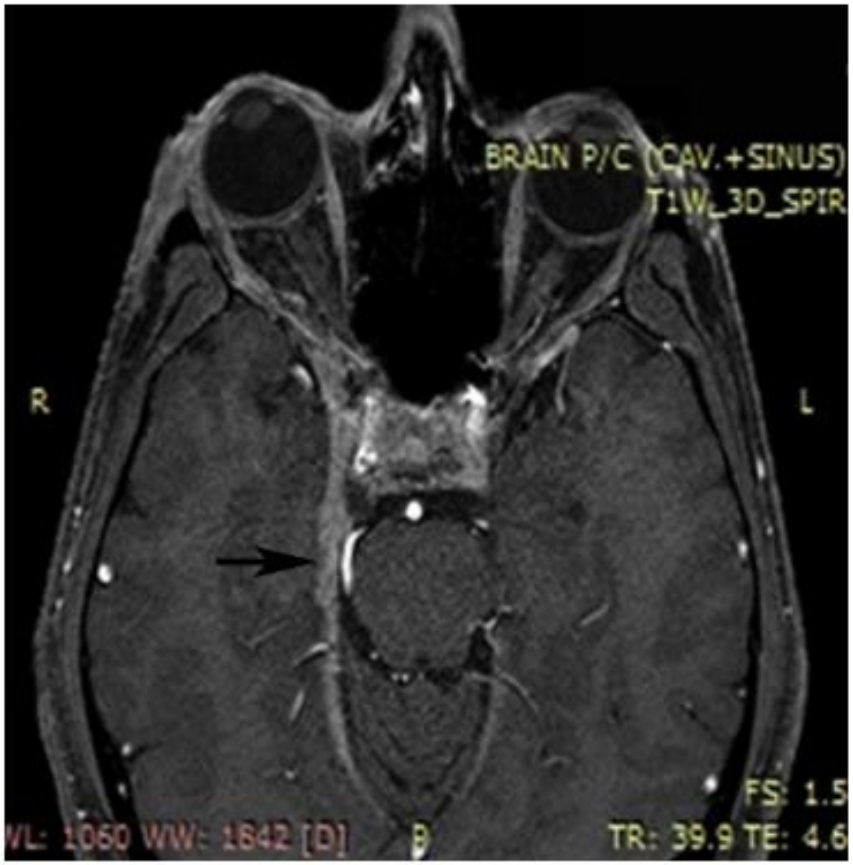


Figure 3. T1 postcontrast axial magnetic resonance imaging study showing heterogenous enhancing soft tissue in the right cavernous sinus extending posteriorly along the tentorium cerebri (arrow).

Pannu AK et al. Danger Triangle of Face and Septic Cavernous Sinus Thrombosis. J Emerg Med. (2017)

Septic Cavernous-Sinus Thrombosis

- Differential diagnosis
  - Meningoencephalitis
  - Orbital cellulites
  - Preseptal cellulites
  - Orbital apex syndrome
  - Non-septic thrombosis

Kojan S et al. Infection related cerebral venous thrombosis. J Pak Med Assoc.(2006)

Septic Cavernous-Sinus Thrombosis

- Signs on imaging

The signs that are usually seen include:

1. Filling defect in the cavernous sinuses
2. Heterogeneous enhancement within the cavernous sinuses
3. Enlargement and/or bulging of the lateral walls of the cavernous sinus
4. Intensive enhancement of the lateral wall
5. Some times indirect orbital signs

a. Exophthalmus
b. Densification of the retro-orbital fat
c. Superior ophthalmic dilatation with partial or no enhancement in case of thrombosis extension

Kojan S et al. Infection related cerebral venous thrombosis. J Pak Med Assoc.(2006)

Septic Cavernous-Sinus Thrombosis

- Blood culture: positive in **70%**
- CSF:
  - usually abnormal with pleocytosis and elevated total protein
  - culture is positive in **<20%**

Kojan S et al. Infection related cerebral venous thrombosis. J Pak Med Assoc.(2006)

Stroke and Infection: Management

Management of stroke due to infections

- Preventive measures
  - Primary prevention
  - Secondary prevention
- Curative measures
  - Symptomatic treatment
  - Etiological treatment

AbdelRazek MA. Intravenous Thrombolysis for Stroke and Presumed Stroke in Human Immunodeficiency Virus-Infected Adults: A Retrospective, Multicenter US Study. Stroke. (2018)

Implications for treatment strategies in preceding infection

- Recognition of vulnerable individuals and **prevention of infection** (ex.: stroke-prone state in patients with transient ischaemic attack)

- Pleiotropic effects of **statins**(stabilisation of atherosclerotic plaques, modulation of immune and inflammatory responses):
  - Protection against endothelial dysfunction related to acute infection)
  - BUT: simvastatin:
    - Improvement of clinical outcomes in stroke
    - increasing poststroke infection

  } Balance

- **Influenza vaccination** in patients:
  - History of cerebrovascular disease
  - at high risk of stroke

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

Implications for treatment strategies in preceding infection

Influenza Vaccination Is Associated With a Reduced Risk of Stroke

Conclusions—These results support the hypothesis that influenza vaccination may be associated with reduced stroke risk. However, residual confounding cannot be excluded, and interventional studies are required to evaluate the role of influenza vaccination in stroke prevention. (***Stroke***. **2005;36:1501-1506.**)

Risk Factor	OR	95% CI	*P* Value
Recent influenza vaccination	0.46	0.28–0.77	0.0028
Recent other vaccinations	0.80	0.42–1.53	0.49
Hypertension	2.08	1.33–2.33	0.0012
Diabetes mellitus	1.36	0.71–2.61	0.35
Hyperlipidemia	1.39	0.88–2.21	0.16
Previous stroke/TIA	7.07	3.55–14.08	<0.0001
Peripheral arterial disease	0.82	0.43–1.53	0.52
Current smoking	1.62	0.96–2.73	0.072
Alcohol abstinence	2.30	1.29–4.09	0.0048
High alcohol consumption	2.65	1.09–6.47	0.033
Family history of stroke	1.58	0.96–2.59	0.070
School education ≥10 y	0.82	0.61–1.10	0.18
Current sports	0.60	0.38–0.96	0.033
Chronic bronchitis	1.57	0.72–3.42	0.26
Frequent flue-like illnesses	3.09	1.22–7.80	0.017
Behavior in febrile infection*	2.75	1.65–4.59	0.0001

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

Grau et al, Influenza vaccination is associated with a reduced risk of stroke. Stroke. (2005)

Implications for treatment strategies in preceding infection

Influenza Vaccination for Secondary Prevention of Cardiovascular Events: A Systematic Review

JCPH – Vol. 70, n° 1 – janvier–février 2017

Conclusions: Given the limitations of these data, it is unclear whether the cardiovascular benefit with influenza vaccination in patients with cardiovascular disease is a true effect. Nevertheless, because of the potential benefit and the low risk of adverse events, the annual influenza vaccine should be recommended for all patients with established cardiovascular disease.

Study (Year)	GRADE Score	Design	Country	No. of Patients	Baseline Characteristics	Intervention	Control	Duration
FLUVACS (2002 and 2004)[29,30]	Low	Randomized, single-blind	Argentina	301	Mean age 65 years, 66% with acute MI, 34% with elective PCI	Single 0.5-mL IM dose of A/Moscow/ 10/99-like virus, A/New Caledonia/ 20/99 (H1N1)-like virus, and AB/Sichuan/ 379/99-like virus	Saline	6 months
FLUCAD (2008)[31]	Moderate	Randomized, double-blind	Poland	658	Median age 60 years, 73% male, 56% with stable CAD, 24% with PCI for ACS, 20% with PCI for stable angina	Single 0.5-mL IM dose of A/New Caledonia/ 20/99 (H1N1), A/Christchurch/ 28/03 (H3N2), and B/Jiangsu/ 10/03	Placebo	14 months
Phrommintikul et al. (2011)[32]	Moderate	Randomized, open-label	Thailand	439	Mean age 66 years, 57% male, 47% NSTEMI, 36% STEMI, 16% with unstable angina	Single 0.5-mL IM dose of split, inactivated influenza vaccine (type not reported)	No treatment	12 months
IVCAD (2009)[33]	NA	Randomized, single-blind	Iran	281	NR	Single 0.5-mL IM dose of 2007/2008 influenza vaccine	Placebo	6 months
FLUVACS-IC*[34]	NA	Randomized, single-blind	Argentina	117	NR	Single IM dose of influenza vaccine	Conventional medical therapy	6 months

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.. Lancet Neurol (2008)

LeBras et al, Influenza Vaccination for Secondary Prevention of Cardiovascular Events: A Systematic Review. Can J Hosp Pharm. (2017)

Stroke, Infection and Thrombolysis

- Infectious etiology: Not contra-indication of:
  - thrombolysis
  - Antiplatelets
  - Anticoagulants
- HIV: 6% of hemorrhagic transformation

AbdelRazek MA. Intravenous Thrombolysis for Stroke and Presumed Stroke in Human Immunodeficiency Virus-Infected Adults: A Retrospective, Multicenter US Study. Stroke. (2018)

Stroke
Journal of the American Heart Association

American Heart Association | American Stroke Association

Intravenous Thrombolysis for Stroke and Presumed Stroke in Human Immunodeficiency Virus–Infected Adults

A Retrospective, Multicenter US Study

Conclusions—Most HIV-infected patients treated with intravenous tPA for presumed and actual acute ischemic stroke had no complications, and we observed no fatalities. Stroke mimics were common, and thrombolysis seems safe in this group. We found no data to suggest an increased risk of intravenous tPA-related complications because of concomitant opportunistic infections or intravenous drug abuse. (***Stroke*****. 2018;49:228-231. DOI: 10.1161/STROKEAHA.117.019570.)**

Values Given in n (%) or Mean (Range) Unless Otherwise Noted	All Patients (n=33)	Stroke Mimics (n=10)	True AIS (n=23)
CNS opportunistic infections	3 (9%)¶	0	3 (13%)
Hemorrhagic transformation	2 (6%)	0	2 (9%)
mRS score mean, median, range, (follow-up mean, median days)	1.7, 1, [0–5], (79, 90)	0.4, 0, [0–1], (105, 90)	2.3, 2, [0–5], (68, 90 days)
Stroke mechanism per TOAST criteria[7]			
Cardioembolic	8 (35%)	n/a	8 (35%)
Large artery disease	4 (17%)	n/a	4 (17%)
Small vessel disease	2 (9%)	n/a	2 (9%)
Other	3 (13%)¶	n/a	3 (13%)¶
Undetermined	6 (26%)	n/a	6 (26%)

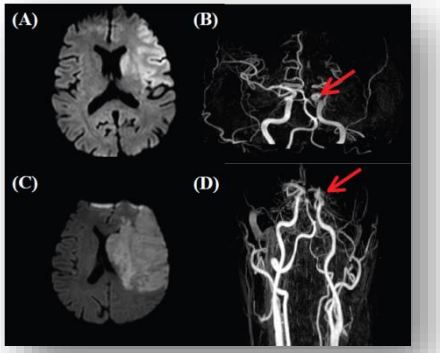
AbdelRazek MA. Intravenous Thrombolysis for Stroke and Presumed Stroke in Human Immunodeficiency Virus-Infected Adults: A Retrospective, Multicenter US Study. Stroke. (2018)

Stroke and infective endocarditis

Safety of intravenous thrombolysis in embolic stroke by infective endocarditis

Jin-Man Jung *MD*, Moon Ho Park *MD PhD*, Do-Young Kwon *MD PhD*

Department of Neurology, Korea University Medical College, Ansan, Republic of Korea



Stroke
Journal of the American Heart Association

American Heart Association | American Stroke Association

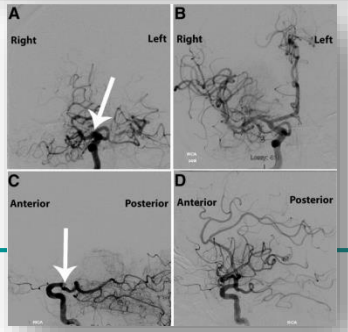
Anticoagulation in Patients With Stroke With Infective Endocarditis: The Sword of Damocles

Carlos A. Molina and Magdy H. Selim

Stroke. 2011;42:1799-1800; originally published online May 5, 2011;

Endovascular Treatment for Cerebral Septic Embolic Stroke

Hadi D. Toeg, MD, MSc,* Talal Al-Atassi, MD, MPH,* Navya Kalidindi, MD,† Daniela Iancu, MD, MSc,‡ Delara Zamani, MD,* Roberto Giaccone, MD,† and Roy G. Masters, MD*



Journal of Stroke and Cerebrovascular Diseases, Vol. ■, No. ■ (■-■), 2014: pp 1-3

Neurology Asia 2013; 18(2) : 209 – 211

Stroke and IE: management

- Preventive measures: early antibiotherapy

- Curative treatment:
  - Antibiotics
  - Anticoagulation
  - Thrombolysis??? (not recommanded)
  - Endovascular treatment
  - Surgical treatment (cardiac, neurosurgery)

- Treatment of complications

AbdelRazek MA. Intravenous Thrombolysis for Stroke and Presumed Stroke in Human Immunodeficiency Virus-Infected Adults: A Retrospective, Multicenter US Study. Stroke. (2018)

J Neurol
DOI 10.1007/s00415-012-6802-1

ORIGINAL COMMUNICATION

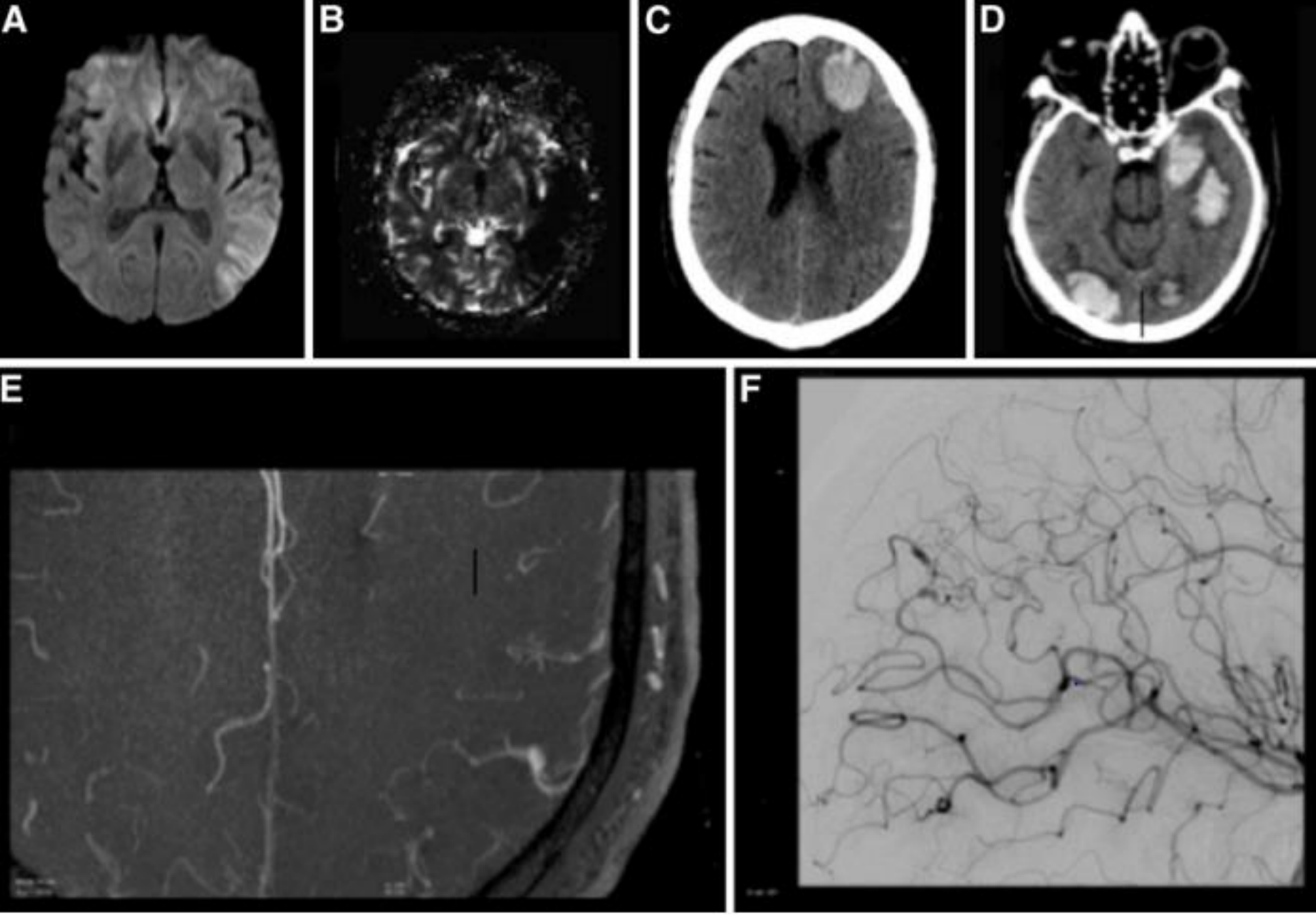
Thrombolysis for stroke caused by infective endocarditis: an illustrative case and review of the literature

Table 1 Case series reporting thrombolysis for AIS related to IE

Case series	Age (years) and gender	Baseline NIHSS score	Presence of mycotic aneurysm	Modalities of thrombolysis and delay from stroke onset	ICH	sICH	Recanalisation	Clinical outcome
Siccoli et al. [3]	31, female	13	None on angiography	IA urokinase 750,000 IU 5 h	No	No	Unknown	NIHSS score = 5 (3 weeks later)
Junna et al. [4]	56, male	15	Unknown	IV tPA 2 h	No	No	Unknown	NIHSS score = 4 (48 h later)
Tan et al. [5]	12, female	18	None on angiography	IA tPA 0.16 mg/kg 6 h	No	No	Yes	NIHSS score = 5 (6 weeks later)
Sontineni et al. [6]	70, male	13	None on MR angiography	IV tPA 2 h 30 min	Unknown	Unknown	Unknown	NIHSS score = 5 (6 weeks later)
Bhuva et al. [10]	46, male	15	None on angiography	IV tPA 1 h 50 min	Yes	No	Unknown	Dead (7 days later)
	65, female	21	None on angiography	IV tPA 2 h	Yes	No	No	Unknown
	61, male	17	None on angiography	IV tPA 1 h 30 min	Yes	No	Unknown	Unknown
Present case 2012	68, male	12	Angiography: 2 left distal aneurysms	IV tPA 2 h 15 min	Yes	Yes	Yes	NIHSS score = 1 (7 months later)

IA intra-arterial, *IV* intravenous, *NIHSS* National Institute of Health Stroke Scale, *ICH* intracranial hemorrhage, *sICH* symptomatic intracranial hemorrhage

Ong E et al. Thrombolysis for stroke caused by infective endocarditis: an illustrative case and review of the literature. J Neurol.(2013)



Ong E et al. Thrombolysis for stroke caused by infective endocarditis: an illustrative case and review of the literature. J Neurol.(2013)

Surgical Management of Infective Endocarditis Complicated by Embolic Stroke

Practical Recommendations for Clinicians

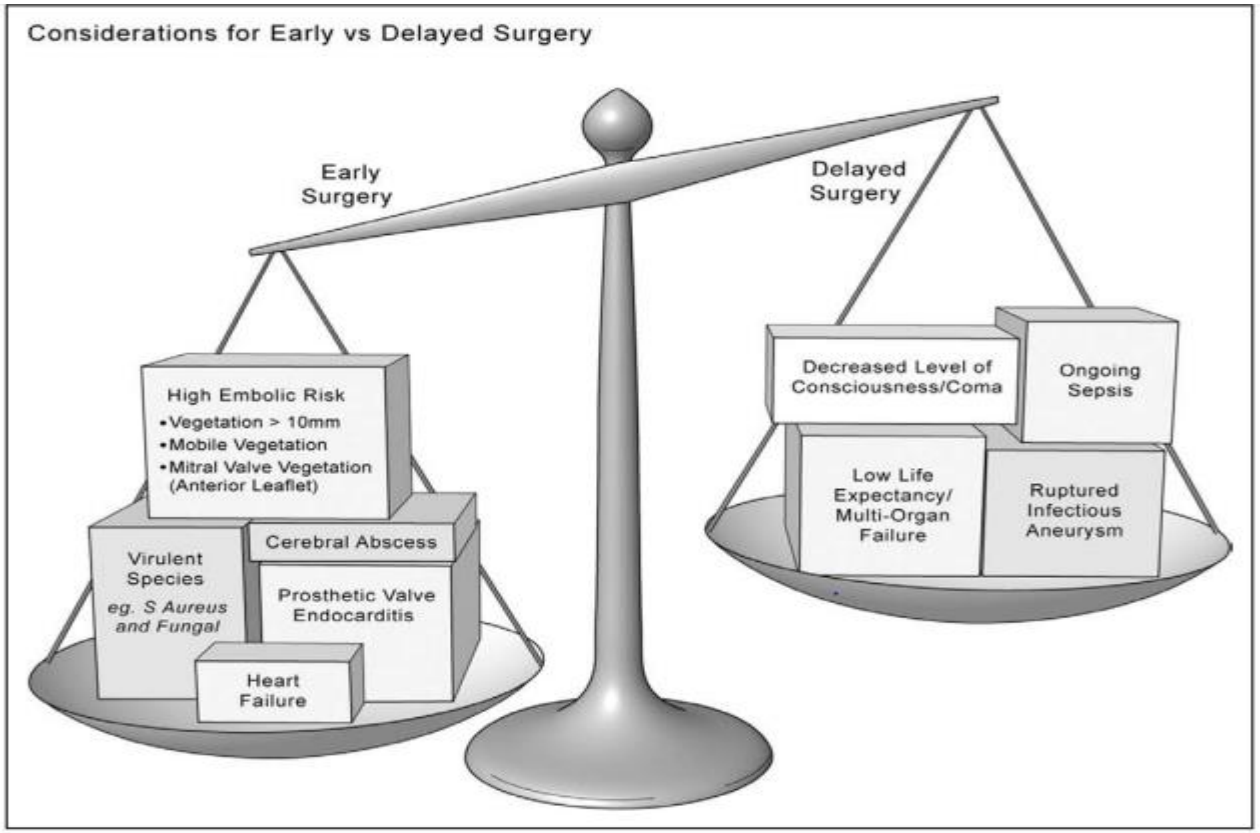


Figure 1. Conceptual diagram of arguments for early and delayed surgery in patients with infective endocarditis with stroke and other cerebral complications.

Yanagawa B et al. Surgical Management of Infective Endocarditis Complicated by Embolic Stroke: Practical Recommendations for Clinicians. Circulation.(2016)

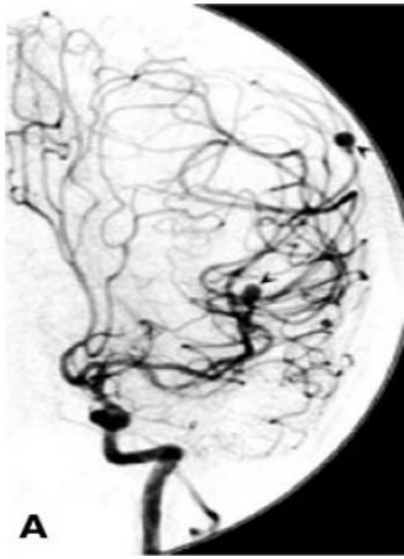
J Neurol (2010) 257:315–321
DOI 10.1007/s00415-009-5364-3

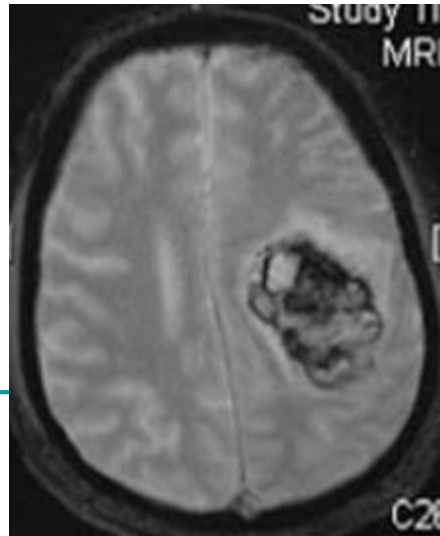
REVIEW

Impact of stroke on therapeutic decision making in infective endocarditis

Laurent Derex · Eric Bonnefoy · François Delahaye

essential steps in making the therapeutic decision. Surgery should be delayed if possible in the event of large cerebral infarction or ICH in order to prevent neurological deterioration. It has been suggested that valve replacement should be considered within the first 72 h if the patients with brain infarction have severe heart failure, otherwise after 4 weeks. Early surgery appears safe in patients presenting transient ischemic attacks or "silent" cerebral embolism.





Management of Septic Cavernous-Sinus Thrombosis

- Early wide antimicrobial coverage
  - Initial: IV Vancomycin + ceftriaxone + metronidazole
  - Period of treatment: at least 3-4 weeks
- Role of anticoagulation in septic CST: uncertain
- Role of corticosteroids:
  - Uncertain
  - Favorable response :
    - Reduction of inflammation and oedema
    - Improvement of cranial nerve dysfunction and orbital oedema

Kojan S et al. Infection related cerebral venous thrombosis. J Pak Med Assoc.(2006)

Outcome of Septic Cavernous-Sinus Thrombosis

- Improvement of prognosis of septic CST :
  - Recent advances in antibiotic therapy
  - Early recognition and management
- Mortality rates improved:
  - 100% before antibiotic era ➔ 20-30% with the current management strategies
- Complications and morbidities:
  - improved from 75% to 22%
- Full recovery:
  - achieved in <50%

Kojan S et al. Infection related cerebral venous thrombosis. J Pak Med Assoc.(2006)

European Archives of Oto-Rhino-Laryngology (2018) 275:2387–2395
https://doi.org/10.1007/s00405-018-5062-9

MISCELLANEOUS

Prognosis of septic cavernous sinus thrombosis remarkably improved: a case series of 12 patients and literature review

Abstract

Purpose Septic cavernous sinus thrombosis (CST) is a rare complication of infections in the head and neck area. CST is notorious for its bad prognosis, with high mortality and morbidity rates described in literature. However, these rates are based on old series. We question whether the prognosis of CST is currently still as devastating. The primary purpose of this study is to assess the mortality and morbidity of CST.

Methods Using the databases of all relevant specialties in our tertiary referral hospital, we collected all the patients treated for CST in the period 2005–2017. In addition, a PubMed search, using the mesh term 'cavernous sinus thrombosis', was performed.

Results We found 12 patients with CST in the study period. Of the 12 patients, 11 survived and 9 recovered without any permanent deficits. Seven patients were treated with anticoagulation, and in none of the patients we saw hemorrhagic complications. In literature, older articles describe higher mortality rates (14–80%), but more recent articles report mortality and morbidity rates similar to our results.

Conclusions The prognosis of CST nowadays is more favorable than previously described. Anticoagulation seems to be a safe addition to antibiotic and surgical treatment, at least in patients without central nervous system infection.

van der Poel NA et al. Prognosis of septic cavernous sinus thrombosis remarkably improved: a case series of 12 patients and literature review. Eur Arch Otorhinolaryngol. (2018)

Outcome of Septic Cavernous-Sinus Thrombosis

- Potential complications:
  - Meningitis
  - Subdural empyema
  - Pituitary necrosis
  - Visual loss (due to corneal ulceration, anterior ischemic optic neuropathy, central retinal artery occlusion, etc.)
  - Stroke
  - AV fistula

Kojan S et al. Infection related cerebral venous thrombosis. J Pak Med Assoc.(2006)

Cerebral venous thrombosis: comparing characteristics of infective and non-infective aetiologies: a 12-year retrospective study

Pat Korathanakhun,[1] Wongchan Petpichetchian,[2] Pornchai Sathirapanya,[1] Sarayut Lucien Geater[1]

Conclusions Cavernous sinus thrombosis is a distinctive clinical presentation of IACVT, whereas focal neurological syndrome is a hallmark feature of NIACVT. Paracranial fungal infections are highly virulent and frequently associated with intracranial complications.

Table 1 Comparison of the clinical presentation and radiological findings of infection-associated and non-infection-associated cerebral venous sinus thrombosis (CVT)

	Infection-associated CVT (n=20)		Non-infection-associated CVT (n=63)	
	N	Per cent	N	Per cent
Clinical presentation				
Focal neurological deficits	3	15.0	32	50.8
Isolated intracranial hypertension	1	5.0	8	12.7
Cavernous sinus syndrome	16	80.0	7	11.1
Encephalopathy	0	0.0	16	25.4
mRS 3–5 on admission	14	70.0	39	61.9
Radiological finding				
CVT≥1 site	3	15.0	41	65.1
Superficial cortical vein	0	0.0	13	20.6
Superior sagittal sinus	3	15.0	42	66.7
Transverse sinus	3	15.0	35	55.6
Deep cerebral vein	0	0.0	5	7.9
Cavernous sinus	16	80.0	7	11.1
Sigmoid sinus	0	0.0	19	30.2
Straight sinus	0	0.0	9	14.3
Jugular vein	1	5.0	6	9.5
Presence of haemorrhage	0	0.0	33	52.4

mRS, modified Rankin Scale.

Korathanakhun P et al. Cerebral venous thrombosis: comparing characteristics of infective and non-infective aetiologies: a 12-year retrospective study. Postgrad Med J.(2015)

Take-home messages

- Infections (acute/chronic) and stroke:
  - Trigger
  - Risk factor
  - Cause
- Common:
  - younger patients
  - Developing countries
- Infectious and tropical diseases should be included in ***differential diagnosis of stroke***
- Recognition ➔ *Primary+secondary prevention*++

Thank you for your attention