CNS infections causing ischemic and/or hemorrhagic stroke

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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
Stroke and Infection: Complex relationship:

- **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)

Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts. Lancet Neurol (2008)*
Stroke and Infection: Complex relationship:

Studies on infections preceding stroke: 5-43%

<table>
<thead>
<tr>
<th>Study design</th>
<th>Type of Infection(s)</th>
<th>Number of patients with infection (%)</th>
<th>Prestroke interval (for prevalence estimate)</th>
<th>Number of patients (controls)</th>
<th>Prestroke interval (for risk analysis)</th>
<th>Outcome statistic (95% CI)</th>
<th>Description of outcome statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syrjänen and co-workers⁵</td>
<td>Case-control</td>
<td>Infections (80% respiratory)</td>
<td>19 (35%)</td>
<td>1 m</td>
<td>54 (54)</td>
<td>RR 9.0 (2.2-80.0)</td>
<td>RR of stroke after infection</td>
</tr>
<tr>
<td>Ameriso and co-workers⁶</td>
<td>Consecutive series</td>
<td>Mostly respiratory tract infections</td>
<td>17 (34%)</td>
<td>1 m</td>
<td>50</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Grau and co-workers⁷</td>
<td>Case-control</td>
<td>Mostly respiratory tract bacterial infections</td>
<td>31 (16%)</td>
<td>1 w</td>
<td>197 (197)</td>
<td>OR 4.6 (1.9-11.3)*</td>
<td>Estimated OR for stroke after infection</td>
</tr>
<tr>
<td>Macko and co-workers⁸</td>
<td>Case-control</td>
<td>Infections or inflammatory events (mostly upper respiratory tract)</td>
<td>13 (35%)</td>
<td>1 w</td>
<td>37 (47.34)†</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Bova and co-workers⁹</td>
<td>Case-control</td>
<td>Infections (mostly respiratory tract or urinary tract)</td>
<td>41 (23%)</td>
<td>1 w</td>
<td>182 (194)</td>
<td>OR 2.9 (1.6-5.3)</td>
<td>Risk of preceding infection in patients with acute ischaemic stroke</td>
</tr>
<tr>
<td>Grau and co-workers¹⁰</td>
<td>Case-control</td>
<td>Infections (bacterial or viral)</td>
<td>8 (5%)</td>
<td>2-4 w</td>
<td>166 (166)</td>
<td>OR 2.9 (1.3-6.4)</td>
<td>Risk of cerebrovascular ischaemia after infection</td>
</tr>
<tr>
<td>Nagaraja and co-workers¹¹</td>
<td>Case-control</td>
<td>Infections (bacterial or viral)</td>
<td>6 (10%)</td>
<td>1 w</td>
<td>60 (60)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Paganini-Hill and co-workers¹²</td>
<td>Case-control and crossover</td>
<td>Infectious or inflammatory events</td>
<td>26 (43%)</td>
<td>&gt;2 W</td>
<td>233 (363)</td>
<td>RR 1.8 (0.6-3.6)</td>
<td>RR of large-vessel or cardioembolic stroke after respiratory tract infection</td>
</tr>
<tr>
<td>Nencini and co-workers¹³</td>
<td>Case-control</td>
<td>Infective or non-infective inflammatory events</td>
<td>17 (18%)</td>
<td>7 d</td>
<td>93 (200)</td>
<td>OR 2.5 (1.1-5.4)</td>
<td>Risk of ischaemic stroke after inflammatory event</td>
</tr>
<tr>
<td>Smethe and co-workers¹⁴</td>
<td>Case series</td>
<td>Systemic respiratory tract infections</td>
<td>--</td>
<td>--</td>
<td>244</td>
<td>IR 3.2 (2.8-3.6)</td>
<td>IR for first stroke after systemic respiratory tract infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urinary tract infections</td>
<td>--</td>
<td>--</td>
<td>152</td>
<td>IR 2.7 (2.3-3.2)</td>
<td>IR for first stroke after urinary tract infections</td>
</tr>
</tbody>
</table>

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.* † Two control groups (47 community, 34 hospitalised). ‡22 400 participants exposed. §14 603 participants exposed.

Table 1: Studies that report infections preceding stroke

# 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

<table>
<thead>
<tr>
<th>Genetic factors/genotypes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin-converting enzyme genotype</td>
<td></td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td></td>
</tr>
<tr>
<td>Prothrombin G20210A</td>
<td></td>
</tr>
<tr>
<td>MTHFR</td>
<td></td>
</tr>
<tr>
<td>Human platelet antigen type 1</td>
<td></td>
</tr>
<tr>
<td>Factor XIII</td>
<td></td>
</tr>
<tr>
<td>Apo E</td>
<td></td>
</tr>
<tr>
<td>Plasminogen activator inhibitor-1 4G/5G genotypes</td>
<td></td>
</tr>
<tr>
<td>Phosphodiesterase 4D</td>
<td></td>
</tr>
<tr>
<td>5-Lipoxygenase—activating protein</td>
<td></td>
</tr>
</tbody>
</table>

| 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                                                                       |                      |

# Organisms implicated in stroke

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

**Infection and Stroke: an Update on Recent Progress**

Eliza C. Miller - Mitchell S. V. Elkind

<table>
<thead>
<tr>
<th>Mechanism of pathogenesis</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct invasion of arterial wall, endotheliopathy</td>
<td>Syphilis, VZV, HSV, HIV, parvovirus B19</td>
</tr>
<tr>
<td>Acceleration of atherosclerosis through induction of cytokines (TNF-alpha, interleukin 2)</td>
<td>Herpesviruses, <em>Chlamydia pneumoniae</em></td>
</tr>
<tr>
<td>Acute systemic infection as stroke trigger (platelet activation, dehydration, infection-induced cardiac arrhythmias)</td>
<td>Influenza, upper respiratory infections, urinary tract infections</td>
</tr>
<tr>
<td>Chronic inflammation due to multiple infections (infectious burden)</td>
<td>Periodontal infection, <em>Chlamydia pneumoniae</em>, herpesviruses</td>
</tr>
<tr>
<td>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</td>
<td>Urinary tract infections, pneumonia, hospital acquired line infections</td>
</tr>
</tbody>
</table>
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

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%

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 1 year and 0.4 at 5 years
  - Grau et al.: Reduced risk of *stroke or transient ischaemic attack* (OR 0·46, 0·27–0·77), no protective effect in summer months

---

*Association between influenza vaccination and reduced risk of brain infarction.*

Lavallée P¹, Perchaud V, Gautier-Bertrand M, Grabli D, Amarenco P.

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%
  - <1 week: 10% to 35%

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

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

<table>
<thead>
<tr>
<th>Outcome and Risk Period</th>
<th>Influenza Vaccination (N=20,486)</th>
<th>Tetanus Vaccination (N=7,966)</th>
<th>Pneumococcal Vaccination (N=5,925)</th>
<th>Systemic Respiratory Tract Infection (N=20,921)</th>
<th>Urinary Tract Infection (N=10,448)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>IR (95% CI)</td>
<td>No. of Cases</td>
<td>IR (95% CI)</td>
<td>No. of Cases</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–3 days</td>
<td>77</td>
<td>0.75 (0.60–0.94)</td>
<td>12</td>
<td>1.10 (0.62–1.92)</td>
<td>4</td>
</tr>
<tr>
<td>4–7 days</td>
<td>94</td>
<td>0.68 (0.56–0.84)</td>
<td>17</td>
<td>1.16 (0.72–1.87)</td>
<td>12</td>
</tr>
<tr>
<td>8–14 days</td>
<td>176</td>
<td>0.73 (0.63–0.85)</td>
<td>25</td>
<td>0.97 (0.66–1.44)</td>
<td>23</td>
</tr>
<tr>
<td>15–28 days</td>
<td>417</td>
<td>0.87 (0.79–0.96)</td>
<td>46</td>
<td>0.89 (0.66–1.19)</td>
<td>43</td>
</tr>
<tr>
<td>29–91 days</td>
<td>2,154</td>
<td>1.03 (0.98–1.08)</td>
<td>253</td>
<td>1.07 (0.94–1.21)</td>
<td>177</td>
</tr>
<tr>
<td>Baseline period</td>
<td>17,533</td>
<td>1.00</td>
<td>7,605</td>
<td>1.00</td>
<td>5,662</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–3 days</td>
<td>76</td>
<td>0.77 (0.61–0.96)</td>
<td>11</td>
<td>1.33 (0.74–2.41)</td>
<td>9</td>
</tr>
<tr>
<td>4–7 days</td>
<td>95</td>
<td>0.72 (0.59–0.88)</td>
<td>15</td>
<td>1.36 (0.82–2.26)</td>
<td>10</td>
</tr>
<tr>
<td>8–14 days</td>
<td>194</td>
<td>0.84 (0.73–0.96)</td>
<td>15</td>
<td>0.77 (0.46–1.28)</td>
<td>19</td>
</tr>
<tr>
<td>15–28 days</td>
<td>409</td>
<td>0.88 (0.80–0.97)</td>
<td>40</td>
<td>1.02 (0.74–1.39)</td>
<td>29</td>
</tr>
<tr>
<td>29–91 days</td>
<td>2,051</td>
<td>1.01 (0.96–1.06)</td>
<td>209</td>
<td>1.15 (1.00–1.32)</td>
<td>160</td>
</tr>
<tr>
<td>Baseline period</td>
<td>16,188</td>
<td>1.00</td>
<td>5,853</td>
<td>1.00</td>
<td>4,184</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Outcome and Risk Period</th>
<th>Influenza Vaccination (N=4010)</th>
<th>Tetanus Vaccination (N=1889)</th>
<th>Pneumococcal Vaccination (N=1686)</th>
<th>Systemic Respiratory Tract Infection (N=5259)</th>
<th>Urinary Tract Infection (N=2408)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>IR (95% CI)</td>
<td>No. of Cases</td>
<td>IR (95% CI)</td>
<td>No. of Cases</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–3 days</td>
<td>11</td>
<td>0.34 (0.19–0.61)</td>
<td>1</td>
<td>0.42 (0.16–2.51)</td>
<td>2</td>
</tr>
<tr>
<td>4–7 days</td>
<td>34</td>
<td>0.77 (0.55–1.09)</td>
<td>2</td>
<td>0.63 (0.16–2.51)</td>
<td>2</td>
</tr>
<tr>
<td>8–14 days</td>
<td>71</td>
<td>0.93 (0.73–1.18)</td>
<td>7</td>
<td>1.24 (0.59–2.62)</td>
<td>9</td>
</tr>
<tr>
<td>15–28 days</td>
<td>146</td>
<td>0.97 (0.82–1.16)</td>
<td>7</td>
<td>0.61 (0.29–1.28)</td>
<td>14</td>
</tr>
<tr>
<td>29–91 days</td>
<td>607</td>
<td>0.97 (0.88–1.06)</td>
<td>58</td>
<td>1.04 (0.79–1.36)</td>
<td>79</td>
</tr>
<tr>
<td>Baseline period</td>
<td>3131</td>
<td>1.00</td>
<td>1812</td>
<td>1.00</td>
<td>1578</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–3 days</td>
<td>19</td>
<td>0.56 (0.35–0.89)</td>
<td>3</td>
<td>2.05 (0.66–6.41)</td>
<td>2</td>
</tr>
<tr>
<td>4–7 days</td>
<td>33</td>
<td>0.74 (0.52–1.05)</td>
<td>1</td>
<td>0.49 (0.07–3.52)</td>
<td>3</td>
</tr>
<tr>
<td>8–14 days</td>
<td>56</td>
<td>0.72 (0.55–0.94)</td>
<td>2</td>
<td>0.54 (0.13–2.20)</td>
<td>3</td>
</tr>
<tr>
<td>15–28 days</td>
<td>105</td>
<td>0.69 (0.57–0.85)</td>
<td>5</td>
<td>0.63 (0.26–1.55)</td>
<td>10</td>
</tr>
<tr>
<td>29–91 days</td>
<td>516</td>
<td>0.79 (0.71–0.87)</td>
<td>38</td>
<td>0.96 (0.67–1.37)</td>
<td>46</td>
</tr>
<tr>
<td>Baseline period</td>
<td>3396</td>
<td>1.00</td>
<td>1301</td>
<td>1.00</td>
<td>1053</td>
</tr>
</tbody>
</table>

Acute infection as a trigger for stroke

- Highest stroke risk: <1 week 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

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

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

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>
<thead>
<tr>
<th>TABLE 3. Type of Infections Diagnosed in Cases and Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases</strong></td>
</tr>
<tr>
<td>Respiratory tract</td>
</tr>
<tr>
<td>Upper respiratory tract*</td>
</tr>
<tr>
<td>Bronchitis</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
</tr>
<tr>
<td>Flu syndrome</td>
</tr>
</tbody>
</table>

*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)_

Severity and clinical outcome of ischemic stroke: worse when preceded by infection: Greater severity of \textit{neurological deficit at presentation} (discordant results)

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
 & 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 \\
\hline
Age, years & 1,703 & 79 [71–84] & 77 [67–83] & 0.025\textsuperscript{b} & & 278 & 79 [66–86] & 75 [63–82] & 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 & 0.21 (0.42–9.57) \\
Atrial fibrillation, % & 1,703 & 27.6 & 29.3 & 0.661 & 0.92 (0.65–1.30) & 275 & 47.4 & 13.5 & 0.001\textsuperscript{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\textsuperscript{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\textsuperscript{b} & 1.89 (1.32–2.69) & 274 & 38.9 & 18.0 & 0.039\textsuperscript{b} & 2.89 (1.06–7.86) \\
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 & 0.63 (0.28–1.92) \\
\hline
\end{tabular}
\caption{Demographics, vascular risk factors and characteristics of patients with acute IS and ICH according to the PI}
\end{table}

\begin{itemize}
\item \textit{Emsley et al, Acute ischaemic stroke and infection: recent and emerging concepts.} Lancet Neurol (2008)
\item \textit{Roquer et al, Previous Infection and Stroke:A Prospective Study.} Cerebrovasc Dis (2012)
\end{itemize}
Severity and clinical outcome of ischemic stroke: worse when preceded by infection: Greater severity of *neurological deficit at presentation* (discordant results)

**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).
Higher **inflammatory markers** (CRP, white blood cell count)

Worse **neurological impairment** (at day1 and day4)

---


**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++** \(\rightarrow\) detrimental effect on outcome:
  - brain damage + neurological deficit

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

Effects of preceding infection on stroke outcome

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

**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)_
Lipopolysaccharide priming: protective effects in experimental models of stroke, with reductions in infarct volume and inflammatory cell activation and infiltration.

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


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

- **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**

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

**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.

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Bacterial Infections and Stroke
# Bacterial infections implicated in stroke

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

Neurosyphilis

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

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.
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
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)
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*
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

Incidence of stroke in neurotuberculosis

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

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

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

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

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

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

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

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

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, amblyacusia and intractable headaches
- Brucella+: plasma and CSF
- Imaging: infarction of the left thalamus.
- A 34-year-old man with neurobrucellosis
- Intracerebral haemorrhage (ICH)
Three mycotic aneurysms were detected in the vicinity of middle cerebral artery (MCA).
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.
# Vasculitis and neurobrucellosis: Evaluation of nine cases using radiologic findings

<table>
<thead>
<tr>
<th>Case</th>
<th>Cranial imaging findings</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MRI: common T2W hyperintense signal change, subdural hygroma, and right frontal hygroma on postcontrast images with leptomeningeal contrast enhancement (Figure 1).</td>
<td>Neurobrucellosis small vessel vasculitis and granuloma</td>
</tr>
<tr>
<td>2</td>
<td>3D TOF MR angiography showed signal loss in the right ICA and right MCA (Figure 2).</td>
<td>Neurobrucellosis great vessel vasculitis</td>
</tr>
<tr>
<td>3</td>
<td>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).</td>
<td>Neurobrucellosis great vessel vasculitis</td>
</tr>
<tr>
<td>4</td>
<td>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).</td>
<td>Neurobrucellosis meningoencephalitis and pons abscess</td>
</tr>
<tr>
<td>5</td>
<td>Cranial MRI imaging revealed T2W hyperintense ischemic glotic lesions of diffuse nodular appearance</td>
<td>Neurobrucellosis small vessel vasculitis</td>
</tr>
<tr>
<td>6</td>
<td>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).</td>
<td>Neurobrucellosis great vessel vasculitis and saccular aneurysm</td>
</tr>
<tr>
<td>7</td>
<td>Widespread and large numbers of demyelinating plaques and amyloid angiopathy on Cranial MR (Figure 6).</td>
<td>Neurobrucellosis small vessel vasculitis</td>
</tr>
<tr>
<td>8</td>
<td>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).</td>
<td>Neurobrucellosis small vessel vasculitis</td>
</tr>
<tr>
<td>9</td>
<td>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).</td>
<td>Neurobrucellosis small vessel vasculitis and granuloma</td>
</tr>
</tbody>
</table>

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

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Vasculitis and neurobrucellosis: Evaluation of nine cases using radiologic findings

Aneurysm in the anterior communicating artery location

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
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.
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


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

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

<table>
<thead>
<tr>
<th>Variables</th>
<th>HP-I</th>
<th>Compared to non-HP-I</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Stroke Event</td>
<td>Stroke Rate*</td>
<td>Stroke Event</td>
</tr>
<tr>
<td>All</td>
<td>2103</td>
<td>8.45</td>
</tr>
<tr>
<td>Subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Embolic IS</td>
<td>35</td>
<td>0.14</td>
</tr>
<tr>
<td>Nonembolic IS</td>
<td>2068</td>
<td>8.31</td>
</tr>
</tbody>
</table>

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

Huang et al, Helicobacter pylori infection increases subsequent ischemic stroke risk: a nationwide population based retrospective cohort study. QJM. (2014)
10 prospective observational studies

Overall combined odds ratio for Helicobacter pylori infection and stroke = 0.96 (95% confidence interval, 0.78-1.14).

No strong association between H. pylori infection and stroke neither in those with cytotoxin-associated gene-A-positive infection.
- 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 ➔ abscess: 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 Fusobacterium necrophorum. Neuropediatrics. (2014)*
Stroke in two children with *Mycoplasma pneumoniae* infection. A causal or casual relationship?

Leonardi S, 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**


Progressive intracranial arteriopathy after Leptospira interrogans infection

Involvement of large intracranial arteries

Viral Infections and Stroke
**Viral infections implicated in stroke**

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

*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+++

**Search results**
- Items: 1 to 20 of 87

**Search results**
- Items: 1 to 20 of 26
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

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

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
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
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*¶

140 PubMed abstracts screened

118 excluded:
- 84 Not stroke
- 14 Too few patients with HIV and stroke
- 7 Not from SS Africa
- 9 Not original research
- 2 In children
- 2 Duplicate

22 full text reports assessed

8 excluded:
- 7 No clear description of parameters of interest
- 1 Venous infarction

14 studies included for data extraction

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

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Ref</th>
<th>Mean Age (years)</th>
<th>Sex (M:F ratio)</th>
<th>Mean CD4 (cells/mm³)</th>
<th>CD4 &lt; 200 or &lt;250+ (cells/mm³) (%)</th>
<th>On ART (%)</th>
<th>Unknown HIV status at stroke diagnosis (%)</th>
<th>Elevated NIHSS (%)</th>
<th>Ischemic Stroke (%)</th>
<th>Anterior circulation (ischemic, %)</th>
<th>Posterior circulation (ischemic, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>South Africa</td>
<td>22</td>
<td>NR</td>
<td>1.4:1.0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>100.0</td>
<td>81.0</td>
<td>10.0</td>
</tr>
<tr>
<td>2003</td>
<td>South Africa</td>
<td>10</td>
<td>32.1</td>
<td>1.5:1.0</td>
<td>NR</td>
<td>40.0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>94.0</td>
<td>94.0</td>
<td>6.0</td>
</tr>
<tr>
<td>2007</td>
<td>Kenya</td>
<td>29</td>
<td>39.0</td>
<td>1.4:1.0</td>
<td>120.0</td>
<td>51.3</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>96.0</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>2007</td>
<td>South Africa</td>
<td>11</td>
<td>33.4</td>
<td>0.5:1.0</td>
<td>NR</td>
<td>46.0</td>
<td>11.9</td>
<td>42.0</td>
<td>NR</td>
<td>96.0</td>
<td>89.0</td>
<td>13.0</td>
</tr>
<tr>
<td>2011</td>
<td>Congo</td>
<td>30</td>
<td>NR</td>
<td>NR</td>
<td>107.6</td>
<td>100.0</td>
<td>66.7</td>
<td>94.0</td>
<td>NR</td>
<td>94.0</td>
<td>82.4</td>
<td>17.6</td>
</tr>
<tr>
<td>2012</td>
<td>Malawi</td>
<td>31</td>
<td>39.8</td>
<td>0.9:1.0</td>
<td>NR</td>
<td>62.8+</td>
<td>22.0</td>
<td>63.1 (&gt;12)</td>
<td>NR</td>
<td>80.0</td>
<td>94.0</td>
<td>6.0</td>
</tr>
<tr>
<td>2013</td>
<td>Benin</td>
<td>20</td>
<td>43.1</td>
<td>1.0:1.0</td>
<td>119.0</td>
<td>NR</td>
<td>100.0</td>
<td>71.7 (&gt;13)</td>
<td>NR</td>
<td>67.3</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>201215</td>
<td>Nigeria</td>
<td>34</td>
<td>36.4</td>
<td>1.4:1.0</td>
<td>224.9</td>
<td>69.0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

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

Stroke + HIV in SSA occurs:

- at a **young age**
- in those with **advanced disease**
- with **worse** outcomes
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)*
A meta-analysis of stroke risk following herpes zoster infection

Fawziah Marra1*, Jeremy Ruckenste1 and Kathryn Richardson2

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.
A meta-analysis of stroke risk following herpes zoster infection

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
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*
VZV vasculopathy

- CSF: +
- Digital subtraction angiography: +

- Acyclovir + prednisolone ➔ no further vascular events
Biological Plausibility of a Link Between Arterial Ischemic Stroke and Infection With Varicella-Zoster Virus or Herpes Simplex Virus

Cytomegalovirus (CMV):

- DNA virus
- belongs to the herpes family of virus
- widely distributed in population
- role in the development of atherosclerosis
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.
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; Xirong Hu, MD; Dongliang Liu, MD

Associations between CMV infection and relative risk of IHD, stroke, and cardiovascular mortality
Association of herpesviruses and stroke: Systematic review and meta-analysis

Harriet J. Forbes, Elizabeth Williamson, Laura Benjamin, Judith Breuer, Martin M. Brown, Sinead M. Langan, Caroline Minassian, Liam Smethurst, Sara L. Thomas, Charlotte Warren-Gash

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


<table>
<thead>
<tr>
<th>Antibodies</th>
<th>Study design</th>
<th>Year</th>
<th>Odds Ratio (95% CI)</th>
<th>Effect estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG (positive)</td>
<td>Case-control</td>
<td>2005</td>
<td>3.72 (1.79, 7.75)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>IgM (positive)</td>
<td>Case-control</td>
<td>2006</td>
<td>3.74 (1.77, 7.83)</td>
<td>OR (95% CI)</td>
</tr>
</tbody>
</table>

CMV

<table>
<thead>
<tr>
<th>Acute phase</th>
<th>Study design</th>
<th>Year</th>
<th>Odds Ratio (95% CI)</th>
<th>Effect estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG (positive)</td>
<td>Case-control</td>
<td>2007</td>
<td>3.50 (1.52, 7.94)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>IgM (positive)</td>
<td>Case-control</td>
<td>2008</td>
<td>3.50 (1.52, 7.94)</td>
<td>OR (95% CI)</td>
</tr>
</tbody>
</table>

EBV, HSV, VZV

<table>
<thead>
<tr>
<th>Acute phase</th>
<th>Study design</th>
<th>Year</th>
<th>Odds Ratio (95% CI)</th>
<th>Effect estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG (positive)</td>
<td>Case-control</td>
<td>2009</td>
<td>3.50 (1.52, 7.94)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>IgM (positive)</td>
<td>Case-control</td>
<td>2010</td>
<td>3.50 (1.52, 7.94)</td>
<td>OR (95% CI)</td>
</tr>
</tbody>
</table>

Herpes simplex virus (HSV), varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6), human herpesvirus 7 (HHV-7)

Increased levels of HHV specific IgG and IgM in stroke patients compared to controls

<table>
<thead>
<tr>
<th>HHV</th>
<th>Study design</th>
<th>Year</th>
<th>Odds Ratio (95% CI)</th>
<th>Effect estimate</th>
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</thead>
<tbody>
<tr>
<td>HSV</td>
<td>Case-control</td>
<td>2011</td>
<td>3.50 (1.52, 7.94)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>VZV</td>
<td>Case-control</td>
<td>2012</td>
<td>3.50 (1.52, 7.94)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>CMV</td>
<td>Case-control</td>
<td>2013</td>
<td>3.50 (1.52, 7.94)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>EBV</td>
<td>Case-control</td>
<td>2014</td>
<td>3.50 (1.52, 7.94)</td>
<td>OR (95% CI)</td>
</tr>
</tbody>
</table>

Note: Odds ratios provide evidence for the association between herpesviruses and stroke risk.
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

HCV infected patients:

- At **higher** and **earlier** risk of stroke
- **Inflammation** = key mediator

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>O.R.</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV</td>
<td>2.04</td>
<td>1.69–2.46</td>
<td>0.00001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.12</td>
<td>1.01–1.27</td>
<td>0.031</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.14</td>
<td>1.01–1.26</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Adinolfi et al.: Chronic HCV infection is a risk factor of ischemic stroke. Atherosclerosis. (2013)
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)
- 11 year population-based study
- Taiwan
- 97198 HCV infected patients
- Higher Hemorrhagic stroke in untreated patients (p=0.0014)
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

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)
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*

### Table

<table>
<thead>
<tr>
<th>Study</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henry Vößke, 2004</td>
<td>1.10 (0.55, 2.19)</td>
<td>0.98</td>
</tr>
<tr>
<td>Joo-Hoon Sung, 2007</td>
<td>0.74 (0.62, 0.87)</td>
<td>42.28</td>
</tr>
<tr>
<td>Tseng CL, 2016</td>
<td>0.77 (0.66, 0.89)</td>
<td>46.92</td>
</tr>
<tr>
<td>Chih-Hao Wang, 2010</td>
<td>1.00 (0.69, 1.44)</td>
<td>4.70</td>
</tr>
<tr>
<td>Jennifer Gilles, 2014</td>
<td>1.05 (0.63, 1.74)</td>
<td>2.14</td>
</tr>
<tr>
<td>Overall (I² squared = 0.0%, p = 0.515)</td>
<td>0.78 (0.70, 0.86)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

*NOTE: Weights are from random effects analysis*
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.

Newborn infant, parvovirus B19 + factor V Leiden mutation.

This case study describes the clinical course of a patient who had multiple strokes due to disseminated intravascular coagulation triggered by H1N1 infection.
Emerging viral infections associated with stroke

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

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
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
West Nile Virus (WNV) vasculitis and stroke

- Isolated vasculitis and chronic perivascular inflammation involving the parenchymal vessels in the autopsies of fatal WNV disease 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 WNV disease

- Viral antigens in perivascular tissue in patients with other forms of viral central nervous system vasculitis, such as varicella-zoster virus–associated vasculitis
Parasitic Infections and Stroke
Parasitic infections implicated in stroke

<table>
<thead>
<tr>
<th>Parasitic infections</th>
<th>Cardioembolism</th>
<th>Arachnoiditis/small artery vasculitis; direct compression of large arteries by cysts</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Trypanosoma cruzi</em></td>
<td></td>
<td>Occlusion of cerebral arteries by infected erythrocytes</td>
</tr>
<tr>
<td><em>Taenia solium</em></td>
<td>Neurocysticercosis</td>
<td>Cardioembolism; arterial compression from cerebral cysts</td>
</tr>
<tr>
<td><em>Plasmodium falciparum</em></td>
<td>Cerebral malaria</td>
<td></td>
</tr>
<tr>
<td><em>Echinococcus granulosis</em></td>
<td>Cardiac hydatidosis</td>
<td>Cerebral cystic echinococcosis</td>
</tr>
<tr>
<td><em>Schistosoma mansoni</em></td>
<td>Schistosomiasis</td>
<td>Microembolic borderzone infarction</td>
</tr>
<tr>
<td><em>Toxocara canis</em></td>
<td>Toxocariasis</td>
<td>Arachnoiditis; vasculitis</td>
</tr>
<tr>
<td>Spirometa species (tapeworm)</td>
<td>Cerebral sparganosis</td>
<td>Vasculitis</td>
</tr>
<tr>
<td><em>Trichinella spiralis</em></td>
<td>Neurotrichinellias</td>
<td>Microinfarction due to direct obstruction of small vessels with larvae; vasculitis</td>
</tr>
</tbody>
</table>
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

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

Cerebral malaria

Cerebral malaria

CASE REPORT

*Plasmodium falciparum* malaria presenting with vertebrobasilar stroke.

# Brief Communication

**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)

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

- endarteritis of small penetrating arteries
- deep lacunar infarctions
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

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Fungal Infections and Stroke
Fungal infections implicated in stroke

- **Cryptococcus**
  - Systemic and CNS infections
  - (usually immunocompromised)

- **Aspergillus**
  - Systemic and CNS infections

- **Mucorales (including Rhizopus, Mucor, etc.)**
  - Mucormycosis

- **Meningitis; vasculitis**

- **Arteritis, vasculopathy**

- **Vascular invasion of fungus, aneurysmal dilatation, vascular necrosis**

Cerebrovascular complications of mycosis

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

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

Kao CD, 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.
Stroke + Fever? First diagnosis?  

Infective endocarditis (IE) +++++

Diagnostic and therapeutic EMERGENCY +++++++

Cerebral embolic Complications : 10-65%

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

References:

**Mechanisme of Stroke in IE**

- *Embolisation* of CNS by unstable valvular vegetations (Left+++)$\Rightarrow$ Occlusion of cerebral arteries
Infracts: (MRI> CT scan)

- **Multiple**, bilateral
- **Small** size
- **Different Age**
- Régions corticales et sous-corticales (Territoires jonctionnels)
- Territory: *Middle cerebral artery***
- Association *other neurological complications* (cerebral hemorrhage, mycotic aneurysm, cerebral abscess)

*T2*, Diffusion
Cardiac manifestations of IE

- Heart murmur+++++
- Systematic heart auscultation + ECG
- If normal: diagnosis NOT excluded
- TTE and TOE+++++
- Vegetations (TOE>>>TTE)
Systemic manifestations of IE

**Signes cliniques extra-cardiaques de l'endocardite bactérienne: SEPHORA**

- Splénomégalie
- Erythème palmo-plantaire de JANEWAY
- Purpura vasculaire
- Hippocratismes digital et hémorragies sous-unguéales et conjonctivales
- Osler : faux panaris
- Roth : rétinite associant exsudats et hémorragies
- Anévrysmes mycotiques

- Kidney: infarction, hematuria
- Spleen: infarction, abscess
- Fingernail beds: splinter hemorrhages

*IMAJ • VOL 12 • AUGUST 2010*
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)

<table>
<thead>
<tr>
<th>Finding</th>
<th>Per cent of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever above 38°C</td>
<td>96</td>
</tr>
<tr>
<td>Splinter haemorrhages</td>
<td>8</td>
</tr>
<tr>
<td>Osler nodes</td>
<td>3</td>
</tr>
<tr>
<td>Janeway lesions</td>
<td>5</td>
</tr>
<tr>
<td>Roth spots</td>
<td>2</td>
</tr>
<tr>
<td>Vascular embolic event</td>
<td>17</td>
</tr>
<tr>
<td>Conjunctival haemorrhage</td>
<td>5</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>11</td>
</tr>
<tr>
<td>New cardiac murmur</td>
<td>48</td>
</tr>
<tr>
<td>Worsening of old cardiac murmur</td>
<td>20</td>
</tr>
<tr>
<td>Elevated erythrocyte sedimentation rate</td>
<td>61</td>
</tr>
<tr>
<td>Elevated serum C reactive protein</td>
<td>62</td>
</tr>
<tr>
<td>Elevated rheumatoid factor</td>
<td>5</td>
</tr>
<tr>
<td>Haematuria</td>
<td>26</td>
</tr>
</tbody>
</table>
Stroke and infective endocarditis

- Hemoculture+++ 
- Biological inflammatory tests 
- Imaging
Stroke and IE: Prognosis

- Stroke in IE: independent predictive factor of mortality
- Death:
  - 35% during hospitalization
  - 52% at 1 year
- Other predictive independent factors of mortality:
  - Symptomatic stroke
  - Consciousness disorders
  - Mechanical valvular prosthesis
Septic cerebral venous thrombosis
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
A Multicenter Study of 1144 Patients with Cerebral Venous Thrombosis: The VENOST Study

### Table 5. Etiological comparisons among studies

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

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

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

Septic sinus thrombosis and meningitis

- **Pneumococcal** meningitis

- Other causes:
  - Coccidioidomycosis
  - Cytomegalovirus
  - Herpes simplex
  - Measles

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

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)

Management of septic CVT

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

- **Anticoagulation**: IV heparin infusion

- **Corticosteroids**

---

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 mass of testicle and epididymis)

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

* tuberculous meningitis

---

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

Fig 2. T1-weighted coronal image with enhanced left parietal area after contrast administration.
**TUBERCULOSIS**

An uncommon cause of cerebral venous thrombosis?

**Fig 3.** T1-weighted sagital image with irregular signals in the sagittal sinus.

**Fig 4.** Venous phase of an angiogram shows irregular signals in the sagittal sinus.
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
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)

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

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.
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.
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 extensive radiological involvement.
Profile of 26 HIV Seropositive individuals with Cerebral Venous 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

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

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)

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).
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.
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).
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 2. (A) Right lateral rectus palsy. (B) Right medial rectus palsy.
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).
Septic Cavernous-Sinus Thrombosis

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

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

Blood culture: positive in 70%

CSF:

- usually abnormal with pleocytosis and elevated total protein
- culture is positive in <20%
Stroke and Infection: Management
Management of stroke due to infections

- Preventive measures
  - Primary prevention
  - Secondary prevention

- Curative measures
  - Symptomatic treatment
  - Etiological treatment
**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

- **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.)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent influenza vaccination</td>
<td>0.46</td>
<td>0.28–0.77</td>
<td>0.0028</td>
</tr>
<tr>
<td>Recent other vaccinations</td>
<td>0.80</td>
<td>0.42–1.53</td>
<td>0.49</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.08</td>
<td>1.33–3.33</td>
<td>0.0012</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.36</td>
<td>0.71–2.61</td>
<td>0.35</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.39</td>
<td>0.88–2.11</td>
<td>0.16</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>7.07</td>
<td>3.55–14.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>0.82</td>
<td>0.43–1.53</td>
<td>0.52</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.62</td>
<td>0.96–2.73</td>
<td>0.072</td>
</tr>
<tr>
<td>Alcohol abstinence</td>
<td>2.30</td>
<td>1.29–4.09</td>
<td>0.0048</td>
</tr>
<tr>
<td>High alcohol consumption</td>
<td>2.65</td>
<td>1.09–6.47</td>
<td>0.033</td>
</tr>
<tr>
<td>Family history of stroke</td>
<td>1.58</td>
<td>0.96–2.59</td>
<td>0.070</td>
</tr>
<tr>
<td>School education ≥10 y</td>
<td>0.82</td>
<td>0.61–1.10</td>
<td>0.18</td>
</tr>
<tr>
<td>Current sports</td>
<td>0.60</td>
<td>0.38–0.96</td>
<td>0.033</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>1.57</td>
<td>0.72–3.42</td>
<td>0.26</td>
</tr>
<tr>
<td>Frequent flu-like illnesses</td>
<td>3.09</td>
<td>1.22–7.80</td>
<td>0.017</td>
</tr>
<tr>
<td>Behavior in febrile infection*</td>
<td>2.75</td>
<td>1.65–4.59</td>
<td>0.0001</td>
</tr>
</tbody>
</table>


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

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

**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.

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Infectious etiology: Not contra-indication of:

- thrombolysis
- Antiplatelets
- Anticoagulants

HIV: 6% of hemorrhagic transformation
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.)*

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

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


Stroke and IE: management

- Preventive measures: early antibiotherapy

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

- Treatment of complications

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

<table>
<thead>
<tr>
<th>Case series</th>
<th>Age (years) and gender</th>
<th>Baseline NIHSS score</th>
<th>Presence of mycotic aneurysm</th>
<th>Modalities of thrombolysis and delay from stroke onset</th>
<th>ICH</th>
<th>sICH</th>
<th>Recanalisation</th>
<th>Clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siccoli et al. [3]</td>
<td>31, female</td>
<td>13</td>
<td>None on angiography</td>
<td>IA urokinase 750,000 IU 5 h</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
<td>NIHSS score = 5 (3 weeks later)</td>
</tr>
<tr>
<td>Junna et al. [4]</td>
<td>56, male</td>
<td>15</td>
<td>Unknown</td>
<td>IV tPA 2 h</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
<td>NIHSS score = 4 (48 h later)</td>
</tr>
<tr>
<td>Tan et al. [5]</td>
<td>12, female</td>
<td>18</td>
<td>None on angiography</td>
<td>IA tPA 0.16 mg/kg 6 h</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>NIHSS score = 5 (6 weeks later)</td>
</tr>
<tr>
<td>Sontineni et al. [6]</td>
<td>70, male</td>
<td>13</td>
<td>None on MR angiography</td>
<td>IV tPA 2 h 30 min</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>NIHSS score = 5 (6 weeks later)</td>
</tr>
<tr>
<td>Bhuvan et al. [11]</td>
<td>65, female</td>
<td>21</td>
<td>None on angiography</td>
<td>IV tPA 1 h 50 min</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
</tr>
<tr>
<td>Present case 2012</td>
<td>61, male</td>
<td>17</td>
<td>None on angiography</td>
<td>IV tPA 2 h</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>68, male</td>
<td>12</td>
<td>Angiography: 2 left distal aneurysms</td>
<td>IV tPA 2 h 15 min</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>NIHSS score = 1 (7 months later)</td>
</tr>
</tbody>
</table>

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)
Figure 1. Conceptual diagram of arguments for early and delayed surgery in patients with infective endocarditis with stroke and other cerebral complications.
Impact of stroke on therapeutic decision making in infective endocarditis

Laurent Derex · Eric Bonnefoy · François Delahaye

esential 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

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%

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.
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
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 Geater³

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)

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Infection-associated CVT (n=20)</th>
<th>Non-infection-associated CVT (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Per cent</td>
</tr>
<tr>
<td>Focal neurological deficits</td>
<td>3</td>
<td>15.0</td>
</tr>
<tr>
<td>Isolated intracranial hypertension</td>
<td>1</td>
<td>5.0</td>
</tr>
<tr>
<td>Cavernous sinus syndrome</td>
<td>16</td>
<td>80.0</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>mRS 3-5 on admission</td>
<td>14</td>
<td>70.0</td>
</tr>
<tr>
<td>Radiological finding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVT≥1 site</td>
<td>3</td>
<td>15.0</td>
</tr>
<tr>
<td>Superficial cortical vein</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Superior sagittal sinus</td>
<td>3</td>
<td>15.0</td>
</tr>
<tr>
<td>Transverse sinus</td>
<td>3</td>
<td>15.0</td>
</tr>
<tr>
<td>Deep cerebral vein</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Cavernous sinus</td>
<td>16</td>
<td>80.0</td>
</tr>
<tr>
<td>Sigmoid sinus</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Straight sinus</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Jugular vein</td>
<td>1</td>
<td>5.0</td>
</tr>
<tr>
<td>Presence of haemorrhage</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

mRS, modified Rankin Scale.

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