Neuropathology lecture series

III. Neuropathology of Cerebrovascular Disease

Physiology of cerebral blood flow
Brain makes up only 2% of body weight
Percentage of cardiac output: 15-20%
Percentage of O₂ consumption (resting): 15%
Distribution of circulation:
- anterior circulation > posterior circulation (70%) (30%)
- gray matter > white matter

Relatively constant blood flow primarily governed by autoregulatory mechanism

Blood flow is a function of:
- perfusion pressure
- resistance of vascular bed as modified by:
  - arterial pressure
  - pCO₂, pH, and oxygen
  - intracranial pressure
  - blood viscosity
  - neurotransmitters???
Epidemiology of stroke
American Heart Association:
USA - almost 4 million stroke survivors
- almost 730,000 new strokes occur per year
Overall age adjusted incidence rates: 100 to 300 / 100,000
Overall, stroke accounts for about 10% of all deaths in most industrialized countries.
Most of these deaths are among persons over the age of 65.
Average age-adjusted stroke mortality in US: 50 to 100/100,000

Stroke
Cerebrovascular accident
“Brain attack”
Defined as an abrupt onset of focal or global neurological symptoms caused by ischemia or hemorrhage.
By convention, symptoms must continue for >24 hours and is usually associated with permanent damage to brain tissue.
If symptoms resolve within 24 hours the episode is called a transient ischemic attack - TIA.

Frequencies of stroke subtypes
- Cerebral infarction 60-80%
- Intracerebral hemorrhage 10-30%
- Subarachnoid hemorrhage 5-10%
- Other (unspecified) 3-25%

Determinants of stroke
Nonmodifiable risk factors
- Age
- Gender
- Ethnicity
- Heredity
Modifiable risk factors
- Hypertension
- Diabetes
- Cardiac disease (atrial fibrillation)
- Hypercholesterolemia
- Cigarette smoking
- Alcohol abuse
- Physical inactivity
Annual risk of stroke (all subtypes combined)

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Approximate population risk</th>
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<tbody>
<tr>
<td>0-14</td>
<td>1 in 100,000</td>
</tr>
<tr>
<td>15-24</td>
<td>1 in 20,000</td>
</tr>
<tr>
<td>25-34</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>35-44</td>
<td>1 in 5,000</td>
</tr>
<tr>
<td>45-54</td>
<td>1 in 1,000</td>
</tr>
<tr>
<td>55-64</td>
<td>1 in 300</td>
</tr>
<tr>
<td>65-74</td>
<td>1 in 100</td>
</tr>
<tr>
<td>75-85</td>
<td>1 in 50</td>
</tr>
<tr>
<td>&gt;85</td>
<td>1 in 33</td>
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</table>

Cerebral infarction

Morphologic Evolution

Sequence of microscopic changes in brain infarcts

> 1 hour
- Microvacuoles within neurons (swollen mitochondria)
- Perineuronal vacuolation (swollen astrocytic processes)

4-12 hours
- Neuronal cytoplasmic eosinophilia
- Disappearance of Nissl bodies
- Pyknotic nuclei
- Leakage of blood-brain barrier

15-24 hours
- Neutrophil infiltration begins

2-3 days
- Macrophages (foam cells) appear

5 days
- Neutrophilic infiltration ceases

~ 1 week
- Proliferation of astrocytes around core infarct
### Sequence of microscopic changes in brain infarcts

<table>
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<tr>
<th>Time</th>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1 hour</td>
<td>Microvacuoles within neurons (swollen mitochondria), Perineuronal vacuolation</td>
</tr>
<tr>
<td>4-12 hours</td>
<td>Neuronal cytoplasmic eosinophilia, Disappearance of Nissl bodies, Pyknotic nuclei, Leakage of blood-brain barrier</td>
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<td>15-24 hours</td>
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<td>2-3 days</td>
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<td>5 days</td>
<td>Neutrophilic infiltration ceases</td>
</tr>
<tr>
<td>~ 1 week</td>
<td>Proliferation of astrocytes around core infarct</td>
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### Topographic features – size & extent of infarct
- Site of occlusion
- Presence/absence of anastomosis
  - Ophthalmic artery (EC-IC)
  - The circle of Willis
  - Leptomeningial anastomosis

### Underlying conditions of infarction

1. Atherosclerosis
Underlying conditions of infarction

II. Arteriolar sclerosis
(small artery disease)

• aging
• sustained systemic hypertension
• diabetes mellitus

Underlying conditions of infarction

III. Cerebral embolism
Some causes of cerebral embolism

Large or small emboli:
- atrial fibrillation
- myocardial infarction
- bacterial endocarditis
- rheumatic endocarditis
- nonbacterial endocarditis
- cardiac surgery
- arterial thrombosis

Small emboli:
- ulcerated atheroma
- trauma (fat emboli)

Underlying conditions of infarction

IV. Vasculitis/vasculitides
Inflammatory CNS vascular diseases
Non-infectious vasculitides
Primary cranial and/or cerebral inflammations
- Takayasu’s arteritis
- giant cell or temporal arteritis
- primary angiitis of the CNS
  (granulomatous angiitis)
Manifestations of systemic diseases
- systemic lupus erythematosus
- polyarteritis nodosa
- Wegener’s granulomatosis
- Churg-Strauss syndrome
- Behcet’s syndrome
- malignancy related
- Drug induced vasculitis
Infectious vasculitis

Cerebral hemorrhage
- intracerebral
- subarachnoid
  - epidural/subdural (trauma)

Intracerebral hemorrhage
Incidence:
Caucasian populations - 16-32 / 100,000
Asians > African Americans > Caucasians
Causes of non-traumatic ICH:
hypertension 50%
cerebral amyloid angiopathy 12%
anticoagulants 10%
tumors 8%
illicit and licit drugs 6%
arteriovenous malformations and aneurysms 5%
miscellaneous 9%

Cerebral hemorrhage
I. Hypertensive hemorrhage
Cerebral hemorrhage

II. SAH subarachnodial hemorrhage
Frequency: 5-9% of all strokes
Reported annual incidence: 10-11 / 100,000

- Non-traumatic conditions
  - rupture of aneurysm* 80%
  - arteriovenous malformations** 5-10%
  - unidentified cause 10-15%

- Secondary
  - intracerebral hemorrhage
  - intraventricular hemorrhage
- Traumatic
**Underlying conditions of SAH**

1. **Intracranial (saccular) aneurysms**

<table>
<thead>
<tr>
<th>Frequency at autopsy:</th>
<th>1 to 6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at autopsy:</td>
<td>30 - 70 yrs</td>
</tr>
<tr>
<td>Sex ratio:</td>
<td>F:M = 3:2</td>
</tr>
<tr>
<td>Associated hypertension:</td>
<td>50%</td>
</tr>
<tr>
<td>Familial:</td>
<td>Rare</td>
</tr>
<tr>
<td>Location:</td>
<td>Anterior circulation &gt; 80%</td>
</tr>
<tr>
<td></td>
<td>Posterior circulation &lt; 20%</td>
</tr>
<tr>
<td>Multiple:</td>
<td>20%</td>
</tr>
<tr>
<td>Ruptured aneurysms:</td>
<td>Size &gt; 0.5 cm</td>
</tr>
<tr>
<td>Mortality:</td>
<td>60%</td>
</tr>
</tbody>
</table>

[Diagram showing approximate 90% of aneurysms]

**Underlying conditions of SAH/IPH**

2. **Vascular malformations**
**Arteriovenous malformations**

<table>
<thead>
<tr>
<th>Clinical onset:</th>
<th>Age 10 to 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio:</td>
<td>M:F = 2:1</td>
</tr>
<tr>
<td>Location:</td>
<td>Usually supratentorial</td>
</tr>
<tr>
<td>Clinical presentation:</td>
<td>Headache, seizures, focal neurologic deficit, hemorrhage</td>
</tr>
<tr>
<td>Angiography:</td>
<td>Evidence of arteriovenous shunt and abnormal blood vessels</td>
</tr>
<tr>
<td>Mortality after hemorrhage:</td>
<td>20%</td>
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</table>
Genetics and Stroke

**Genetic cardiovascular disorders** leading to thromboemboli in CNS
- Arterial dissection, Cardiomyopathies, Neuromuscular diseases, Metabolic conditions (e.g. Homocysteinuria, Coagulopathies, Dyslipidaemia)

**Genetic metabolic disorders** prone to obstruct CNS vessels (e.g. Fabry’s disease)

**CADASIL** (AD arteriopathy with subcortical infarcts and leukoencephalopathy)
- notch 3

**MELAS** (Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes)
- mitochondrial DNA mutations