DIFFERENT STROKES FOR DIFFERENT FOLKS!!

Identifying Stroke Subtypes

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Disclosures

- None
Outline

• Stroke, TIA and Mimics
• Ischemic Stroke Subtypes
• Cryptogenic Stroke
• Adequate Stroke Workup
• Workup specific to stroke type
• Conclusion
Stroke Definition

• Stroke is a *sudden focal neurological deficit, attributed to a vascular cause*

  – Ischemic (lack of blood flow) > 85%
  – Hemorrhagic < 15%, including both intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH)

• *sudden* onset of *focal* brain dysfunction-- hallmark of stroke
Stroke Mimics

- Seizure (post-ictal paralysis)
- Other structural lesions (tumor, abscess, subdural hematoma, encephalitis, etc.)
- Metabolic derangements (hypo/hyperglycemia)
- Migraine
- Psychiatric disease
Transient ischemic attack (TIA)

- sudden-onset focal neurologic deficit resolving within 24 hours (traditional definition)
- attributed to ischemia/vascular cause
- duration usually minutes to a few hours
- transient focal neurologic deficit due to ischemia without evidence of infarction by imaging or pathologic study (new definition)
TIA is a warning of stroke!

- High risk of stroke in the immediate future:
  - 9.2% within 90 days
  - 5.5% within 7 days
  - 3.9% within 48 hours
  - 20% of patients with strokes died
- Diagnostic evaluation the same as for ischemic stroke
- Neuroimaging (MRI) now recommended to rule out subclinical stroke

Subtypes
Cardioembolism (20%)
Large vessel (20%)
Lacunar (25%)
Cryptogenic (30%)
Unusual cause (5%)

Ischemic (85%)
Venous sinus thrombosis

Hemorrhagic conversion of ischemic infarct

Hemorrhagic (15%)
ICH
SAH

HTN
Amyloid angiopathy
AVM
Other

STROKE

STROKE
Stroke Subtypes and Incidence

- Ischemic stroke: 85%
- Hemorrhagic stroke: 15%
- Cryptogenic: 30%
- Cardiogenic embolism: 20%
- Atheroembolic cerebrovascular disease: 20%
- Small vessel disease “lacunes”: 25%
- Other: 5%

Source: Albers et al. Chest 2004; 126 (3 Suppl): 438S–512S.
Relative proportions of etiologic subgroups (TOAST) in age-groups

Large artery atherothromboembolism

• **Extracranial**
  - Internal carotid artery (ICA)
  - Common carotid artery (CCA)
  - Vertebral artery (VA)

• **Intracranial**
  - Internal carotid artery (ICA)
  - Middle cerebral artery (MCA)
  - Anterior cerebral artery (ACA)
  - Vertebral artery (VA)
  - Basilar artery (BA)
  - Posterior cerebral artery (PCA)
Extra & Intra-cranial stenosis

Stroke due to artery-artery embolism more than hypoperfusion
Cardioembolism

- Aortic Arch Plaque
- Atrial Myxoma
- Aortic Valve (Thrombus, Vegetation, Prosthesis)
- Left Atrial Appendage
- Left Atrial Appendage Thrombus
- Mitral Valve (Thrombus, Vegetation, Prosthesis)
- Dilated Cardiomyopathy
- Left Ventricle Thrombus (after Myocardial Infarction)
Cardioembolic Sources

**High risk**
- Mechanical valve
- Mitral stenosis with AFib
- Atrial fibrillation
- Sick sinus syndrome
- Left atrial appendage thrombus
- Recent MI (<4 weeks)
- LV thrombus
- Dilated cardiomyopathy
- Akinetic LV segment
- Atrial myxoma
- Infective endocarditis

**Medium/low risk**
- Mitral valve prolapse
- Mitral annular calcification
- Mitral stenosis without Afib
- Atrial septal aneurysm
- Patent foramen ovale
- Atrial flutter
- Bioprosthetic valve
- Nonbacterial thrombotic endocarditis
- Congestive heart failure
- Hypokinetid LV segment
- MI (>4 weeks, <6 mo.)
Not all cardioembolic strokes Rx with anti-coagulation!

Endocarditis - antibiotics, ? surgery
Atrial myxoma - surgery

Figure 1. Transesophageal echocardiogram demonstrating multiple mitral valve vegetations (arrows). Associated findings included mitral valve prolapse with severe mitral valve regurgitation (Figure 1, A) and moderate posterior mitral annular calcification with mobile vegetation (arrowhead, Figure 1, B).
Small Vessel Occlusive Disease
“Lacunar Stroke”

• Small infarcts involving subcortical structures of the brain:
  ➢ Internal capsule, basal ganglia, thalamus

• Refers to size (<15 mm), not etiology
  • Lipohyalinosis of penetrating end-arteries off major intracranial vessels (e.g. MCA lenticulostriates)
  • Microatheroma
  • Emboli
Lacunar Infarcts
Lacunar Syndromes

- Pure motor
- Pure sensory
- Sensorimotor
- Ataxic hemiparesis
- Clumsy hand-dysarthria
- Hemiballismus-hemichorea
Is This a Lacunar Stroke?
Small vessel strokes accounted for almost half of the events in our study (48%) with a subset of these in the distribution of small penetrator vessels (23%).
“25 symptomatic lacunar infarcts were studied ... Four types of penetrating artery occlusion were found: (1) occlusion by an atheroma with superimposed thrombus... (2) blockage of the mouth of a penetrating artery by atheroma in the wall of the parent artery; (3) dissection in the wall of the parent artery, causing obstruction of the penetrator; and (4) lipohyalinosis. In 5 of the 25 lacunes, the artery... appeared to be essentially normal and fully patent, a finding consistent with microembolism. The riddle of the nature and cause of lacunes had been solved.”

Stroke, 2001
Other **KNOWN** causes of stroke (~5%)

- Dissection
- Vasculitis (Infec/Inflamm)
  - Systemic
  - Primary CNS angiitis
- Drug-associated vasculopathy
- RCVS
- Moya-moya
- Genetic
  - Sickle cell disease
  - Fabry’s disease
  - CADASIL
- Hypercoagulable states
  - Systemic malignancy
  - Antiphospholipid antibodies
  - Heritable
    - Factor V Leiden
    - Prothrombin mutation
    - Protein C, S, antithrombin III deficiency
- Pregnancy, OCP, HRT
- Polycythemia
- Myeloproliferative disorders
Cryptogenic stroke

- Idiopathic--we cannot find a cause
- Accounts for ~25% of all strokes
- Thorough but negative evaluation

Vs. Insufficient evaluation

- Diagnose only after comprehensive search for etiology
What Is An Adequate Work Up?

√ History and examination
√ Vascular Imaging
√ EKG
√ Telemetry in hospital
√ Echocardiogram
√ Routine lab tests
CT vs. MRI
CT vs MRI
Cerebral Vessels

- Carotid US / Transcranial Doppler
- CT Angiography
- MR Angiography
- Conventional Cerebral Angiography
CUS & TCD

- Non-invasive
- Least sensitive
- Tends to overestimate
- Nonetheless, still has a role in today's practice
CT vs MR Angiography

• Sensitivity & Specificity almost identical
• Patient profile dictates modality
  - Contrast vs Gad
  - Metal / implants
  - claustrophobia
• Certain sequences help in diagnosis – mips / t1fat-sats
• Pick one
Conventional Cerebral Angiogram

- Non-invasive modalities do not nail it.
- Vasculitis
- RCVS
- Moya-Moya
- Hypo-perfusion
TTE Vs TEE Age-old question

TEE is more sensitive for detection of:

- LAA thrombus
- PFO
- ASA
- Aortic arch plaque
- Valve vegetations

Sebastiaan F.T.M. de Bruijn et al Stroke 2006
Who Should Get a TEE?

• Stroke in the young, age limit ??
• High suspicion for cardio-embolism, but no proven source
  – Stroke in multiple vascular distributions
  – History of cardiac disease
PFO – A never ending story….

• PFO has low Risk for stroke recurrence
• Among 15 studies with medically treated PFO patients, the absolute rate of recurrent ischemic stroke was:

1.6 events per 100 person-years (95% CI: 1.1 – 2.1)

The Neurologist’s Perspective on PFO & Stroke

• Biologically plausible interventions have failed numerous times in the past when tested rigorously: CLOSURE I, RESPECT, PC TRIAL.

• The risk of recurrent stroke on aspirin is low

• Percutaneous PFO closure is expensive, has a small but real risk of complication, and is unproven

• Off-label PFO closure is rampant and undermines studies
Toward a better understanding of PFO and stroke risk

Steven R. Messé, MD
Walter N. Kernan, MD

A patent foramen ovale (PFO) is a remnant of the fetal circulation and may be found in approximately 25% of adults.¹ Multiple case-control studies have demonstrated an association between PFO and cryptogenic stroke (the PFO-attributable fraction), the less likely the patient was to have a recurrent event. For young patients without vascular risk factors, the risk of recurrent stroke or TIA was only 2% at 2 years. Of note.
“Clinicians who encounter patients with cryptogenic stroke and PFO (and/or atrial septal aneurysm) should encourage them to consider participating in research protocols.”
Mobile Cardiac Outpatient Telemonitoring (MCOT)
Penn Experience With MCOT

- 101 patients with cryptogenic stroke/TIA
- 16% had AF detected
- AF Dx occurred a median of 7d (range 2-25)

<table>
<thead>
<tr>
<th></th>
<th>AF Detected</th>
<th>No AF Detected</th>
<th>p</th>
<th>Multivariate OR (95% CI)</th>
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<tbody>
<tr>
<td>Age</td>
<td>66 ± 12</td>
<td>59 ± 14</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Female Gender</td>
<td>44%</td>
<td>55%</td>
<td>0.42</td>
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<tr>
<td>HTN</td>
<td>81%</td>
<td>64%</td>
<td>0.13</td>
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<tr>
<td>DM</td>
<td>31%</td>
<td>21%</td>
<td>0.44</td>
<td></td>
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<tr>
<td>CHF</td>
<td>0%</td>
<td>1%</td>
<td>0.32</td>
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<tr>
<td>Vascular Disease</td>
<td>19%</td>
<td>12%</td>
<td>0.52</td>
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<tr>
<td>CHADS2</td>
<td>3.4 ± 0.8</td>
<td>3.0 ± 0.9</td>
<td>0.06</td>
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<tr>
<td>CHA2DS2VaSC</td>
<td>4.5 ± 1.4</td>
<td>3.9 ± 1.3</td>
<td>0.12</td>
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<tr>
<td>LAd</td>
<td>4.0 ± 0.4</td>
<td>3.6 ± 0.6</td>
<td>0.01</td>
<td>2.7 (1.02-7.22)</td>
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<tr>
<td>LVEF</td>
<td>62 ± 7</td>
<td>62 ± 9</td>
<td>0.73</td>
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<tr>
<td>PFO/ASD</td>
<td>13%</td>
<td>13%</td>
<td>0.96</td>
<td></td>
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</tbody>
</table>

HTN - hypertension; DM - diabetes; CHF - congestive heart failure; LAd - left atrial diameter; LVEF - left ventricular ejection fraction; PFO - patent foramen ovale; ASD - atrial septal defect
Outpatient cardiac telemetry detects a high rate of atrial fibrillation in cryptogenic stroke

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Atrial fibrillation detected by mobile cardiac outpatient telemetry in cryptogenic TIA or stroke

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ABSTRACT

Objective: Atrial fibrillation (AF) may be present within a subset of patients with presumed cryptogenic TIA or stroke and remains undetected by standard diagnostic methods. We hypothesized that AF may be an under-recognized mechanism for cryptogenic TIA/stroke.
Look Harder for Occult AFib

• About 15 - 20% of cryptogenic stroke pts have occult AF
  – Older patients, women, and those with LA enlargement
• Up to 90% AF episodes are asymptomatic
• AF yield increased with longer monitoring duration
  – >60% AF >30d after initiating monitoring
  – Unknown optimal duration
• Treatment options for AFib expanding
Stroke Labs

Routine
• Fasting Lipid
• HbA1c
• PT/PTT/INR
• CBC
• CMP

Specific
• Lumbar puncture
• Cardiac enzymes
• Rheumatologic work up
• SPEP / UPEP
  HB Electrophoresis
• Toxicology screen
• VDRL / FTA
• ESR
Hypercoagulability & Stroke

• Hypercoagulability should be suspected in patients with ischemic stroke who:
  – < 50 years with no obvious cause of stroke
  – History of multiple unexplained strokes
  – Previous history of venous thrombosis
  – Family history of thrombosis
  – Abnormalities on routine screening coagulation tests
# Hypercoagulable States

## Inherited
- Factor V Leiden
- Prothrombin gene mutation
- Anti-thrombin deficiency
- Protein C & S deficiencies
- Elevated homocysteine
- Dysfibrinogenemia
- Elevated Factor VIII levels
- Abnormal fibrinolytic system
- Sickle Cell disease

## Acquired
- Antiphospholipid antibody syndrome
- Supplemental estrogen use
- HIT
- Cancer
- Medications
- Central venous catheter
- Obesity
- Pregnancy
Hypercoagulable workup

- PT and PTT
- Protein C
- Protein S
- Antithrombin III activity
- Prothrombin gene mutations
- Factor V Leiden gene mutation
- Activated Protein C resistance
- Anticardiolipin antibodies (IgG and IgM)

- Beta2-glycoprotein I antibodies (IgG and IgM)
- Lupus anticoagulant tests
  - dilute Russell viper venom time
  - dilute activated PTT
  - hexagonal phospholipid
- Homocysteine
- Factor VIII activity
- D-dimer
- Lipoprotein (a)
- MTHFR
CANCER

- Autopsy study of patients with cancer, 15% had cerebrovascular disease (7% had clinical symptoms)
- Arterial and venous infarcts
- Elevated D-dimer, DIC, non-bacterial thrombotic endocarditis

Consider:
- CT CAP
- Biomarkers
When is enough, enough?

Only when you find the answer,
or else

Its never enough !!!