Cryptogenic Stroke

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Disclosures

• No financial disclosures
Objectives

• Defining cryptogenic stroke

• Investigating cryptogenic strokes

• Treatment of cryptogenic strokes
What is Cryptogenic?

• Stroke of unknown etiology
• Implies appropriate work up
• TOAST Classification
  • Subtypes of ischemic stroke
• Etiology helps determine appropriate secondary prevention strategy
Etiologies

- Large Artery
  - Plaque in the major vessels of head/neck
  - Most commonly carotid bifurcation
  - Vascular RF’s

- Small Vessel
  - Small “penetrating” vessels deep within the brain
  - Vascular RF’s

- Cardioembolic
  - From heart travel down stream.
  - Many potential causes, atrial fib/flutter most common
Small Vessel
Large Vessel
Stroke of Other Determined Etiology
Cardioembolism
Appropriate Stroke Up

• Hx and Physical
  • Trauma, palpitations, prior neuro symptoms, substance abuse, chest pain (dissection, STEMI), neck/head pain (dissection), neck manipulation, radiation therapy

• Labs
  • Lipids, A1C, UDS, troponin, INR/PTT, CBC

• EKG
• Echocardiogram
• Vessel Imaging
• MRI brain
MRI Brain

- Knowing size/location can be helpful
- ~7% of strokes are MRI negative
  - Posterior fossa
- Detect infarcts in multiple vascular territories that may be silent
Vascular Imaging

• Pros/Cons of different modalities
• Carotid Duplex
  • Limited evaluation – carotid bifurcation only
• CTA
  • Head and neck imaging of posterior and anterior circulation
• MRA
  • Head and neck imaging of posterior and anterior circulation
• Need intracranial and extracranial vessel imaging before considering cryptogenic
Cardiac Rhythm Monitoring

- EKG on presentation
  - Irregular rhythms, NSTEMI/STEMI
- Telemetry monitoring while in ER/Hospital
  - Atrial fibrillation/flutter
  - Often paroxysmal and asymptomatic
- Minimum of 24 hours before considering cryptogenic
- Long term rhythm monitoring if suspicious for atrial fibrillation/flutter and/or cryptogenic stroke
  - Holter
  - Zio/MCOT
  - Insertable Loop
- Longer monitoring is more sensitive
  - Optimal duration unknown
  - Pick up for subclinical atrial fibrillation?
- 30% of cryptogenic strokes will end up being a fib related with long term heart monitoring
  - Changes management
## ADDITIONAL WORKUP: CARDIAC MONITORING

### Conventional Monitoring Strategies

<table>
<thead>
<tr>
<th>TYPE OF MONITORING</th>
<th>SETTING</th>
<th>INVASIVE VS. NONINVASIVE</th>
<th>DURATION</th>
<th>RATE OF DETECTION OF ATRIAL FIBRILLATION, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission ECG</td>
<td>Inpatient</td>
<td>Noninvasive</td>
<td>N/A</td>
<td>2.7</td>
</tr>
<tr>
<td>Inpatient continuous telemetry</td>
<td>Inpatient</td>
<td>Noninvasive</td>
<td>3-5 d</td>
<td>5.5-7.6</td>
</tr>
<tr>
<td>Holter monitor</td>
<td>Outpatient</td>
<td>Noninvasive</td>
<td>24 h</td>
<td>3.2-4.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>48 h</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7 d</td>
<td>12.5</td>
</tr>
<tr>
<td>Mobile continuous outpatient telemetry</td>
<td>Outpatient</td>
<td>Noninvasive</td>
<td>21-30 d</td>
<td>16-25</td>
</tr>
<tr>
<td>Implantable loop recorders</td>
<td>Outpatient</td>
<td>Invasive</td>
<td>6 mo</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>36 mo</td>
<td>30</td>
</tr>
</tbody>
</table>

Types of monitoring and detection of paroxysmal atrial fibrillation in patients with cryptogenic stroke.
Echo

- Structural cardiac imaging
- Potential etiologies
  - PFO, LV thrombus, atrial myxoma, papillary fibroelastoma, vegetations, low EF, aortic athero
- TTE vs TEE
  - TEE considered more sensitive/specific
    - 5% chance of finding pathologies that change management
  - TTE with appropriate maneuvers very sensitive for PFO
  - TTE better for LV thrombus
  - TEE preferred if valvular disease suspected
  - TEE better at imaging left atrium/appendage
Potential Cryptogenic Etiologies

- Unidentified arrhythmia
- Aortic atheromatous disease
- Paradoxical emboli from PFO
- Unidentified Thrombophilia
- Hypercoagulability of Malignancy
- Vasculitis
- Cardiac Tumors
ESUS

- Embolic stroke of undetermined source
  - Embolic appearance with negative workup
  - Non lacunar with no embolism source identified
- Subset of cryptogenic stroke
- Large number of trials on this specific diagnosis
PFO

- 15-25% of adult population
  - Likelihood these are coincidental
- Higher rate in patients with cryptogenic stroke
  - 40% of patients with cryptogenic stroke
  - Association
- How does it lead to stroke?
  - “Paradoxical emboli” – most likely
  - Intrinsic thrombus formation
  - Higher rates of atrial arrhythmias
- LE doppler +/- pelvic MRV
PFO cont.

- Evidence for benefit of PFO closure
  - High ROPE score
    - 7 or higher
    - Probable PASCAL
- Consider closure
  - Age 18-60
  - No other source identified
  - Non lacunar
  - At least 30 days of negative cardiac rhythm monitoring
  - High ROPE, Probable PASCAL
  - High risk PFO features
    - Atrial septal aneurysm, shunt size, presence of venous clot

![Diagram of atrial septum and cardiac structures](image)
PFO Treatment

• Options
  • Antiplatelet therapy
  • Anticoagulation
    • More likely to have bleeding event
  • Closure + Antiplatelet therapy
    • Reduces risk of ischemic strokes

• Closure
  • Small risk from procedure
  • Development of atrial fibrillation
  • If not candidate, unsure if antiplatelet or anticoagulation better
TREATMENT OF PFO

RCTs on the efficacy of PFO closure

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Journal/Date</th>
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<tbody>
<tr>
<td>CLOSURE I</td>
<td>NEJM, 2012</td>
</tr>
<tr>
<td>PC</td>
<td>NEJM, 2013</td>
</tr>
<tr>
<td>RESPECT</td>
<td>NEJM, 2013</td>
</tr>
<tr>
<td>CLOSE</td>
<td>NEJM, 2017</td>
</tr>
<tr>
<td>REDUCE</td>
<td>NEJM, 2017</td>
</tr>
<tr>
<td>DEFENSE-PFO</td>
<td>JACC, 2018</td>
</tr>
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</table>

Decrease in stroke/year (%) with PFO closure: 0.1 to 5.3%

Rate of procedure/device-related adverse events (not including atrial fibrillation): 1 to 3.6%

Appropriate patients:
- Age < 60
- Embolic appearing stroke
- Large shunt
- Other stroke etiologies ruled out
## Risk of Paradoxical Embolism (RoPE) score

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Points</th>
<th>RoPE score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No history of hypertension</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No history of diabetes</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No history of stroke or TIA</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cortical infarct on imaging</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 to 29</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>30 to 39</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>40 to 49</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>50 to 59</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>60 to 69</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>≥70</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

### Total score (sum of individual points)

| Maximum score (a patient <30 years with no hypertension, no diabetes, no history of stroke or TIA, nonsmoker, and cortical infarct) | 10 |
| Minimum score (a patient ≥70 years with hypertension, diabetes, prior stroke, current smoker, and no cortical infarct) | 0  |
Proposed flexible clinical practice approach to classifying patent foramen ovale causal association in patients with embolic infarct topography and without other major stroke sources*

<table>
<thead>
<tr>
<th>Risk source</th>
<th>Features</th>
<th>RoPE score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high</td>
<td>A PFO and a straddling thrombus</td>
<td>Definite</td>
</tr>
<tr>
<td>High</td>
<td>(1) Concomitant pulmonary embolism or deep venous thrombosis preceding an index infarct combined with either (2a) a PFO and an atrial septal aneurysm or (2b) a large-shunt PFO</td>
<td>Probable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Highly probable</td>
</tr>
<tr>
<td>Medium</td>
<td>Either (1) a PFO and an atrial septal aneurysm or (2) a large-shunt PFO</td>
<td>Possible</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Probable</td>
</tr>
<tr>
<td>Low</td>
<td>A small-shunt PFO without an atrial septal aneurysm</td>
<td>Unlikely</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Possible</td>
</tr>
</tbody>
</table>
Inherited Stroke Syndromes

- Low yield evaluation
- Consider if stroke family hx, recurrent strokes, lack of traditional RF’s
- Small vessel appearance
- CADASIL, CARASIL, Fabry, MELAS, COL4A1/2
- Cerebral Autosomal Dominant Arteriopathy with subcortical infarcts and Leukoencephalopathy
  - NOTCH3 gene
  - Clues on MRI
  - Personal and/or family hx of migraine with aura, stroke, cognitive deficits...
Hypercoagulable Evaluation

• Genetic or acquired conditions leading to predisposition for clot formation
• Low yield if testing is indiscriminate
  • Certain clues: young age (<60), lack of vascular RF’s, hx of clotting, family hx of clotting, miscarriages
• Testing results in treatment change 1-8% of the time
• Many hypercoagulable states prevent with venous clotting
  • Warranted in cerebral sinus thrombosis and/or unprovoked DVT
  • Protein C/S, AT III, Factor V Leiden and Prothrombin gene mutation, MTHFR mutation
  • Unlikely associated with arterial clotting
• Sickle Cell
Antiphospholipid Antibody Syndrome

- Acquired hypercoagulable state with recurrent clotting and pregnancy complications
- Clearly associated with arterial events
  - 4x increase in risk for stroke
- Diagnosis
  - Lab abnormalities
    - Lupus anticoagulant
    - B2 glycoprotein ab’s
    - Anticardiolipin ab’s
  - Certain conditions temporarily raise these antibodies
    - Especially in acute setting
    - Persistent lab abnormalities (12 weeks apart) + 1 or more clinical thrombotic event
- Management changes.
  - Warfarin
Infectious Etiologies

- Rare but delayed treatment significant consequences
- Embolism from infective endocarditis
- Ischemic lesions, microbleeds, mycotic aneurysms
- TEE more sensitive
CNS Vasculitis

- RARE
- Rheum disorders, Giant cell arteritis, Takayasu disease, eosinophilic granulomatosis, polyarteritis nodosa, infection....
- Can be challenging to diagnose
  - Labs, CSF, vascular imaging (formal angiogram), brain biopsy
- GCA
  - New onset headache, vision changes/loss, scalp tenderness, jaw claudication, fevers/chills
  - Associated with PMR
  - > age 50
  - Low risk of stroke (1.5-7.5%). Predilection for posterior fossa.
  - Elevated inflammatory markers (ESR, CRP)
  - Temporal artery biopsy
  - Prolonged steroid treatment
    - Fast improvement in symptoms
Aortic Atherosclerotic Disease

- Source of systemic emboli
- Increased risk
  - Complex plaque
  - > 4 mm
  - Ulceration
- Involving ascending aorta and arch
  - Some evidence suggest disease of descending aorta can also cause stroke via retrograde flow
- Treatment involves antiplatelet, statins, RF reduction
MRI of Carotid Plaque

- Specific MRI sequences of carotid bifurcation plaque
  - < 50% luminal narrowing
- Looks for features that suggest vulnerability to embolize
  - Histological look at the plaque
  - intraplaque hemorrhage, lipid-rich necrotic core, thinning of the fibrous cap, plaque ulceration
- Does it change management?
  - If confirms atherosclerotic disease, use high intensity statins and antiplatelets
    - Risk factor modification
  - Surgical intervention?
  - Prevents unnecessary testing
- Not readily available
- Insurance coverage
Covid-19

- Increased association with stroke
  - 2.4% overall risk
  - Thrombo inflammation, pro inflammatory state, cardiac dysfunction...
- Within 1-3 weeks of infection
- Pursue traditional stroke evaluation
- Treatment
  - Thrombolytics +/- thrombectomy for appropriate patients
  - Antiplatelet typically indicated
  - Anticoagulation only if other indication
Atrial Cardiopathy

- Structural or functional changes of the atria
- Increased risk for embolism
  - Even in absence of atrial fibrillation
- LA enlargement, elevated proBNP, EKG findings
- Difficult to establish cause/effect
- Biomarkers being study as is response to treatment

How to Treat if Cryptogenic?

• Secondary prevention
  • Antiplatelet therapy
  • Statin therapy
• Lack of benefit from anticoagulation
  • ESUS trials with anticoagulants not clearly beneficial
• Management of vascular risk factors
References

- “Addressing Patients with Cryptogenic Stroke.” Epidemiology, Pathophysiology, Diagnosis and Follow-up for Patients with Unknown Stroke Etiology. American Stroke Association.