Scope of the Problem: Etiology of Cryptogenic Stroke

Mitchell S. V, Elkind, MD, MS, FAHA
Professor of Neurology and Epidemiology
Columbia University
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Mitchell S. V. Elkind, MD, MS, FAAN, FAHA

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Case

57 year old male economist with no significant past medical history with acute onset of left arm and hand weakness and numbness
Etiologic subtypes ("Causes") of ischemic stroke:
The Northern Manhattan Stroke Study
## Stroke Numbers in US

<table>
<thead>
<tr>
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<th>Prevalence over age 20</th>
<th>Incidence</th>
<th>30 day Mortality</th>
<th>90 day Recurrence</th>
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<tbody>
<tr>
<td><strong>Ischemic Stroke</strong></td>
<td>6.4 million</td>
<td>800,000 per year</td>
<td>5-12%</td>
<td>7%</td>
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<tr>
<td><strong>Cryptogenic Stroke</strong></td>
<td>~2 million</td>
<td>~200,000-250,000 per year</td>
<td>10-15%</td>
<td>4-6%</td>
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NCHS/NHANES ARIC
Racial Imbalance in Ischemic Stroke Incidence

Diagnostic Evaluation

1. History
2. Examination
3. Blood Tests
4. Electrocardiogram
5. Imaging
   • Brain
   • Blood Vessels
   • Heart
51 yo restaurateur with 10 days severe left-sided temple and orbital headache. Mild difficulty swallowing.
Imaging the Brain

48 year old African American woman with history of untreated hypertension with rapidly progressive right weakness

Lacunar infarction: small vessel disease
Atherosclerotic stroke: Imaging the Vessels

- Duplex Doppler
- Transcranial Doppler
- MRI neck/brain
- MRA neck/brain
- CT angiography neck/brain
- Conventional angiography
Extracranial 80-90% L ICA stenosis
Cardioembolic Stroke: “Imaging” the Heart

- EKG
- Transthoracic echocardiography
- Transesophageal echocardiography
- Bubble echocardiography/TCD
- Holter monitoring
- Cardiac MRI
- Extended monitoring
Well-established sources of cardiac embolism

Atrial fibrillation
LA thrombus/LV thrombus
Acute MI
Ischemic/non-ischemic cardiomyopathy
Prosthetic valves
Valvular vegetations
Tumors (myxoma)
Etiologic subtypes ("Causes") of ischemic stroke: The Northern Manhattan Stroke Study

- Cryptogenic: 32%
- Lacunar: 27%
- Cardioembolic: 20%
- Atherosclerotic (Intracranial): 9%
- Atherosclerotic (Extracranial): 8%
- Other: 4%
Definition of Cryptogenic Stroke

Stroke of Undetermined Origin:
Brain infarct not attributed to a definite source of large-vessel atherosclerosis, cardioembolism, or small-vessel disease, in the presence of:
(1) extensive cardiac, vascular, hematologic, and serologic evaluation;
(2) incomplete evaluation; or
(3) evidence of more than one competing cause.

--“TOAST criteria”
“There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns. There are things we don't know we don't know.”

Donald Rumsfeld
Embolic stroke of undetermined source (ESUS)

Requires full evaluation to establish the following:

• Non-lacunar stroke detected by CT or MRI
• Absence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying territory
• No major-risk cardioembolic source of embolism based on TTE and ≥24 hr monitoring (AF/flutter, prosthetic valve, LVEF<30%, etc.)
• No other specific cause identified (dissection, vasculitis, spasm, etc.)

Embolic Stroke of Undetermined Source (ESUS):

Panel 3: Proposed diagnostic assessment for embolic stroke of undetermined source

- Brain CT or MRI
- 12-lead ECG
- Precordial echocardiography
- Cardiac monitoring for ≥24 h with automated rhythm detection†
- Imaging of both the extracranial and intracranial arteries supplying the area of brain ischaemia (catheter, MR, or CT angiography, or cervical duplex plus transcranial doppler ultrasonography)

*Imaging of the proximal aortic arch is not needed; special blood tests for prothrombotic states only if the patient has a personal or family history of unusual thrombosis or associated systematic signs or disorder. †Cardiac telemetry is not sufficient.

Suggested approach to the identification and further evaluation of cryptogenic stroke

Stroke or TIA

1- History/exam/routine labs
2- Initial neurovascular assessment: CT/MRI, vascular imaging
3- Initial cardiac assessment: ECG/inpatient telemetry/TTE

Stroke mechanism identified

No stroke mechanism identified

Presence of risk factors for cardiovascular disease

Lacunar infarction by history/exam/imaging

Absence of risk factors for cardiovascular disease

Cryptogenic infarction: Consider additional testing

“Known knowns”

“Known unknowns”

Tranesophageal echocardiography
(evaluation for Patent Foramen Ovale, Aortic arch atheroma, Spontaneous echo contrast, Mitral valve strands, others)

Holter monitor/Prolonged outpatient telemetry
(evaluation for occult paroxysmal atrial fibrillation)

Intracranial arterial wall imaging
(evaluation for substenotic atherosclerotic plaque)

Additional laboratory testing
(CSF examination, RPR, autoimmune serologies, hypercoagulability testing, etc.)

Potential causes of cryptogenic stroke

- Migraine
- Genetic disorders
  - Fabry disease
  - CADASIL
  - Collagen mutations
  - Actin mutations
- Vasculopathies
  - Vasculitis
  - Reversible Vasoconstriction Syndrome
  - Inflammation (CRP)
- Infections
  - Syphilis
  - HIV
  - Varicella zoster virus
  - Occult Endocarditis
- Homocysteine
- Sleep apnea
- Hypercoagulable states
  - Factor V Leiden
  - Antiphospholipid antibodies
- Cardiac diseases
  - Patent foramen ovale
  - Atrial septal aneurysm
  - Aortic arch atheroma
  - Valvular strands
  - Mitral annular calcification

Etc.
“Unknown unknowns”
Common potential causes of cryptogenic stroke (“Known unknowns”)

- Occult atrial fibrillation
- Less well-documented sources of cardiac embolism
  - PFO
  - Aortic arch atheroma
- Vasculopathies
  - Non-stenosing plaque
- Hypercoagulable states
Transesophageal echocardiogram: PFO
Axial 3D-time-of-flight source image demonstrates signal hyperintensity in the plaque (arrow) of a nonstenosing left-sided carotid artery plaque.

6/27 patients (22.2%) had intraplaque high-intensity signal nonstenosing carotid plaque on side of stroke compared to 0 patients with IHIS-positive plaques on opposite side (p=0.01).
Atrial fibrillation as a cause of stroke

Atrial fibrillation
- Chronic AF
- Paroxysmal AF

“Occult” AF
Other arrhythmias
Serum biomarkers of cardiac dysfunction
Enlarged left atrium
P wave abnormalities on EKG
Genetic markers of atrial fibrillation
“Atrial cardiopathy” as a cause of stroke

Atrial fibrillation
  Chronic AF
  Paroxysmal AF
  Occult AF

Other arrhythmias

Serum biomarkers of cardiac dysfunction
Enlarged left atrium
P wave abnormalities on EKG
Genetic markers of atrial fibrillation
P wave abnormalities

Reflects left atrial structure and function

P-terminal Force in V1 = duration x amplitude (depth) of the negative component of the P-wave in V1 (microvolt.millisecond)
# PTV1 in NOMAS: Case-cohort analysis

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<th>Outcome</th>
<th>Unadj</th>
<th>Adj</th>
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<tr>
<td>Any ischemic stroke</td>
<td>1.24 (1.07-1.42)</td>
<td>1.20 (1.03-1.39)</td>
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<tr>
<td>Ischemic stroke subtypes</td>
<td></td>
<td></td>
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<tr>
<td>Cryptogenic or cardioembolic</td>
<td>1.31 (1.10-1.55)</td>
<td>1.31 (1.08-1.58)</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>1.29 (0.99-1.68)</td>
<td>1.29 (0.96-1.72)</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>1.32 (1.07-1.62)</td>
<td>1.23 (0.97-1.56)</td>
</tr>
<tr>
<td>Non-cardioembolic</td>
<td>1.14 (0.94-1.40)</td>
<td>1.14 (0.92-1.40)</td>
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Results are reported as the hazard ratio (95% CI) for each 1-standard deviation increase in PWV1. Adjusted model includes age, sex, race, education, smoking status, diabetes, hypertension, lipid levels, atrial fibrillation, and heart failure.

INTERSTROKE 2010

90% OF THE ATTRIBUTABLE RISK OF STROKE EXPLAINED BY 10 RISK FACTORS

3000 cases/3000 controls; 84 centers; 22 countries

Hypertension 52%
Physical inactivity 29%
Abdominal obesity 27%
Hyperlipidemia 25%
Diet 19%
Current smoking 19%
Cardiac disease 7%
Diabetes 5%
Psychosocial stress/depression 5%
Alcohol consumption 4%

80%
Cryptogenic Stroke: Explaining the Unexplained

1. Cryptogenic Stroke Is Common

2. What You See Is What You Get:
   • Diagnosis of Cryptogenic Stroke is a Diagnosis of Exclusion (Exclude the Known Knowns)

3. An Absence of Evidence is Not Always Evidence of Absence:
   • Exclusion Depends on How Hard One Looks for Other Causes (the Known Unknowns)

4. It Is…Until It Isn’t:
   • Once a Cause Is Found, the Stroke Is No Longer Unexplained

5. “There Are Things We Don't Know We Don't Know”:
   • Methods to Detect Causes of Stroke Continue to Improve (Unknown Unknowns)

6. Why We Care:
   • Identifying the Cause is the Best Way to Prevent Recurrence
Thanks for your attention!