Ischemic Stroke: Overview & Management

James Klaas, M.D.
Stroke Center Medical Director
Mayo Clinic, Rochester, MN
Objectives/Disclosures

• Ischemic stroke:
  • Approach to a patient with acute stroke
  • Stroke localization and mechanism
  • Secondary prevention

• No disclosures or conflicts of interest
Why care?

• >7,000,000 stroke survivors in the U.S.

• **800,000** strokes/year in the U.S.
  • A stroke occurs every 40 seconds

• **5th** leading cause of death in the U.S.
  • Every 3 minutes someone dies

• **#1 cause of disability**
  • 66% survivors have disability, 33% permanently disabled

• Annual cost: ~$54 billion
ISCHEMIC STROKE/TIA
Systematic Approach to Stroke/TIA

1) Are the symptoms caused by a TIA or ischemic stroke?

2) Is the patient in the time window for acute intervention?

3) Localize the symptoms

4) What is the mechanism?

5) Decide on best medical/surgical means of stroke prevention
Case

HPI
65 RHF transient monocular vision loss 1 week ago, now w/ acute difficulty speaking & R face & arm weakness

SocHx
- Tobacco (1ppd)

FamHx
- Ø

Meds
- Ø

Exam
VS: BP 160/85, P 70, RR 15
General: Awake, alert
CV: RRR, L carotid bruit
Neuro: Aphasia, R arm>leg weakness

PMHx
- HTN
- HLD
- GERD
Did the patient have a TIA?

1) Yes
2) No
3) Need more information
4) Don’t know
TIA

• Transient neurologic deficit from cerebral ischemia w/o infarction
  • Historically: time based (<24hrs)
  • Now: tissue based (imaging)

• Most TIAs <15 min
  • 90% resolve w/in 1 hr

• High-risk for stroke
  • ~12% w/in 1-year
  • ~33% lifetime

• Factors* that increase stroke risk after TIA:
  • Age >60 years
  • Deficits
    • weakness
    • speech disturbance
  • Duration >60 min
  • HTN
  • DM

*Components of ABCD2 score
Systematic Approach to Stroke/TIA

1) Are the symptoms caused by a TIA or ischemic stroke?

2) Is the patient in the time window for acute intervention?

3) Localize the symptoms

4) What is the mechanism?

5) Decide on best medical/surgical means of stroke prevention
ACUTE STROKE
Historical Timeline

- 400 B.C.: "Apoplexy"
- 1599: "Stroke"
- 1899: Aspirin
- 1995: tPA
- 1990s: Aspirin + Acute Stroke
- 1998/2005: Endovascular
Case

• 65F with acute aphasia, R face and arm weakness

• Assessment:
  • Establish time onset/last normal
  • Brief neuro exam (NIHSS)
  • Blood pressure
  • Glucose level
  • CT scan
<table>
<thead>
<tr>
<th>Response</th>
<th>(Score)</th>
<th>Response</th>
<th>(Score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of consciousness</td>
<td></td>
<td>Motor arm (left and right)</td>
<td></td>
</tr>
<tr>
<td>alert</td>
<td>(0)</td>
<td>no drift</td>
<td>(0)</td>
</tr>
<tr>
<td>drowsy</td>
<td>(1)</td>
<td>drift before 10 seconds</td>
<td>(1)</td>
</tr>
<tr>
<td>stuporous</td>
<td>(2)</td>
<td>falls before 10 seconds</td>
<td>(2)</td>
</tr>
<tr>
<td>coma</td>
<td>(3)</td>
<td>no effort against gravity</td>
<td>(3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no movement</td>
<td>(4)</td>
</tr>
<tr>
<td>Response to level of</td>
<td></td>
<td>Motor leg (left and right)</td>
<td></td>
</tr>
<tr>
<td>consciousness questions*</td>
<td></td>
<td>no drift</td>
<td>(0)</td>
</tr>
<tr>
<td>answers both correctly</td>
<td>(0)</td>
<td>drift before 5-10 seconds</td>
<td>(1)</td>
</tr>
<tr>
<td>answers one correctly</td>
<td>(1)</td>
<td>falls before 5-10 seconds</td>
<td>(2)</td>
</tr>
<tr>
<td>answers neither correctly</td>
<td>(2)</td>
<td>no effort against gravity</td>
<td>(3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no movement</td>
<td>(4)</td>
</tr>
<tr>
<td>Response to level of</td>
<td></td>
<td>Ataxia</td>
<td></td>
</tr>
<tr>
<td>consciousness commands†</td>
<td></td>
<td>absent</td>
<td>(0)</td>
</tr>
<tr>
<td>obeys both correctly</td>
<td>(0)</td>
<td>one limb</td>
<td>(1)</td>
</tr>
<tr>
<td>obeys one correctly</td>
<td>(1)</td>
<td>two limbs</td>
<td>(2)</td>
</tr>
<tr>
<td>obeys neither</td>
<td>(2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pupillary response</td>
<td></td>
<td>Sensory</td>
<td></td>
</tr>
<tr>
<td>both reactive</td>
<td>(0)</td>
<td>normal</td>
<td>(0)</td>
</tr>
<tr>
<td>one reactive</td>
<td>(1)</td>
<td>mild</td>
<td>(1)</td>
</tr>
<tr>
<td>neither reactive</td>
<td>(2)</td>
<td>severe loss</td>
<td>(2)</td>
</tr>
<tr>
<td>Gaze</td>
<td></td>
<td>Language</td>
<td></td>
</tr>
<tr>
<td>normal</td>
<td>(0)</td>
<td>normal</td>
<td>(0)</td>
</tr>
<tr>
<td>partial gaze palsy</td>
<td>(1)</td>
<td>mild aphasia</td>
<td>(1)</td>
</tr>
<tr>
<td>total gaze palsy</td>
<td>(2)</td>
<td>severe aphasia</td>
<td>(2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mute or global aphasia</td>
<td>(3)</td>
</tr>
<tr>
<td>Visual fields</td>
<td></td>
<td>Facial palsy</td>
<td></td>
</tr>
<tr>
<td>no visual loss</td>
<td>(0)</td>
<td>normal</td>
<td>(0)</td>
</tr>
<tr>
<td>partial hemianopsia</td>
<td>(1)</td>
<td>minor paralysis</td>
<td>(1)</td>
</tr>
<tr>
<td>complete hemianopsia</td>
<td>(2)</td>
<td>partial paralysis</td>
<td>(2)</td>
</tr>
<tr>
<td>bilateral hemianopsia</td>
<td>(3)</td>
<td>complete paralysis</td>
<td>(3)</td>
</tr>
<tr>
<td>Dysarthria</td>
<td></td>
<td>Extinction/inattention</td>
<td></td>
</tr>
<tr>
<td>normal</td>
<td>(0)</td>
<td>normal</td>
<td>(0)</td>
</tr>
<tr>
<td>mild</td>
<td>(1)</td>
<td>mild</td>
<td>(1)</td>
</tr>
<tr>
<td>severe</td>
<td>(2)</td>
<td>severe</td>
<td>(2)</td>
</tr>
</tbody>
</table>

* Level of consciousness questions: "How old are you?" "What month is this?"
† Level of consciousness commands: "Squeeze my hand" (using nonparetic hand), "Close your eyes.">

<4 = Good prognosis -- No tPA  4-20 = mild to moderate - ideal tPA  >20 = severe deficit -- No tPA
Case

- 65F with acute aphasia, R face and arm weakness

- Assessment:
  - Establish time onset/last normal
  - Brief neuro exam (NIHSS)
  - Blood pressure
  - Glucose level
  - CT scan

- Candidate for IV tPA?
What is the time window for IV tPA?

1) <2 hours
2) <3 hours
3) <4.5 hours
4) <6 hours
5) <6.5 hours
6) <8 hours
IV TPA
IV tPA <3 hours
## NINDS: Efficacy

### Outcome at three months

<table>
<thead>
<tr>
<th>Assessment</th>
<th>tPA (n=168) % good outcome</th>
<th>Placebo (n=165) % good outcome</th>
<th>OR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barthel index</td>
<td>50</td>
<td>38</td>
<td>1.6 (1.1-2.5)</td>
<td>0.026</td>
</tr>
<tr>
<td>Rankin</td>
<td>39</td>
<td>26</td>
<td>1.7 (1.1-2.6)</td>
<td>0.019</td>
</tr>
<tr>
<td>Glasgow</td>
<td>44</td>
<td>32</td>
<td>1.6 (1.1-2.5)</td>
<td>0.025</td>
</tr>
<tr>
<td>NIHSS</td>
<td>31</td>
<td>20</td>
<td>1.7 (1.0-2.8)</td>
<td>0.033</td>
</tr>
</tbody>
</table>
IV tPA Criteria

Exclusion:
- Active bleeding
- History of intracranial hemorrhage or bleeding diathesis
- Arterial puncture at non-compressible site
- Blood pressure >185/110
- Recent intracranial/intraspinal surgery
- Aortic dissection
- Serum glucose <50
- Bleeding diathesis:
  - INR >1.7
  - Heparin within 48 hours and elevated APTT
  - NOAC (48 hours)
  - Platelets <100,000
- Imaging
  - Hemorrhage
  - Large established infarct (on CT)
  - Intracranial tumor
  - AVM

Relative contraindication:
- Minor/rapidly improving deficit
- Recent ischemic stroke or head injury
- Major surgery or trauma (14 days)
- Recent STEMI (3 months)
- GI or UT hemorrhage (21 days)
- Pregnancy
- Seizure
NINDS: Safety

- **Symptomatic hemorrhage higher with t-PA**
  - t-PA: 6.4%
    - **Fatal**: 3%  **Non-fatal**: 4%
  - Placebo: 0.6%
- All cause 90-day mortality no different
Use of Intravenous Thrombolysis Beyond 3 hours

Any Data Supporting Use Beyond 3 Hours?
IV tPA 3-4.5 hours
ECASS III

• Compared IV tPA to placebo at 3-4.5 hours post acute ischemic stroke

• Similar criteria for <3 hours, except also excluded:
  • Patients older than 80 years
  • Warfarin use, even if ≤ INR 1.7
  • Baseline NIHSS >25
  • Those with a history of stroke and diabetes
ECASS III: Efficacy & Safety

- **Efficacy:**
  - Higher chance of favorable outcome at 3 months
    - Absolute benefit: 7 per 100 treated

- **Safety:**
  - Symptomatic hemorrhage risk increased
    - t-PA: 2.4% Placebo: 0.2%
    - No difference in mortality or other adverse events

- **Considered off-label**
  - AHA guidelines recommend extending the window
Save a Minute, Save a Day

- Time matters!
  - 2 million neurons die every minute
  - Every minute is 1.8 days of life
  - tPA given at:
    - <1.5 hours
      - Disability-free OR 2.6, NNT 5
    - 3-4.5 hours
      - Disability-free OR 1.3, NNT 14

Meretoja, et al. Stroke. 2014;45
Case

• 65F presents with acute aphasia, R face and arm weakness

• Assessment:
  • Establish time onset/last normal 2 hours
  • Brief neuro exam (NIHSS) 9
  • Blood pressure 170/95
  • Glucose level 110
  • CT scan No blood or hypodensity

• Candidate for IV tPA? Yes!
But what if:

Symptoms don’t improve following tPA

or

A patient presents >4.5 hours

or

Time of onset unknown

Are there any other options?
Endovascular Treatment

- MR CLEAN
- ESCAPE
- EXTEND IA
- SWIFT PRIME
- REVASCAT

**ORIGINAL ARTICLE**

A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke


**ORIGINAL ARTICLE**

Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke

M. Goyal, A.M. Dernchuk, B.K. Menon, M. Eesa, J.L. Rempel, J. Thornton, D. Roy

**ORIGINAL ARTICLE**

Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection

B.C.V. Campbell, P.J. Mitchell, T.J. Kleinig, H.M. Dewey, L. Churilov, N. Yassi

**ORIGINAL ARTICLE**

Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke

Jeffrey L. Saver, M.D., Mayank Goyal, M.D., Alain Bonafe, M.D., Hans-Christoph Diener, M.D., Ph.D., Elad I. Levy, M.D., Vitor M. Pereira, M.D.
• MERCI Retriever
• Penumbra
• Retrievable stents
Acute Ischemic Stroke Management: 
*Thrombolytic/Endovascular Summary*

- Less than 3 hours after onset: IV t-PA
- Between 3 and 4.5 hours: off-label use of IV t-PA
- 3-6 hours*:
  - Anterior circulation: consider endovascular
  - Basilar distribution: consider endovascular
- 6-12 hours:
  - Anterior circulation: supportive care
  - Basilar distribution: consider endovascular?

*In addition to IV tPA*
Acute Stroke Treatment

- Airway/O2
- Treat Hyperthermia
- Fluid management
- Treat Hyperglycemia
- Blood pressure
- IV thrombolysis
- Endovascular options
- Aspirin/Antiplatelet
Blood Pressure Issues in Acute Ischemic Stroke

- Frequently elevated for 24-48 hours
- No aggressive treatment unless >220/110 or:
  - tPA used → <185/110
  - Other reason:
    - Cardiac indication, such as MI
    - Hemorrhage
    - PRES/HTN encephalopathy
- Consider secondary causes:
  - Pain, bladder distention, anxiety, etc.
- Avoid over-treatment!
Systematic Approach to Stroke/TIA

1) Are the symptoms caused by a TIA or ischemic stroke?
2) Is the patient in the time window for acute intervention?
3) Localize the symptoms
4) What is the mechanism?
5) Decide on best medical/surgical means of stroke prevention
VASCULAR ANATOMY
Right MCA
Left PCA
Right PICA
POP QUIZ!
Vascular territory?

- 1) ACA
- 2) MCA
- 3) PCA
- 4) PICA
- 5) ACA + MCA
- 6) Other
Vascular territory?

- 1) ACA
- 2) MCA
- 3) PCA
- 4) PICA
- 5) ACA + MCA
- 6) Other
Vascular territory?

- 1) ACA
- 2) MCA
- 3) PCA
- 4) PICA
- 5) ACA + MCA
- 6) Other
Vascular territory?

1) ACA
2) MCA
3) PCA
4) PICA
5) ACA + MCA
6) Other
Vascular territory?

- 1) ACA
- 2) MCA
- 3) PCA
- 4) PICA
- 5) ACA + MCA
- 6) Other
FUNCTIONAL ANATOMY
Case

- 65F with acute aphasia, R face and arm weakness

- **Localize:**
What vascular territory is involved?

1) Left MCA
2) Right MCA
3) Left ACA
4) Right ACA
5) Left PCA
6) Right PCA
7) Other
Functional Anatomy

Anterior Circulation: Carotid Arteries

- **Ophthalmic artery:**
  - Amaurosis fugax

- **Anterior cerebral**
  - Contralateral weakness/sensory: leg

- **Middle cerebral**
  - Contralateral weakness/sensory: arm/face
  - Aphasia
  - Homonymous hemianopsia
Homonculus

ACA
Homonculus

MCA
Functional Anatomy

Posterior Circulation: Vertebrobasilar system

- In isolation or in combination:
  - Diplopia
  - Dysarthria
  - Ataxic gait or limbs
  - Unilateral or bilateral visual changes
  - Facial sensation change or weakness
  - Vertigo
  - Unilateral or bilateral motor / sensory changes
Systematic Approach to Stroke/TIA

1) Are the symptoms caused by a TIA or ischemic stroke?
2) Is the patient in the time window for acute intervention?
3) Localize the symptoms
4) What is the mechanism?
5) Decide on best medical/surgical means of stroke prevention
Defining the Mechanism of a TIA or Cerebral Infarction: 
**Four Major Categories**

1. **Cardiac**
   - Intracardiac thrombus
   - Cardiac mass lesions
   - Valve disease
   - Arrhythmias
   - Venous source with right-to-left shunt (PFO)

2. **Large vessel disease**
   - Atherosclerosis
   - Dissection, fibromuscular dysplasia
   - Vasculitis
Defining the Mechanism of a TIA or Cerebral Infarction:

Four Major Categories

3. Small vessel disease
   - Atherosclerosis/lipohyalinosis
     - Hypertension
     - Hyperlipidemia
     - Smoking
     - Diabetes
   - Vasculitis

4. Hematologic
   - Hgb, Plt, or WBC disorder
     - Polycythemia vera
     - Sickle cell
   - Hypercoagulable
     - Antiphospholipid syndrome
     - Protein C or S deficiency
Systematic Approach to Stroke/TIA

1) Are the symptoms caused by a TIA or ischemic stroke?

2) Is the patient in the time window for acute intervention?

3) Localize the symptoms

4) What is the mechanism?

5) Decide on best medical/surgical means of stroke prevention
Secondary Prevention

Antithrombotics
Antithrombotics

- Anticoagulation
  - Warfarin
  - NOACs
    - Apixaban (F Xa)
    - Rivaroxaban (F Xa)
    - Dabigatran (F II)

- Antiplatelet
  - Aspirin
  - Clopidogrel
  - Dipyridamole/ASA

When is anticoagulation indicated?

- Cardiac source
- Hypercoagulable state
- Extracranial dissection with TIA or Stroke
  - *Non-superior (CADISS Lancet 2015)
- Aortic arch thrombus or mobile debris
  - *Inconclusive (ARCH Stroke 2014)
Antiplatelets

• ASA, clopidogrel (______), dipyridamole/ASA (______) are all appropriate initial therapies

• But which one?
Secondary Prevention: Selecting an Antiplatelet

- **Clopidogrel > ASA**
  - CAPRIE *Lancet* 1996

- **Dypridamole/ASA > ASA**
  - ESPS2 *J Neurol Sci* 1996
  - ESPRIT *Lancet* 2006

- **Clopidogrel = Dypridamole/ASA**
  - PROFESS *NEJM* 2008

- Decision based on comorbidities, side effects, cost, etc.
Secondary Prevention: Dual-Antiplatelet?

• No!*
  • MATCH Lancet 2004
  • CHARISMA NEJM 2006

• *Well, maybe in certain circumstances...
Secondary Prevention: Dual-Antiplatelet

- **Intracranial stenosis**
  - SAMMPRIS *NEJM* 2011
    - Stenting v. maximal medical therapy
    - ASA + clopidogrel 90 days

- **Acute minor stroke/TIA**
  - CHANCE *NEJM* 2013
    - NIHSS<4, Initiated within 24 hours of stroke/TIA
    - ASA + clopidogrel 21 days
  - POINT trial?

- **Aortic arch thrombus or mobile debris**
  - ARCH *Stroke* 2014
    - ASA + clopidogrel v. warfarin
Secondary Prevention

Carotid disease
Carotid Revascularization

The New England Journal of Medicine

©Copyright, 1991, by the Massachusetts Medical Society

Volume 325  AUGUST 15, 1991  Number 7

BENEFICIAL EFFECT OF CAROTID ENDARTERECTOMY IN SYMPTOMATIC PATIENTS WITH HIGH-GRADE CAROTID STENOSIS

North American Symptomatic Carotid Endarterectomy Trial Collaborators*
Carotid Revascularization

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812  JULY 1, 2010  VOL. 363  NO. 1

Stenting versus Endarterectomy for Treatment of Carotid-Artery Stenosis

Diagram showing different stages of carotid artery procedures.

ICA, ECA, CCA
## Carotid Revascularization

<table>
<thead>
<tr>
<th>Carotid revascularization (Stent or CEA)</th>
<th>Outcome (Ipsilateral stroke)</th>
<th>Control</th>
<th>Intervention</th>
<th>RRR</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic, 70-99%</td>
<td>5 years</td>
<td>33%</td>
<td>17%</td>
<td>48%</td>
<td>16%</td>
<td>6</td>
</tr>
<tr>
<td>Symptomatic, 50-69%</td>
<td>5 years</td>
<td>27%</td>
<td>19%</td>
<td>28%</td>
<td>8%</td>
<td>12</td>
</tr>
</tbody>
</table>

NASCET NEJM 1991
CREST NEJM 2010
Hankey et al. Lancet Neurol 2014
Carotid Revascularization

• Benefits of CEA greatest:
  • Men
  • Older patients
  • Recent cerebral ischemia (as opposed to the eye)
  • Ulcerated plaque

• CEA has lower risk of:
  • Periprocedural stroke or death
  • Less risk of restenosis

• Stenting has lower risk of:
  • Cranial nerve injury
  • MI

Hankey et al. Lancet Neurol 2014
Secondary Prevention

Modifiable Risk Factors
What is the most important modifiable risk factor?

1) High blood pressure
2) Cigarette smoking
3) Elevated cholesterol
4) Diabetes
5) Metabolic syndrome
6) Excess alcohol intake
7) Obesity
8) Physical inactivity
9) Obstructive sleep apnea