ED-Venture: Neurology: Brain Strain

Karen Greenberg, DO, FACOEP
Disclosure

• I have the following financial relationship with the manufacturer of any commercial product and/or provider of commercial services discussed in this CME activity:

  – Speakers bureau for Genentech

• I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.
Objectives

• Differentiate worrisome headache from common primary headache

• Discuss current recommendations for acute stroke
- 47 yo male presents with HA x 3 days
- Hx of HAs as a child, no recent Headaches
- No prior visits to ED
- BP 243/151
- Physicians document gradual onset
- Nurse documents worst headache of life
Subarachnoid Hemorrhage

- Headache is a chief complaint that accounts for 4.5% of emergency department visits, with aneurysmal subarachnoid hemorrhage accounting for 1% of headaches overall.

- The majority (85%) of nontraumatic, or spontaneous SAH are related to aneurysm rupture.

- aSAH can pose diagnostic challenges in the Emergency Department.

### High Risk Historical Features

- Sudden-onset
- No similar HAs in past
- Concominat infection
- Altered mental status or seizure
- Headache with exertion
- Age over 50

- HIV and immunosuppression
- Visual Disturbances
- Pregnancy and postpartum state
- Location of pain
- Family History
- Medications (Anticoagulants)
- Illicit Drugs
- Toxic Exposure

High Risk Examination Findings

• Abnormal Vital Signs
• Toxic Appearance
• Decreased LOC
• Neurologic abnormalities
• Meningismus
• Ophthalmologic findings

Imaging

• CT or MRI is preferred

• CTA or MRA for imaging of the vessels

• Catheter angiography
Diagnostic approach for subarachnoid haemorrhage in patients presenting with more than 6 hours of headache onset. CTA, computed tomography angiography; DSA, digital subtraction angiography; LP, lumbar puncture; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NCCT, noncontrast computed tomography; OR, operating room.
To LP or not to LP??

• Because the consequences of missing SAH are potentially dire, most guidelines state that an LP should be performed in all patients with suspected SAH in whom the CT is normal.

• However, if a high-quality CT is obtained within six hours of the onset of symptoms and interpreted by an expert radiologist to be normal, LP is probably not necessary.

<table>
<thead>
<tr>
<th>Limitations of CT</th>
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<tbody>
<tr>
<td><strong>Time</strong></td>
<td>Sensitivity decreases as time from symptom onset increases</td>
</tr>
<tr>
<td><strong>Volume</strong></td>
<td>Small volume bleeds may not be detected by CT</td>
</tr>
<tr>
<td><strong>Interpreter Experience</strong></td>
<td>Less experienced radiologists or emergency clinicians/general practitioners may have decreased sensitivity compared with experienced neuroradiologists</td>
</tr>
<tr>
<td><strong>Technology</strong></td>
<td>Modern scanners with thinner cuts without motion artifact will have greater likelihood of identifying SAH compared to older scanners with thicker cuts or cases with motion artifact</td>
</tr>
<tr>
<td><strong>Anemia</strong></td>
<td>Patients who have a hematocrit &lt;30% may have a CT that is falsely negative due to isodense blood</td>
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Thoughts about Imaging . . .

• Unfortunately, gold standard for ED diagnosis even in 2020 is non contrast CT head followed by LP, if history and physical are strongly suggestive of suspicious for SAH.
  
  – This is Class I, Level B evidence in the AHA/ASA Guidelines for the diagnosis of aSAH
  – CTA is Class IIb, Level C evidence in the AHA/ASA Guidelines for the diagnosis of aSAH
  – MRI/MRA could possibly be an alternative if accessible

• CT head alone if done after 6 hours of onset of HA, is not sensitive or specific enough to rule out this life threatening diagnosis.

Thoughts about LP . . .

• Only performed about 25-50% of the time

• If LP is performed within 12 hours, **xanthochromia** may be absent

• However, if true aSAH is present, early cases will show **bloody CSF**

• Therefore, finding normal CSF, even in the first few hours, successfully excludes aSAH.

• For all of these reasons, do not delay LP. Instead, accept either **RBCs** or **xanthrochromia** as a positive finding.
Technologic Advances

• The criteria are specific to utilize a normal head CT alone to rule out aSAH:
  
  - acute severe thunder-clap headache
  - imaging performed within 6 hours
  - no neurological deficit
  - and must be reported by a neuroradiologist or a radiologist experienced in reading CT head scans

**Patients cannot have neck pain or associated with their headache**

**Hematocrit > 30%**

**CT scanner is a modern, 3rd generation or newer machine**
CT Angiography - Positives

- CTA is very sensitive and specific for the detection of aneurysms in the setting of SAH.

- 64-slice CTA to be 98% sensitive and 100% specific for detecting aneurysms larger than 3 mm.

CT Angiography - Negatives

• Discovery of aneurysms that are not the cause of the headache with the consequent exposure of the patient to the risks of additional testing and potentially unnecessary procedures. *(Now doing LP anyway)*

• 4 msv of radiation

• Possible harm from the administration of IV contrast

• Expensive study and can require significant time to perform/interpret.
MRI/MRA - Positives

- Sensitive to subarachnoid blood, able to visualize it well in first 12 hours typically as a **hyperintensity in the subarachnoid space on FLAIR**

- The FLAIR MRI sequence is comparable with NCCT in detecting acute SAH, and is superior for subacute and chronic hemorrhage

- MRI is also a powerful tool in the differential diagnosis of intracranial pathologies, including tumors, inflammatory, and infectious processes.
MRI/MRA - Negatives

• Availability

• Contraindications

• Claustrophobia

• Time
<table>
<thead>
<tr>
<th>Approach</th>
<th>Benefits</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT plus LP</td>
<td>Well known performance (rules out disease well)</td>
<td>Pain, HA, small risk of serious complications, possibly test will not give diagnostic results (traumatic tap), radiation from CT scan, additional time to await results from LP</td>
</tr>
<tr>
<td>CT alone</td>
<td>Simple, quick, likely performs well within 6 hours of headache onset</td>
<td>Does not exclude aneurysm, radiation, may not pick up older (a headache that started 24 hours ago or more) blood well.</td>
</tr>
<tr>
<td>CT plus CTA</td>
<td>Reliably identifies aneurysms (can rule out disease well)</td>
<td>More radiation, IV contrast, time, cost. May identify aneurysms or other findings that have nothing to do with HA and lead to additional testing or surgeries that aren’t needed</td>
</tr>
<tr>
<td>MRI alone</td>
<td>Likely identifies blood well, although not historically used much in emergency setting; no radiation. Can identify a large number of alternate causes of headache (although most headaches have no structural cause)</td>
<td>Less certain performance of test. Similar to CT alone, will not necessarily identify aneurysms. Cost, claustrophobia, access to scanner can be limited in many EDs</td>
</tr>
<tr>
<td>MRI plus MRA</td>
<td>Reliably identifies aneurysms and also blood (again, not used frequently in ED setting), no radiation</td>
<td>Same as MRI. In addition, same problem as CTA in potentially identifying aneurysms or other findings that have nothing to do with headache and lead to additional testing or surgeries that isn’t needed and might be harmful</td>
</tr>
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</table>
47 yo male with headache
Top Things to Know:

2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke
• Each year, about 795,000 persons experience stroke; about 690,000 are new acute ischemic strokes (AIS) and about 140,000 deaths can be attributed to stroke per year.

• Prehospital procedures need to be developed to identify and rapidly triage and transport IV fibrinolytic ineligible patients with a high likelihood of large vessel occlusion and potentially eligible for thrombectomy to the nearest healthcare facility that can perform these procedures.
Prehospital Scales for Large Vessel Occlusion

- Currently multiple stroke scales in place to identify LVO prehospital.

- The 4 most commonly used stroke scales are:
  1) Cincinnati Prehospital Stroke Scale (CPSS)
  2) Los Angeles Prehospital Stroke Scale (LAPSS)
  3) LA Motor Scale (LAMS)
  4) Rapid Arterial Occlusion Evaluation (RACE)
     - RACE score ≥5

- Unfortunately, none of the scales has sufficient accuracy to identify strokes and eliminate stroke mimics.

- Multiple other tools are being developed to help improve prehospital identification of stroke and LVO.

RACE Scale 0-9

- Face: 0, 1, 2
- Arm: 0, 1, 2
- Leg: 0, 1, 2
- Gaze: 0, 1

- Right sided symptoms
  - Test Aphasia: 0, 1, 2

- Left sided symptoms
  - Test Neglect: 0, 1, 2
Large vessel occlusion screening tools—brain view. 3I-SS, 3 item stroke scale; CPSSS, Cincinnati Prehospital Stroke Severity Scale; LAMS, Los Angeles Motor Scale; LEGS, legs, eyes, gaze, speech (Texas Stroke Intervention Prehospital Stroke Severity Scale); RACE, Rapid Arterial Occlusion Evaluation Scale; VAN, vision, aphasia, neglect.
<table>
<thead>
<tr>
<th>Patient #1  08:32 am</th>
<th>Patient #2  10:47 am</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>75 yo female</strong> last seen normal at midnight, lives at home. Found with right gaze and left sided weakness. Hx strokes in past, takes ASA and eliquis</td>
<td><strong>71 yo female</strong> last seen normal 09:00 at SAR. Found with right sided weakness, slurred speech, altered MS Hx CAD, HTN. No anticoagulants listed</td>
</tr>
<tr>
<td>BP 200/73, Accuecheck 188, <strong>Weight 70 kg</strong></td>
<td>BP 197/91, Accuecheck 101, <strong>Weight 97 kg</strong></td>
</tr>
<tr>
<td>Exam: complete left facial droop, rightward gaze, 2/5 strength LUE, 0/5 strength LLE, + dysarthria, + neglect, <strong>NIHSS 26</strong></td>
<td>Exam: + mild right facial droop, + leftward gaze, + right hemiparesis, + receptive and expressive aphasia, + dysarthria, <strong>NIHSS 21</strong></td>
</tr>
<tr>
<td><strong>RACE Score: 8</strong></td>
<td><strong>RACE Score: 8</strong></td>
</tr>
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</table>
Patient #1 – LVO??
CTA Head and Neck – No LVO
Patient #1

DWI

ADC
Patient #2 – LVO???
Hydralazine, Labetalol, Alteplase

+ LVO Left MCA and Left ACA

MCA opened TICI 2b flow, ACA persistently occluded
Top Things to Know

• **Standard IV alteplase dosing (0.9mg/kg over an hour, with a 10% bolus over one minute) can be beneficial in patients who wake-up (within 4.5 hours) with AIS symptoms, or in patients who have an unclear time of onset of (>4.5 hours) of stroke symptoms from last known well time and who have a DWI lesion smaller than one-third of the middle cerebral artery (MCA) territory and no visible signal change on fluid-attenuated inversion recovery (FLAIR) imaging.**
Intravenous Thrombolysis in Unwitnessed Stroke Onset: MR WITNESS Trial Results

Lee H. Schwamm, MD,1* Ona Wu, PhD,2* Shlee S. Song, MD,3
Lawrence L. Latour, PhD,4 Andria L. Ford, MD,5 Amie W. Hsia, MD,4,6
Alona Muzikansky, MA,7 Rebecca A. Betensky, PhD,7,8 Albert J. Yoo, MD,9,10
Michael H. Lev, MD,10 Gregoire Boulouis, MD,1,11 Arne Lauer, MD,1
Pedro Cougo, MD,1 William A. Copen, MD,10 Gordon J. Harris, PhD,10 and
Steven Warach, MD, PhD8,12 on behalf of the MR WITNESS Investigators
MR WITNESS

- Quantitative mismatch of diffusion-weighted MRI with FLAIR (qDFM) might indicate stroke duration within guideline-recommended thrombolysis.

- Tested whether IV thrombolysis ≤ 4.5 hours from the time of symptom discovery is safe in patients with qDFM

- The primary outcome was the risk of sICH. Secondary outcomes included symptomatic brain edema risk, and functional outcomes of 90-day modified Rankin Scale (mRS).

- *Intravenous thrombolysis within 4.5 hours of symptom discovery in patients with unwitnessed stroke selected by qDFM, who are beyond the recommended time windows, is safe.*
Can patients with stroke with an unknown time of onset and features suggesting recent cerebral infarction on MRI benefit from the use of IV alteplase?

All patients had an ischemic lesion that was visible on MRI DWI but no parenchymal hyperintensity on fluid-attenuated inversion recovery (FLAIR), which indicated that the stroke had occurred approx within the previous 4.5 hours.

The primary end point was favorable outcome, as defined by a score of 0 or 1 on the modified Rankin scale at 90 days.

In patients with acute stroke with an unknown time of onset, IV alteplase guided by a mismatch between DWI and FLAIR in the region of ischemia resulted in a significantly better functional outcome and numerically more intracranial hemorrhages than placebo at 90 days. (2% vs 0.4%)
Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke

Henry Ma, Ph.D., Bruce C.V. Campbell, Ph.D., Mark W. Parsons, Ph.D., Leonid Churilov, Ph.D., Christopher R. Levi, M.B., B.S., Chung Hsu, Ph.D., Timothy J. Kleinig, Ph.D., Tissa Wijeratne, M.D., Sami Curtze, Ph.D., Helen M. Dewey, Ph.D., Ferdinand Miteff, M.B., B.S., Chon-Haw Tsai, Ph.D., et al., for the EXTEND Investigators*
Alteplase up to 9 hours

- 4.5-9 hours from onset of stroke
- Salvageable regions of brain detected on CTP

- Use of alteplase resulted in a higher percentage of patients with no or minor neurologic deficits than the use of placebo (35% vs 29.5%)

- More cases of ICH in alteplase group than in the placebo group (6.2% vs 0.9%)
Extended Window Case

- 71 yo male last known well at 6:30 am

- Found by neighbors in the laundry room with confusion, unsteady gait, and slurred speech

- Arrives to ED at 10:56 am

- PMHx: HTN, high chol, known stenosis left M1, possible seizure

- VS: 165/89    73   16   98.5   100% RA
Extended Window Case

• Weight: 90 kg  Accuchek: 93

• Neuro exam: AAOx2 to person and place, + mild right facial droop, + drift RUE, + drift RLE, mild dysarthria, mild expressive aphasia, abnormal finger to nose RUE

• NIHSS 8
<table>
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<tr>
<th>Inclusion Criteria</th>
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<tr>
<td>Written informed consent from patient or POA</td>
<td>Pregnancy or suspected pregnancy (pregnancy test will be done on women of child-bearing potential)</td>
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<tr>
<td>&gt; 18 years of age</td>
<td>Thrombocytopenia (platelet count &lt; 100,000/mm³)</td>
</tr>
<tr>
<td>Baseline good functional status (mRS &lt; 2)</td>
<td>Generally recognized contraindications to treatment with alteplase (excluding time window)</td>
</tr>
<tr>
<td>NIH Stroke Scale &gt; 4-30</td>
<td>Previous functional disability (modified Rankin &gt; 2)</td>
</tr>
<tr>
<td>Last known well 4.5-9 hours or “wake up stroke”</td>
<td>Stuporous or comatose</td>
</tr>
<tr>
<td>Endovascular patients included</td>
<td>Anticipated life expectancy of at least 3 months</td>
</tr>
<tr>
<td>Anticipated life expectancy of at least 3 months</td>
<td>Willingness to follow up with rehabilitation therapy</td>
</tr>
<tr>
<td>CTP with ischemic core volume &lt; 30% and penumbra &gt; 70%</td>
<td>CTP with ischemic core volume &lt; 30% and penumbra &gt; 70%</td>
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</tbody>
</table>
Extended Window Case

• Patient’s brother gives written consent, patient himself gives verbal consent

• Alteplase given at 11:43 am which is 5 hours and 13 minutes from last known well

• Admit to Neuro ICU
NIHSS 2 next day

Patient discharged to home! With PT/OT/Speech
**Top Things to Know**

**General Supportive Care and Emergency Treatment**

### 3.6 Other IV Fibrinolytics and Sonothrombolysis

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
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<tbody>
<tr>
<td>1. It may be reasonable to choose tenecteplase (single IV bolus of 0.25 mg/kg, maximum 25 mg) over IV alteplase in patients without contraindications for IV fibrinolysis who are also eligible to undergo mechanical thrombectomy.</td>
<td>IIb</td>
<td>B-R</td>
</tr>
<tr>
<td>2. Tenecteplase administered as a 0.4 mg/kg single IV bolus has not been proven to be superior or noninferior to alteplase but might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion.</td>
<td>IIb</td>
<td>B-R</td>
</tr>
<tr>
<td>3. The administration of IV defibrinogenating agents or IV fibrinolytic agents other than alteplase and tenecteplase is not recommended.</td>
<td>III: No Benefit</td>
<td>B-R</td>
</tr>
<tr>
<td>4. The use of sonothrombolysis as adjuvant therapy with IV fibrinolysis is not recommended.</td>
<td>III: No Benefit</td>
<td>A</td>
</tr>
</tbody>
</table>
Tenecteplase

• Higher specificity for fibrin, longer half-life
• Single bolus administration

• mRS 0-1 at 3 mos:  TNK 57.9%  ALT 55.4%
• mRS 0-2 at 3 mos:  TNK 71.9%  ALT 55.4%
• Symptomatic ICH:  TNK 3%  ALT 3%
• Mortality:  TNK 7.6%  ALT 8.1%

Saver, JL and Burgos AM. Evidence that Tenecteplase is Noninferior to Alteplase for Acute Ischemic Stroke. Stroke. 2019 Aug;50(8):2156-2162
So why isn’t Tenecteplase more mainstream?

Not FDA approved for treatment of acute ischemic stroke
Tenecteplase

American Heart Association/American Stroke Association

• Effective with discharges on or after July 1, patients who receive IV TNK within the timeframe of arrival in two hours/treatment in three hours will be accepted in the STK-4 measure numerator along with those who receive IV alteplase.
Target: Stroke Phase III

• Further raises the bar by setting more aggressive targets for timely treatment with IV alteplase.

• But the aim goes beyond faster door-to-needle times . . .

• Phase III introduces a second type of intervention into the mix, setting the *first-ever targets for prompt treatment with endovascular therapy.*
National Goals for Phase III

• PRIMARY GOALS
  • *Achieve DTN within 60 min in 85%*
    • Achieve door-to-device (DTD) times in 50% or more of eligible patients within 90 minutes (for direct arriving patients) and within 60 minutes (for transfer patients)

• SECONDARY GOALS
  • *Achieve DTN within 45 minutes in 75%*
  • *Achieve DTN within 30 minutes in 50%*
**Purpose:** To determine if endovascular therapy (EVT) is as effective as bridging therapy with EVT and intravenous thrombolysis (IVT) in acute ischemic stroke.

**Trial Design:** prospective, multicenter, open-treatment trial. N= 204, mean age 74 years. Patients with ICA and M1 acute ischemic stroke were randomized within 4.5 hours of stroke symptom onset to either EVT alone or to IVT and EVT.

**Primary Endpoints:** Noninferiority: mRS of 0-2 90 days after onset of stroke.

<table>
<thead>
<tr>
<th>@90 Days</th>
<th>EVT</th>
<th>IVT + EVT</th>
<th>OR P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS 0-2</td>
<td>59.4%</td>
<td>57.3%</td>
<td>OR 1.09 P=0.18 for noninferiority</td>
</tr>
<tr>
<td>Intracranial hemorrhage within 36 hours</td>
<td>33.7%</td>
<td>50.5%</td>
<td>OR 0.50 P=0.02</td>
</tr>
<tr>
<td>Mortality @ 90 days</td>
<td>7.9%</td>
<td>8.7%</td>
<td>P=1.00</td>
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</table>

**Results:** Noninferiority of direct EVT to bridging therapy was not demonstrated.

**Impression:**

This trial may help determine whether direct EVT should be recommended as a routine clinical strategy for ischemic stroke patients within 4.5 h from onset. Direct EVT would then become the choice of therapy in stroke centers with endovascular facilities.
Limitations

• Open labeled treatment

• Limited to patients with ICA or M1 occlusion

• Dosage of alteplase was only 0.6mg/kg
Questions and Discussion