2010 Update in Diagnosis and Treatment of Stroke

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Case 1

• A 58 year-old woman with no past medical history presented to the ED after the sudden onset of aphasia and right sided weakness.
• Exam shows a mild expressive aphasia, R face and arm weakness as well as L gaze deviation.
• Her symptoms began at 3 p.m., it is now 6:30 p.m.

What treatment should you initiate?
A. IV t-PA
B. IV heparin
C. Antiplatelets
D. Mechanical Embolectomy
E. Intra-arterial t-PA
The 2010 Acute Stroke Timeline

- Time of onset = last time seen normal
  - 0-4.5 Hours: IV-tPA
  - 0-6 Hours: IA-tPA
  - 0-8 Hours: Mechanical Embolectomy
  - Greater than 8 hours: Anticoagulants or Antiplatelets

Intravenous t-PA: Proven, Approved

- Pivotal IV t-PA NINDS trial (0-3 hours)
  - 30% increase in minimal or no disability at 90 days, not the Lazarus effect
  - Symptomatic hemorrhage risk increased 0.6 to 6.4%, half were serious and fatal
  - No change in mortality
  - Multiple recent studies confirm this result in diverse settings
  - THE EARLIER THE BETTER!!!

Intravenous t-PA: 3-4.5 hours

- ECASS III trial (9/08)
  - 821 pts randomized to t-PA vs placebo
  - Median time: 3h 59min
  - Favorable outcome: 52% vs 45%, p=0.04
  - Symptomatic ICH: 2.4% vs 0.2%, p=0.008
  - No mortality difference

t-PA 3-4.5 Hour: European Experience

• 2376 patients treated between 3-4.5 hrs, around 20,000 treated within 3 hours
• By the end of 2009, this represented 22% of all t-PA treated patients
• Door to needle time DID NOT increase with the additional window
• At 3 months in 60% of those treated from 3-4.5 hours were functionally independent


Future Directions

• Perfusion-Based Time Window

• Ultrasound-enhanced thrombolysis
  – With IV t-PA in 4.5 hour window
• More Neuroprotectant trials: ALIAS, Fast-MAG
• Drip and Ship
• Combination Approaches
We gave t-PA but it’s NOT actually a stroke!

- Previously thought to be a bad idea
- Common mimics: seizure, complicated migraine, conversion disorder
- In a total of 70 patients treated with t-PA with a stroke mimic…
  - Zero instances of sICH
  - 87% had no deficit on discharge

Chernyshov OY et al. Neurology 74:1340, 2010

Case 2

- A 78 year-old man with a history of DM, HTN presents with 2 days of R arm weakness
- Examination shows a mild R facial droop sparing the forehead as well as a R pronator drift and slowed, clumsy movements in the R hand
- The patient is on aspirin, lisinopril, and metformin

Which of the following is not part of the standard stroke workup?

A. Echocardiogram
B. Extended cardiac telemetry
C. Lipid panel
D. B12, TSH, RPR, ESR
E. Carotid evaluation
Standard Large-Vessel Stroke Workup

- Cardioembolic: afib, clot in heart, paradoxical embolus
  - 1. Telemetry
  - 2. TEE with bubble study
- Aortic Arch
  - 2. TEE with bubble study
- Carotids
  - 3. Carotid Imaging (CTA, US, MRA, angio)
- Intracranial Vessels
  - 4. Intracranial Imaging (CTA, MRA, angio)

And evaluate stroke risk factors

TEE vs. TTE

- 231 consecutive TIA and stroke patients of unknown etiology underwent TTE and TEE
- 127 found to have a cardiac cause of emboli, 90 of which (71 percent) only seen on TEE
- 38 of 46 “major risk factors” only found on TEE (most left atrial thrombi)
- TEE superior to TTE for: LA appendage, R to L shunt, examination of aortic arch


WS3 TEE/TTE Protocol for patients with cryptogenic stroke and no established indication for Warfarin

- Age (> 75 years)
- No
- Yes

- Carotid findings
  - No
  - Yes

- Left atrial thrombus
  - No
  - Yes

- No atrial fibrillation
  - No
  - Yes

- No other r/o embolic source
  - No
  - Yes

- Warfarin
  - Yes
  - No
Atrial Fibrillation Detection

- EKG
- 48 Hours of Telemetry
- 30 day cardiac event monitor
  - 20% of patients with cryptogenic stroke otherwise unexplained had afib detected
  - Clearly changes management
  - Probably cost effective

Kamel H et al: Stroke 41:1514, 2010

Approach to Stroke Treatment

Acute Stroke Therapy?

No

Anticoagulants?

No

Antiplatelets

Shrinking Indications for Anticoagulation in Stroke

1. Atrial Fibrillation
2. Some other cardioembolic sources
   - Thrombus seen in heart
   - ?EF<35
   - ?PFO with associated Atrial Septal Aneurysm
3. Vertebral dissection
   - 2009: Questionable in carotid dissection
4. Rare hypercoagulable states: APLA
Afib with anticoagulation contraindicated

- ACTIVE trial (5/09)
  - 7500 patients randomized to ASA vs ASA + Clopidogrel
  - Decreased rate of stroke on combination therapy after mean 3.6 years (2.4% vs 3.3%, p<0.001) with increased major hemorrhage
- Concern re: decreased rates of anticoagulation after this study
  - Don’t forget ACTIVE W (Lancet 2006)

Bridging Heparin

- Absolutely no data at all
- Retrospective review of 204 patients
  - Bridging increased hemorrhage rate with no improvement in secondary prevention
- If you are going to do it
  - Never, never bolus
  - Careful not to make patient supratherapeutic

Case 3

- A 60 year-old man with a history of DM, smoking presents 10 hours after the onset of slurred speech and right arm and leg weakness.
- The patient is on ASA 81mg daily
Stroke workup is unrevealing.
Your Treatment?
A. Increase ASA to 325mg daily
B. Add Plavix
C. Stop ASA, start Plavix
D. Anticoagulate
E. Stop ASA, start Aggrenox

Approach to Stroke Treatment

Acute Stroke Therapy?
\[ \text{No} \]

Anticoagulants?
\[ \text{No} \]

Antiplatelets

Antiplatelet Options

\begin{itemize}
\item 1. ASA
  \begin{itemize}
  \item 50mg to 1.5g equal efficacy long-term
  \end{itemize}
\item 2. Aggrenox
  \begin{itemize}
  \item 25mg ASA/200mg ER Dipyridamole
    \begin{itemize}
    \item ESPS-2, ESPRIT (Lancet 5/06)
    \end{itemize}
  \end{itemize}
\item 3. Clopidogrel (Plavix)
  \begin{itemize}
  \item MATCH (Lancet 7/04)
  \item FASTER (Lancet Neurol 10/07)
  \end{itemize}
\end{itemize}
PRoFESS Trial

- Randomized, double-blind trial of Aggrenox versus Plavix in over 20,000 patients with ischemic stroke
- Recurrent 4-year event rates basically identical between the two medications
  - HR for Aggrenox 1.01 (95% CI, 0.92-1.11)
  - Composite of stroke, MI, vascular death: 13.1% in each
  - Major hemorrhagic events higher in Aggrenox group


Antiplatelet Options

- If on no antiplatelet medication
  - ASA or Plavix vs. Aggrenox
- If already on ASA
  - Switch to Plavix vs. Aggrenox
- If already on Plavix or Aggrenox
  - ???

Other Acute Stroke Management

- Statins for (almost) all
  - SPARCL (NEJM 8/06), 80mg atorvastatin in stroke and TIA if LDL>100
- Permissive HTN
  - To at least 220/120 (unless IV t-PA): Mortality and morbidity increases if lower acutely
  - When to stop remains controversial
- Tight Glucose and Fever control
- Enoxaparin for DVT prophylaxis
  - PREVAIL trial (Lancet 2007)
  - CLOTS trial 1 (Lancet 2009): Compression Stockings
Case 4

• A 72 year-old woman with HTN comes to the ED after a 5 minute episode of aphasia and right arm weakness that has since resolved.
• Exam is normal except blood pressure is 175/40

What would be your triage?

A. Admit to the hospital floor
B. Admit to the ICU
C. Send home and f/u with PCP in 1-2 weeks
D. Send home with f/u the next day
E. No f/u required

TIA versus Stroke

• Up to 50% of TIA have infarct on imaging
• Conceptually the same disorder
  – Same workup, same treatment
• Pendulum swing
  – Pre-2001: Much more aggressive with Stroke
  – 2002-2007: TIA and Stroke equally aggressive
  – 2008-present: Moving to more aggressive approach with TIA
Risk of Future Stroke with TIA: 
\textit{ABCD^2 Score}

- 7-day risk overall 8.6-10.5 percent
- **Age**
  - \( \text{Age} > 60 \): 1 point
- **Blood Pressure**
  - \( \text{SBP} > 140 \text{ or } \text{DBP} > 90 \): 1 point
- **Clinical Features**
  - Unilateral weakness = 2 points
  - Speech disturbance without weakness = 1 point
- **Duration**
  - \( \text{Duration} > 60 \text{ minutes} \): 2 points
  - \( \text{10-59 minutes} \): 1 point
- **Diabetes** = 1 point


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Aggressive Therapy for TIA

- **1. SOS-TIA trial**
  - 1085 patients with TIA admitted to a 24-hour center
  - All treated with standard therapy
  - 74 percent discharged on same day, stroke risk reduced 80 percent from \textit{ABCD^2} prediction

- **2. EXPRESS study**
  - 80 percent reduction in risk with urgent TIA clinic visit versus usual primary care visit in 1278 patients


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When to Fix the Carotid?

- **NASCET in early 1990s**
  - Benefit of endarterectomy in patients with symptoms ipsilateral to 70-99% stenosis
  - \textit{Comparison: best medical management at the time}
  - 50-69% symptomatic stenosis revascularization has limited benefit, especially in women
- **In stroke management don’t miss carotid disease or atrial fibrillation**
How to Fix the Carotid?

- Stenting +/- distal protection
  - SAPPHIRE (NEJM 10/04 and 4/08) in high-risk patients as good as endarterectomy
  - Currently widely practiced: NeuroIR, vascular surgeons, BodyIR, Cardiologists
  - Unique risks: Hypotension, Bradycardia

Randomized Trial Results

- SPACE Trial (Lancet 10/06)
  - 1200 patients with recent stroke/TIA randomized to CEA vs. stenting
- EVA-3S (NEJM 10/06)
  - 527 patients with recent stroke/TIA randomized
- Both failed to demonstrate non-inferiority
  - In EVA-3S, stenting associated with significantly more short-term stroke and death

New Confusing 2010 Data

- CREST (NEJM 2010): 4-year study of 1321 symptomatic and 1181 asymptomatic pts
  - Combined endpoint of stroke, MI, death not significantly different
    - More strokes in first 90 days in stenting group, more MIs in surgical group
    - After 90 days, similar endpoints
- ICSS (Lancet 2010): 1713 symptomatic pts
  - Combined endpoint higher in stenting group
Asymptomatic Carotid Stenosis

• Some benefit for endarterectomy in asymptomatic stenosis
  – >60% or >80% cut-offs
  – Must have a very low perioperative risk of stroke and death to realize 5-year benefit (3%)
• Data much less convincing than symptomatic trials
• When to screen? Who to screen?

Transcranial Doppler to Predict Stroke risk

• 2-year study of nearly 500 patients with asymptomatic (>70%) carotid stenosis
• Embolic signals on TCD predicted risk of stroke
  – Hazard ratio of ipsilateral stroke with emboli compared to without: 5.57
  – Annual risk of stroke 3.6% vs. 0.7%
• Can we stratify those with greatest chance of benefit from surgery/stenting?

Markus HS et al. Lancet Neurol 9:663, 2010
Case 5

• A 52F presented after being found down (last normal 16 hours prior) with a massive R MCA infarction

Surgical Decompressive Hemicraniectomy

• “Malignant MCA infarction” carries an 80% mortality historically
  – No medical therapy has been proven effective
  – Deterioration from 2-5 days (some in 24 hours)
  – No good predictors yet of deterioration on imaging

Surgical Decompressive Hemicraniectomy

• Three randomized trials (Lancet Neur. 3/07)
  – DECIMAL, DESTINY, HAMLET
  – Similar end points and trial design
  – Pooled analysis of all individual patients pre-planned
• Age less than 60
• Mild decrease in LOC, NIHSS > 15
• Infarct more than 1/2 MCA territory
• Irrespective of hemisphere involved
• Early surgery: less than 48 hours from onset
12-month survival: 78% vs. 29% (NNT=2)
12-month mRS<4: 43% vs. 21% (NNT=4)
No subgroups where surgery not beneficial