Intracranial Atherosclerosis in Asians

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Case #1
- 60 yo Chinese-American woman with h/o anxiety/depression, HTN, c/o HAs. MRI/MRA brain shows multiple segments with significant intracranial atherosclerosis.
- Meds: hydrochlorothiazide
  - Start antiplatelet agent
  - Start warfarin
  - Start a statin (HMG-CoA reductase inhibitor)
  - Obtain a diagnostic catheter angiogram
  - Obtain a CTA
  - Refer to Neurointerventional Radiology for intracranial angioplasty/stenting

Case #2
- 66 yo Filipino man h/o HTN, DM, presents with left sided weakness. Found on CT/CTA to have intracranial occlusion of right M2, severe (70-80%) bilateral vertebral stenoses.
- Meds: lisinopril, hydrochlorothiazide, glucophage, aspirin
  - Add clopidogrel to aspirin
  - Switch to clopidogrel monotherapy
  - Switch to aspirin/ER dipyridamole (Aggrenox)
  - Start a statin (HMG-CoA reductase inhibitor)
  - Refer to Neurointerventional Radiology for angioplasty/stenting of vertebral arteries

Disclosures
- Research Support
  - National Institutes of Health
  - American Heart Association
  - National Stroke Association
- Slides Courtesy of Dr. Nguyen-Huynh

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Disclosures
Asians in the US
• ~4% of the U.S. population
• Fastest growing ethnic group in US
• ~10% of the population by 2050
• Many studies focused on race-ethnic disparities in health focus in African Americans & Hispanics…
• …but few studies focused on Asians in the US

Stroke
• #3 cause of mortality in the US, #1 in China
• #1 long-term disability in the world
• Higher incidence rates in Asia compared to US:
  • 39% greater in Japan
  • 23% greater in Taiwan
  • 81% greater in Northern China

Stroke
• ~795,000 strokes per year in the US (2009 cost ~ $68.9 billion)
• ~87% ischemic
• Intracranial atherosclerosis (ICAD): 48,000-60,000 cases/yr (8-10%)
• Extracranial carotid disease: 100,000-140,000 cases/yr
• Atrial fibrillation: 70,000 cases/yr

Cerebrovascular System
Circle of Willis

Epidemiology of ICAD

- Northern Manhattan Stroke Study (NOMAS)
- >39 yo hospitalized w/ acute ischemic stroke
- N=483 (35% black, 46% Hispanic, 19% white)
- 75% with TCD, 12% with catheter angiogram
- 9% with extracranial disease, 8% with ICAD
- ICAD higher in non-whites (OR=4.4, CI 0.6-35; adjusted for age, education, IDDM, hyperlipidemia)

Epidemiology of ICAD

- Consecutive patients admitted with acute ischemic stroke or TIA over 2 years
- N=274 (61% black, 39% white)
- 156 patients (57%) had evaluation of intracranial vessels by MRA, TCD or catheter angiogram
- 12% incidence of ICAD
- 8% incidence of symptomatic ICAD
- No difference between races

Race-Ethnicity & ICAD

- Prevalence varies by race-ethnicity
- ICAD responsible for ischemic stroke:
  - 6-29% in Blacks
  - 11% in Hispanics
  - 22-26% in Asians
- Very limited data on ICAD among Asians in the US
ICAD Incidence in Asia

<table>
<thead>
<tr>
<th>Study Population</th>
<th>N</th>
<th>ICAD</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese (Boston)</td>
<td>24</td>
<td>43%</td>
<td>angiogram</td>
</tr>
<tr>
<td>China</td>
<td>590</td>
<td>7%</td>
<td>TCD</td>
</tr>
<tr>
<td>Hong-Kong</td>
<td>705</td>
<td>37%</td>
<td>TCD</td>
</tr>
<tr>
<td>South Korea</td>
<td>268</td>
<td>52%</td>
<td>angiogram</td>
</tr>
<tr>
<td>Taiwan</td>
<td>108</td>
<td>26%</td>
<td>MRA</td>
</tr>
<tr>
<td>Taiwan</td>
<td>578</td>
<td>41%</td>
<td>TCD</td>
</tr>
</tbody>
</table>

Diagnosing ICAD

- Transcranial Doppler (TCD)
- MR Angiogram (MRA)
- CT Angiogram (CTA)
- Digital Subtraction Angiography (DSA): Gold Standard

Transcranial Doppler (TCD)

- Non-invasive
- Inexpensive
- Widely available
- Not feasible on every patient (inadequate bone windows)
- Results are highly operator-dependent and there are no standardized velocity thresholds
- Stroke Outcomes & Neuroimaging of Intracranial Atherosclerosis (SONIA): 407 patients 50-99% stenosis. Compared to DSA: PPV=55%, NPV=83%

(Feldman, 2007)
Magnetic Resonance Imaging (MRI)

- Minimally invasive
- Better vessel image
- More expensive
- Limited availability
- Flow-dependent signal (Time of Flight, newer contrast-enhanced MRA)
- May overestimates degree of stenosis in higher grade stenoses due to turbulence
- SONIA: PPV=66%, NPV=87%

MR Angiography (Feldman, 2007)

Computed Tomography (CT)

CT Angiogram
CT Angiogram

- Minimally invasive; uses iodinated contrast
- Better visualization of vessel lumen
- Relatively cheap
- Can be readily available
- Potential allergies to IV contrast; radiation exposure
- Compared to DSA, for >50% stenosis: sensitivity = 97.1%, specificity=99.5%

(nguyen-huy nh, 2008)

Digital Subtraction Angiography (DSA)

- Considered gold standard for its high spatial resolution
- Most invasive; uses iodinated contrast
- Most expensive
- Most time consuming
- Limited availability
- Requires highly specialized expertise
- Risk of stroke ~0.25-1%
Risk Factors for ICAD

- **Non-modifiable:**
  - Gender (female > male)
  - Race-ethnicity
  - Age (younger in Asians)

- **Modifiable:**
  - HTN
  - DM
  - Smoking
  - Hyperlipidemia
  - Diet
  - Physical inactivity
  - Obesity

Stroke Risk in Symptomatic ICAD

- Annual stroke risk on medical therapy:
  - 8-10% in the carotid siphon
  - About 22% over 14m in vertebral or basilar artery

- Overall risk of recurrent stroke in patients with symptomatic ICAD is as high as 15-17% per year (WASID)

Treatment Options

- Antiplatelet therapy: Still first-line therapy
- Anticoagulants
- Angioplasty
- Intracranial stenting
  - Bare metal stent
  - Drug-eluting stent
  - Self-expanding intracranial stent

WASID

- Warfarin-Aspirin Symptomatic Intracranial Disease
- Randomized, double-blinded, multi-center trial
- TIA & non-disabling stroke (Feb 1999 to July 2003)
- Warfarin (INR 2.0 – 3.0) vs. Aspirin 1300 mg
- Primary endpoint: ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke (Chimowitz, 2005)
Trial stopped early after 569 enrolled
Mean f/u 1.8 years
Mean INR=2.5
63.1% achieved INR 2.0 – 3.0
Major hemorrhage 3% in ASA, 8% in warfarin (HR 0.39 in favor of ASA, 95% CI 0.18-0.83, p<0.01)
Annual rate of ischemic stroke in territory of stenotic artery = 12% in ASA vs. 11% in warfarin group

(Chimowitz, 2005)
Factors Associated with Increased Risk of Recurrent Stroke

- Severe stenosis (≥70%) HR=2.03
- Enrolled early (≤17 days) HR=1.69
- Female gender HR=1.59
- HTN (SBP ≥140 mmHg) HR=1.79
- Cholesterol (≥200 mg/dL) HR=1.44
- African-Americans with ICAD have higher risk of recurrent stroke than Caucasians (25% vs. 16%). No data on Asians

(WASID) (Chimowitz, 2005)

- Location of stenosis and type of event were not associated with an increased risk of stroke
- Patients who failed anti-thrombotics do not have higher stroke risk
- Co-existing asymptomatic intracranial stenoses (50-99%) have low risk of stroke

(TOSS-2) (XVIII European Stroke Conference, 2009)

- Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis II
- Hong Kong, Korea, Philippines, Thailand, 480 patients > 35 yo with symptomatic M1 or basilar
- Cilostazol + 100mg ASA vs. Clopidogrel + 100 mg ASA
- Outcome: progression rate on MRA

(Intracranial Angioplasty)

- Cochrane Collaboration 2006 review
- No randomized trials
- 79 articles with open-label case series ≥3 cases
- Perioperative stroke rate 7.9% (CI 5.5-10.4)
- Perioperative death rate 3.4% (CI 2.0-4.8)
- No comments could be made on effectiveness
- Insufficient data to recommend angioplasty

(Chimowitz, 2005)
Intracranial Stenting

- **SSYLVIA:** Neurolink bare metal stent, 95% success rate, 32.4% in-stent restenosis @ 6 mos, 13.1% ischemic stroke @ 12 mos
- Drug eluting stent: retrospective review, 90% success rate, 5% of re-stenosis rate intracranially at 4±2 months
- Wingspan self expanding intracranial stent (FDA approved): single arm study, 97.7% success rate, 7.5% in-stent restenosis @ 6 mos, all asymptomatic, 7% ipsilateral stroke or death rate @ 6 mos

(SSYLVIA Investigators, 2004)

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<th></th>
<th>success</th>
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<th>stroke</th>
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<tr>
<td>SSYLVIA bare-metal Stent</td>
<td>95%</td>
<td>32.4%</td>
<td>13.1% @ 12m</td>
</tr>
<tr>
<td>Drug-eluting Stent</td>
<td>90%</td>
<td>5%</td>
<td></td>
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<tr>
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<td>7% @ 6m</td>
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SAMMPRIS

- **Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis**
- NIH-funded, randomized, multi-center
- TIA/stroke within 30 days & 70-99% stenosis of major intracranial artery confirmed on study DSA
- Intracranial Stenting + Intensive Medical Therapy vs. Intensive Medical Therapy
- Open for enrollment at UCSF.

Summary

- ICAD is under-recognized
- Higher prevalence among Asians
- High recurrent stroke risk despite medical therapy
- Need:
  - Fast, readily available, reliable, and minimally-invasive diagnostic methods
  - Better predictors of progression or regression of disease
  - Better predictors of clinical outcomes
  - Better treatment options

www.sammpris.org
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