The Epidemiology of Stroke and Vascular Risk Factors in Cognitive Aging

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Outline

- Stroke
  - Epidemiology and risk factors
  - Management, workup
- Subclinical brain vascular disease
  - Epidemiology and risk factors
  - Management, workup
- HIV
  - Stroke epidemiology and workup
  - Subclinical brain vascular disease and HIV
15 million people experience strokes worldwide each year; of these 5 million die and another 5 million are permanently disabled.

Nearly 800,000 people in the US each year experience a stroke; one of every 17 deaths in the US is due to stroke.
Risk factors for stroke

- Major risk factors include **age**, hypertension, diabetes, cigarette smoking, hyperlipidemia, obesity, atrial fibrillation
  - Rates of obesity are going up: 68.2% of US adults were overweight or obese in 2010 (Go et al., *Circulation* 2013)
  - ~78 million US adults have hypertension, with highest rates among African-Americans; only 53% of persons with known hypertension have adequate control
  - 8.3% of adults in 2010 had diagnosed diabetes, with many more with undiagnosed DM or prediabetes
  - Smoking rates have decreased
Stroke Incidence and Mortality Trends in US Communities, 1987 to 2011

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Figure. Adjusted Stroke Incidence Rate Ratios vs Calendar Time

A) Age <65y

B) Age ≥65y

P value for linear trend = .36

P value for linear trend < .001

Models are adjusted for age, sex, race and center, hypertension, diabetes, coronary heart disease, cholesterol-lowering medication use, and smoking. Dots represent adjusted incidence rate ratio point estimates from model run using a categorical calendar time variable, plotted at midpoint of each 3-year calendar time category, with 1999-2001 as the reference category. The dotted line represents the linear trend in adjusted incidence rate ratios and the shaded area represents the 95% CI with 2000 as the reference point. Models included all study data, but plots exclude time periods in which there were few events.
Mechanism of stroke

- Types of stroke
  - Ischemic
    - Thrombotic
    - Embolic
    - Hypoperfusion
  - Hemorrhagic (caused by the rupture of small blood vessels in the brain)
Types of cerebral infarction (ischemic stroke)

TOAST* Criteria

- Large artery atherosclerosis
  - Location/size
  - No cardiac embolic source
- Cardioembolism
  - Cardiac source
  - >1 territory
- Small-vessel occlusion
  - “Lacune” – brain cavity after loss of infarcted tissue.
  - Clinical lacunar syndrome
  - Imaging: normal or small subcortical infarct (<1.5 cm)
- Stroke of other determined etiology
  - E.g. vasculopathies, hematologic abnormalities
- Stroke of undetermined etiology

*Trial of Org 10172 in acute stroke treatment
Adams HP, 1993
Clinical workup of stroke patients

- Acutely: Stabilize the patient, consider intravenous tPA if within 4.5 hours of presentation
- Conduct tests to evaluate cause/ etiology of stroke
  - Evaluate for cardioembolic source: telemetry monitor, transthoracic echocardiogram
  - Brain and vascular imaging: MRI (when possible), MRA, carotid duplex
  - Check vascular risk factors: HbA1c, lipid profile, assess smoking history, follow BP
  - Search for mimics: RPR (syphilis), thyroid dysfunction, Vitamin B12 deficiency
- Start medications aimed at secondary prevention of stroke
- Start rehabilitation early
Subclinical cerebrovascular disease

- Many people have brain injury, through similar vascular mechanisms, which is “asymptomatic”

- This includes:
  - “silent” strokes (of all types)
    - Often lacunar-type infarcts, detected on MRI or CT but without clear clinical symptoms
    - Microbleeds: small asymptomatic hemorrhages, often due to poorly controlled high blood pressure, or other pathologies (cerebral amyloid angiopathy, cavernous angioma)
  - white matter disease/ leukoaraiosis
  - These different types of small vessel disease are likely related in both etiology and outcome
Risk Factors: Hypertension, Smoking, Diabetes

Cerebral microbleeds

Cognitive decline, Dementia


Dilated perivascular spaces
Lacunar infarcts
Leukoaraiosis
Silent ischemic infarcts are common

Vermeer et al., Stroke 2003; 34: 392.

from Vermeer et al., Lancet Neurology 2007; 6(7): 611-619
Microbleeds

- Reported in 6% of people 45-50, but 35% of people 80 and older (Poels et al., Stroke 2010; 41: S103)
- More cortical location suggests cerebral amyloid angiopathy, whereas more subcortical/brainstem location is more consistent with uncontrolled hypertension

MRI with T2* GRE to detect hemosiderin/old blood products in the brain
White matter disease, aka leukoaraiosis

- **Rotterdam study:**
  - Among 2000 participants, median white matter lesion volume was 1.8 mL (45-59 yo), 3.1 (60-74 yo), and 7.7 mL (75-97 yo).
  - Only 8% of individuals 60-90 had no subcortical white matter lesions, 20% had no periventricular lesions, and 5% had neither. (de Leeuw et al., *JNNP* 2001; 70(1): 9-14).

- **Atherosclerosis Risk in Communities (ARIC) study**
  - 17% of individuals 50-71 yo had a white matter disease grade of 0, median volume was 9.1 mL (range 0-90 mL) at age 61-83 yrs (Unpublished).
Progression of White Matter Disease is Strongly Predicted by Systolic Blood Pressure

ARIC; Gottesman et al., Stroke 2010
Outcome of subclinical brain vascular changes: Small vessel disease as risk factors for stroke

- HR 1.9 (95% CI 1.2-2.8) for incident stroke among persons with multiple silent infarcts vs those without (Cardiovascular Health Study: Bernick et al., *Neurology* 2001)

- Increased risk of stroke in persons with more white matter hyperintensities (3-City study; Buyck et al., *Stroke* 2009)

- In a meta-analysis of stroke patients, microbleeds are associated with an increased risk of *recurrent* stroke (ischemic and hemorrhagic) (Charidimou et al., *Stroke* 2013)
Outcomes: Small vessel disease is associated with cognitive change

Prins et al., *Brain* 2005

Lei et al., *JNNP* 2013
Small vessel disease as a risk factor for dementia

Vermeer et al., *NEJM* 2003

Prins et al., *Arch Neuro* 2004

AGES-Reykjavik; Qiu et al., *Neurology* 2010
Vascular Risk Factors and Cognitive Aging

- Risk factors for stroke have also been shown to be associated with cognitive decline and dementia
  - Hypertension
  - Diabetes
  - Metabolic syndrome
  - Hyperlipidemia
  - Atrial fibrillation
Midlife high blood pressure is associated with more cognitive decline

Gottesman et al., *JAMA Neurol.*, 2014; 71(10): 1218-1227
Is HIV an independent risk factor for stroke?

- HIV does appear in clinical studies to be associated with higher stroke risk.
- ICH risk appears even higher, assoc with HIV:
  - 2.29 per 1000 person-yrs (HIV positive) vs 1.23 cases per 1000 p-yrs (HIV negative) in a health care database (Chow *Neurology* 2014).
- Stroke rates in HIV positive persons with high CD4 count/ low viral load approach that of HIV negative persons (Marcus *AIDS* 2014).
- BUT: autopsy studies of 20-50 yo’s suggest possibly lower stroke rates in HIV positive patients vs controls.
Stroke rates in HIV-positive patients are increasing

Ovbiagele & Nath, *Neurology* 2011
Causes of stroke in the HIV-positive patient: Why are rates going up?

- **Infections: HIV or other associated infections**
  - Varicella-zoster: Primary infection or reactivation
  - TB
  - meningovascular syphilis
  - CMV

- **HIV-associated vasculopathy**
  - Damage and activation of vascular endothelium
  - Chronic inflammation

Benjamin *Lancet Neurology* 2012; Mateen *Neurology* 2013

Nagel *Infect Disord Drug Targets* 2010
Why are HIV stroke rates going up?...
Continued..

- **Coagulopathy, Cardioembolic sources**
  - Antiphospholipid antibody syndrome
  - Bacterial or marantic endocarditis
  - HIV-associated dilated cardiomyopathy

- **Concomitant drug use**
  - Methamphetamine-associated cardiac dysfunction or vasculopathy/ hypertension
Why are HIV stroke rates going up?.. continued...

- **Use of cART**
  - Dyslipidemia, Accelerated atherosclerosis
  - Metabolic syndrome/ obesity
  - BUT: risk of stroke appears to be higher in more immunosuppressed patients (Rasmussen *AIDS* 2011)

- **Aging of the population**

- **Use of Framingham Risk Score may underestimate stroke risk in patients with HIV**
HIV and subclinical vascular disease of the brain

- Although only 1-5% of HIV positive persons have clinical stroke, 4-34% have infarcts seen on autopsy
- Leukoaraiosis/ white matter hyperintensities
  - In one study, 24% of scans with white matter lesions were consistent with cerebral small vessel disease (Haddow et al., *AIDS Patient Care STDS* 2014)
  - Exposure to protease inhibitor-based antiretroviral therapy was associated with cerebral small vessel disease on autopsy (OR 2.8); presence of HIV-associated neurocognitive disorders was also associated with small vessel disease (Soontornniyomkij *AIDS* 2014)
Vascular risk factors and small vessel disease in HIV positive patients

Fig. 3. Regression of white matter lesion volume and systolic blood pressure among HIV-seropositive individuals.

Hawaii Aging with HIV Cohort Study: McMurtray Cerebrovasc Dis 2007
MRI Black Blood imaging demonstrating high rates of lipid core in carotid plaque in young (30-44) people with HIV

Fig. 2. Black blood MRI images of the right carotid bifurcation in a 33-year-old female with HIV infection and cocaine use. Long-axis view used to orient short-axis images shows a focal plaque (arrow) along the outer wall of the carotid bulb. The short-axis view (b) through the plaque (line, a) shows the eccentric wall thickening (arrows, b).
Future Directions in HIV/ Stroke research

- Monitoring stroke rates in HIV cohorts will be important, to determine if estimated rates and increases are accurate
  - Current pilot study in the MACS cohort using methods from the MESA study to adjudicate stroke events (Lisa Jacobson, Wendy Post at Hopkins)
- Studies of subclinical cerebrovascular disease, including vascular imaging, may explain more about mechanism of HIV or cART’s impact on brain arteries
- Evaluation of acute management for stroke in HIV (i.e. tPA)
Conclusions

- Although stroke rates are *decreasing* in the general population, they are *increasing* among HIV positive persons.
- Subclinical cerebrovascular disease is likely to parallel stroke, with shared risk factors and pathophysiology.
- The aging of the HIV-positive population along with metabolic impacts of antiretroviral therapy is likely to contribute to more “garden-variety” vascular disease of the brain.
- Diagnosis and treatment algorithms should consider HIV-specific causes, although stroke is likely to be due to the same causes in persons with vs without HIV.
  - Guidelines for BP and cholesterol management have changed recently; it’s unclear if this change is especially relevant in HIV-positive patients.