Vascular Cognitive Impairment-- NEUROPATHOLOGIC ISSUES

VCI vs. IVD/DEMENTIA with VASCULAR DISEASE (IVD)

—advanced pathology

***HANDLING the BRAIN at AUTOPSY*:**

- **What to FIX vs. what to FREEZE?**
  --no need to be uniform across centers--
  Individual approach should be based upon programmatic strengths

- **ADRC model: *Fix* one hemisphere, *freeze* (slabs) other hemisphere; fix LEFT if decide to freeze one hemisphere only**

- **Centers with major neuroimaging correlative studies may prefer *most* fixed**

- ***ALL CENTERS* should snap freeze at least some material---can get good quality mRNA even with long PMI--needs to be assessed case by case**

- **Sampling fixed brain: CERAD + frontal/posterior white matter blocks**

- **NB: NACC vascular dataset ITEMS #63-75 a reasonable starting point for documenting/assessing CVD, but can be refined to be more informative**

ATHEROSCLEROSIS (BASAL, PERIPHERAL MENINGEAL):

MINIMAL DATA SET…

- Comment on severity of basal atherosclerosis (+/- photograph)—Especially anterior vs. posterior circle of Willis, Lt vs. Rt
- Histologic sections (representative) of major arteries??
- Dolichoectasia—fusiform aneurysm present/absent—severity?
- Assessment of stenosis of major arteries (0-25, 26-50%, etc…) & presence/absence of atherosclerosis in distal (meningeal) arteries

ATHEROSCLEROSIS…

IDEAL DATA SET…

- **Ante-mortem data on cervical arteries, or (*optimally*)…**
- **Cervical arteries examined as part of complete necropsy, which also includes…**
- **Heart, kidneys, documentation of systemic vascular disease**
- **Histologic sections to assess atherosclerosis (incl. plaque hemorrhage, ulceration, mural or complete thrombi, etc.) incl *distal* atherosclerosis**

***MICROVASCULAR DISEASE—ARTERIOSCLEROSIS*:**

- ***Assessment of arteries more important than veins but should document venous adventitial fibrosis (found by some groups to be potentially important)***
- AREAS TO SAMPLE: CERAD + Anterior & Posterior WM (section to include periventricular and deep regions), MCA/ACA watershed zones bilateral—also adequate to screen for CAA

MICROVASCULAR DISEASE…

MINIMAL DATA SET…

- **Severity—semi-quantitative (e.g. using templates/ McKee)**
- **Inflammation (lymphocytes, macrophages; non-infarct-related)**
- **Perivascular hemosiderin (evidence of remote hemorrhage)**
- **Fibrinoid necrosis, Charcot-Bouchard microaneurysm(s)**

MICROVASCULAR DISEASE...

IDEAL DATA SET...

- **Special stains (Masson trichrome, EVG, Movat pentachrome)**
- **Immunohistochem: Using anti-SM actin, collagen subtypes, others?**
- **Quantitative assessment: Arteriosclerotic index (ASI)**

MICROVASCULAR DISEASE—AMYLOID ANGIOPATHY (CAA):

MINIMAL DATA SET…

- **Can be evaluated on H & E-stained sxns, but optimally Congo red/Thioflavin, Abeta immunohistochem (? Perivascular neurite assessment using others?)**
- **KEY ASSESSMENTS: Focal vs. widespread, meningeal vs. cortical, arteriolar vs. capillary**
- **Quantitation: Individual vessel severity X # of arteries affected/section**
- **Evidence of perivascular hemorrhage (old—hemosiderin)**
- **CAA-associated inflammation & other CAA-associated microangiopathies (e.g. microaneurysm formation, fibrinoid necrosis, etc)**

MICROVASCULAR DISEASE—AMYLOID ANGIOPATHY (CAA)...

IDEAL DATA SET...

- **Grid-counting method with Abeta IHC (Frosch/Greenberg ms in press)**

***MISCELLANEOUS MICROANGIOPATHIES*:**

- **Vasculitides (non-CAA associated), intravascular lymphoma, TTP, etc—usually don't present with cognitive impairment**

- **Vigilance for new types of fIVD/ fCVD—e.g. CADASIL-like, HERNS, etc.**

***PARENCHYMAL ABNORMALITIES*:**

General rule—*ALL* infarcts: must assess #, size, location, age—acute lesions likely *unimportant* except as marker of CVD severity/duration

MINIMAL DATA SET of LESION (INFARCT) ASSESSMENT…

- **Large or small cystic**
- **Borderzone/watershed (also a good region to assess microinfarcts)**
- **Lacunar (deep GM & Brainstem, WM)**
- **Microscopic (not visible grossly)**
- **Laminar necrosis**
- **Hippocampal injury (focal, multisegmental, diffuse)**
- **Cribriform change (*etat crible*) & location (WM, deep CGM)**

PARENCHYMAL ABNORMALITIES…

INFARCT + MAJOR HEMORRHAGIC COMPONENT…

- **Resorbed large parenchymal hemorrhages**
- **Large/small/micro- hemorrhages (e.g. with CAA)**
- **Large infarcts with significant hemorrhagic component**

LEUKOENCEPHALOPATHY…

- **Anterior vs. posterior deep white matter**
- **Periventricular vs. deep white matter**
- **Assessed on myelin-stained sections (LFB, K-B), using an internal control—e.g. middle cerebellar peduncle—assess on a semi-quantitative scale (0-3+), diffuse or multi-focal**

PARENCHYMAL ABNORMALITIES…

IDEAL DATA SET…INFARCTS

- **Quantitative assessment of (large) infarct size, #, location--# and location especially important for microinfarcts (?Digitized images of slices?)**
- **Co-register with antemortem imaging (especially if images obtained shortly prior to death)**
- **Value of postmortem imaging—but some MRI sequences not interpretable--whole brain vs. slabs; cortical thickness & 'regularity'**
- **for WHITE MATTER Lesions: Immunohistochem using anti-MBP, ph-NF, GFAP, microglial markers, ubiquitin, amyloid precursor protein**

HIPPOCAMPAL LESIONS:

MINIMAL DATA SET…

- **Should assess anterior and posterior hippocampus, amygdala**
- **Focal microinfarct(s)/scars vs. diffuse or segmental (CA1, prosubiculum)**
  Neuron loss & astrogliosis—spectrum of injury
- **May be difficult to separate from severe AD**
- **Vascular vs. degenerative anatomic features—assistance from IHC (anti-Ubiq)**

IDEAL DATA SET…

- **Include serial blocks of hippocampus**
- **Quantitative assessment of neuron loss and astrocytic gliosis (Zarow et al, *Ann Neurology* in press, 2005)**

***SUB-INFARCTIVE (INCOMPLETE) ISCHEMIC INJURY*:**

- **What the *#$%^@@#$* is it?**
- **How do we assess it using neuropathologic tools?**
- **Immunohistochemistry using primary a/b's that *reflect* injury—microglia, astrocytes—distribution, morphology of these cells may be more important than number/density**
- **Important to establish correlations with neuroimaging**
- **Synaptic, NeuN, dendritic markers in cortex**
- **Assess cerebellum as a structure likely to show Purkinje cell loss with hypoxic-ischemic injury**

***MIXED VASCULAR—PARENCHYMAL PATHOLOGY*:**

- **NACC guidelines for parenchymal pathology (AD, LBD, other dementias)**
- ***WHAT DOES NEUROPATHOLOGIST PROVIDE to CLINICIAN/INVESTIGATOR?***
- **Final list of diagnoses?**
- **Summary of parenchymal/vascular pathology?**