Increasing concern regarding frequency and consequences in Western countries

- Underdiagnosed
- Longer length of stays and use of resources
- Increased rates as population ages
- Multiple types of dementia--dementia serves as a basic framework, but does not speak to etiology.
Dementia Criteria

- Impairment of memory
  - Also requires deterioration in at least 2 other cognitive domains;
    - Aphasia, apraxia, agnosia, executive function
  - Clear consciousness
  - Impairment in ADL’s/social/occupational activities are impaired due to the decline in cognition;
  - Duration of 6 months.

Etiologies

- Associated with multiple conditions
  - Prevalence 9.6% for all types after age 65
  - Incident may double every 5 years after 65
  - DAT 6.5% prevalence (65% of dementia)
  - Remainder of cases secondary to vascular, HIV, mixed, frontotemporal, and others.
  - Mixed vascular/DAT or VaD comprises the second largest group (20-25%).
Vascular and Mixed Dementias

- Often conceived of as a subcortical dementia…except when it’s not.
- Better conceptualized as a disseminated brain disease--systematic workup and treatment required.
- Major differences with DAT, so diagnosis and treatment differ significantly.

Vascular dementia (VaD)

- Dementia resulting from ischemic, ischemic-hypoxic, or hemorrhagic brain lesions due to cerebrovascular or cardiovascular pathology (Roman 2002).
- Heterogeneous concept/presentation;
  - Later in life…or not;
  - Cumulative effects of cerebrovascular disease in all forms--diagnostic criteria acknowledge these differences.
**NINDS-AIREN 1993 Specific Types**
- 1. Multi-infarct dementia (large-vessel infarcts)
- 2. Strategic single-infarct dementia (PCA, ACA, B thalamic, BF)
- 3. Small-vessel disease with dementia-multiple lacunes (basal ganglia, frontal WM, PVWM = Binswanger's)
- 4. Hypoperfusion (global due to arrest or hypotension; watershed)
- 5. Hemorrhagic dementia (chronic SDH, SAH, ICH, CAA)
- 6. Other mechanisms (combinations of above, or unknown)

**Total volume of infarcted brain and total number of infarcts correlate well with VaD severity;**

**Locations of infarcts also common;**
- 2/3--pathological correlate is a lacunar state with multiple lacunar infarcts in subcortical structures (BG & thalamus)

**Vascular cognitive impairment proposed to broaden definition of VaD…why?**
VaD vs. Mixed vs. DAT

- Data show emerging role of vascular disease in DAT & other dementias;
- Pure VaD now considered quite unusual;
- Most DAT have a cerebrovascular comorbid overlay;
- Mixed previously underestimated--now considered quite common;
- VaD & DAT may share pathogenetic mechanisms.

Thus, a heterogeneous presentation of cerebrovascular disease leads to heterogeneous clinical presentations:

- Cortical
  - Infarcts affecting primarily the cortex;
  - Focal neurological signs more common;
- Subcortical
  - History of hypertension
  - Deep lacunae infarcts in white matter;
  - Accumulative white matter destruction.
Subcortical (continued)

- Important variant: subcortical arteriosclerotic encephalopathy (Binswanger’s disease)
  - Pseudobulbar palsy
  - Spasticity
  - Weakness
  - Profound apathy/avolition/amotivation;
  - Extensive diffuse demyelination of white matter in periventricular regions;
  - More frequent than previously estimated.

Vascular dementia

- Commonly understood as a stepwise progression...except when it doesn’t.
- VaD may progress as smoothly as patients with DAT--supported by recent neuroimaging techniques;
- Affective changes common;
- Personality changes uncommon...except when they occur, in which case prominent;
Post-stroke depression
- Stroke is 3rd leading cause of mortality;
- Most common serious neurological disorder--50% of all acute neuro hospitalizations.
- Mean prevalence rates 23% for all ambulatory samples of stroke patients.
- Affects functional rehabilitation & cognitive functioning in post-stroke period.
- Little association b/w location--more likely associated with lesions in subcortical white matter, thalamus, BG, and brain stem (Bogousslavsky 2003).

Diagnosis & Differential
- Early diagnosis important in vascular dementia, as it (theoretically) can be prevented with proper interventions;
- Where cerebrovascular disease exists--so does cardiovascular disease and peripheral vascular disease--surrogate markers for risk.
Clinical history--most important part of the evaluation:
- Search for deterioration in memory, cognition, and function;
- Convincing specific examples needed;
- Outside informant is essential;
- Screening questionnaires for informants may be helpful.

Mental Status Examination
- No single standardized instrument sufficient
  - MMSE is most common, but screens effectively only for cortical dementias;
  - MMSE poor choice for subcortical dementias;
  - Frontal Assessment Battery good for executive function, and may be more sensitive to subcortical deficits.
  - Clock drawing also sensitive.
Neurological Exam:
- Standard neurological exam;
- Attention to gait, praxias, pathological reflexes, and presence of tremor/movement disorders.

Differential diagnosis
- Mental retardation
- Amnestic syndromes (Korsakoff’s)
- Age related memory impairment (benign senescent forgetfulness)
- Pseudodementia syndromes due to emotional or motivational factors
- Delirium
- Mild cognitive impairment
Clinical features suggesting vascular dementia
- Mixed cortical-subcortical features;
- Preservation of insight/judgment;
- Abrupt onset, stepwise course;
- Emotional incontinence, lability;
- History of vascular disease
- Focal neurological signs, symptoms.

Laboratory Tests and Diagnostic Procedures
Screening battery
- CBC
- Serum chemistries
- TSH, fT4
- VDRL/RPR
- B12/folate/methylmalonic acid
- Fasting lipid panel
Other selected tests for new dementia:
- HIV
- Blood/urine screens for EtOH, drugs, heavy metals--based on history;
- ANA, C3, C4, anti-ds-DNA Ab, anticardiolipin antibody if rheumatologic factors considered possible;
- Disease specific tests (Wilson’s disease)

Tests of questionable clinical utility
- Presenilin 1--predicts early-onset DAT, but very low sensitivity;
- APOE--associated with late onset DAT, but marker of poor resilience overall;
- EEG--limited utility due to non-specific changes that only occur in late stages.
  More likely useful in Creutzfeldt-Jacob
Neuroimaging

- MRI with/without contrast
  - Effectively screens for most features of dementia safely and with high sensitivity;
  - Detects vascular lesions, space occupying lesions, hydrocephalus, lobar/structural atrophy, and demyelination;
  - Biggest “bang for buck” neuroimaging procedure, but lengthy, requires cooperation, and costly.

- CT with/without contrast
  - Less sensitive but less expensive than MRI;
  - Requires iodinated contrast—more difficult in patients with renal impairment.

- Positron Emission Tomography (PET)
  - Most specific and sensitive neuroimaging test for early DAT
    - Temporoparietal hypometabolism with relative sparing of visual and sensorimotor cortex;
    - Relatively little assistance in characterizing vascular disease, and typically requires concurrent MRI technique.
    - Perhaps helpful with differential of frontal dx.
SPECT (Single photon emission computed tomography)

- May assist with characterization of fronto-temporal dementias and vascular dementia, but any positive finding typically requires MRI/CT follow-up.
- Not terribly effective for screening and has low sensitivity/specificity.

Vascular Dementia--Prognosis

- Considerable individual variation in survival--highly dependent upon total burden of vascular disease.
  - Typical cause of death is cardiovascular morbidity--so addressing co-morbid CV disease is paramount to improving survival.

- In contrast:
  - Huntington’s disease: 10-15 years
  - Parkinson’s disease: ~15 years
  - Wilson’s disease: normal survival if early.
VaD: Treatment Options

- Address underlying vasculopathic risk factors:
  - Cardiovascular optimization
    - Lipid panel with attempted correction of underlying lipid abnormalities;
    - Baseline EKG;
    - Consider stress studies if EKG abnormalities or concurrent symptoms suggestive of CAD.
  - ASA
  - Beta-blockers
  - Statins

- Anticoagulation
  - ASA to start--remains the backbone of anticoagulation therapy for both cardiovascular and cerebrovascular disease;
  - If cerebrovascular disease progresses, then alternatives include:
    - High dose aspirin;
    - Combination dipyridamole/aspirin;
    - Ticlopidine, clopidogrel (ADP receptor inhibitors);
    - Warfarin.
Control of hypertension

- Preventative treatment of even mild hypertension promising for VaD
- To date, only diuretics & beta-blockers have demonstrated improved survival and reduction of CVA’s.

Management of diabetes mellitus

Obesity

- “Easily” modifiable risk factor for CVA;
- Abdominal adipose tissues;
  - Stronger risk factor than BMI;
  - Stronger predictor of CVA in young;
- For every BMI increase of 1, risk of CVA in late life increases by 5%;
- Dieting and exercise essential to weight loss reduction--foods rich in omega-3 fatty acids.
Obstructive sleep apnea
- Closely correlated with obesity typically, but is an independent risk factor for CVA even when controlling for BMI;
- Other problems include congestive heart failure, daytime sleepiness, and sudden death.
- Various treatments:
  - UPPP (50%) success rate;
  - CPAP
  - Tracheostomy for severe, refractory cases.

Nicotine dependence
- Historic meta-analysis addressed risk of CVA due to smoking (Shinton & Beevers 1989)
  - Disproportionately increased CVA in those less than 55 years of age by OR 2.9;
  - Risk of hemorrhagic CVA increased by OR 2.9;
  - Risk of ischemic CVA increased by OR 1.9.
- Framingham heart study (1988)
  - Risk of CVA proportionate to amount of smoking;
  - >2ppd increased risk of CVA by OR 2.0;
  - Relationship present after controlling for age & HTN;
  - CVA risk drops soon after stopping (2-5 years).
Alcohol dependence

- Data somewhat confusing—the “middle way” seems correct with this. (1 drink = 12 g EtOH)
- Meta analysis (Reynolds et al., 2003)
  - Compared with ND, use of >60g EtOH/daily increased risk of total CVA (OR 1.64), ischemic CVA (OR 1.69), and hemorrhagic CVA (OR 2.18).
  - Compared with ND, use of 12-24g/day was associated with reduced risk of ischemic CVA (OR 0.72);
  - Compared with ND, use of less than 12g/day associated with reduced risk of total (OR 0.83) and ischemic CVA’s (OR 0.82).

Alcohol

- Data confirmed by other studies (Mukamal et al., 2005) that showed moderate drinking of 1-3 drinks/daily on 3-4 days/week was associated with lowest risk of ischemic CVA (OR 0.68);
- Heavier EtOH use associated with increased hemorrhagic and embolic CVA subtypes;
- Modifiable risk factor--screen for EtOH history and those with higher EtOH use, encourage dietary modification or referral to substance abuse treatment.
Special considerations in vascular dementia: Treatment of comorbid psychiatric disease

- Depression
- Cognition
- Behavioral agitation

Treatment of vascular depression

- Antidepressant treatment shown effective in treating vascular depression
  - SSRI’s, SNRI’s historically considered first-line agents due to relative safety;
  - However, serotonergic agents may also increase risk of GI bleeding–use must be weighed in conjunction with risk-benefit analysis;
    - Especially problematic with h/o GIB;
    - Strong argument for PPI therapy if used.
Depression, continued

Agents that have relatively less serotonergic effect may be relatively more safe from GIB perspective, but less data for efficacy in this population.
- Mirtazapine;
- Trazodone;
- Bupropion preparations;
- Desipramine/nortriptyline

Psychostimulants can also be useful.
- Methylphenidate, d-amphetamine;
- Monitor heart rate and blood pressure within 1-2 hours of initial dosing;
- Titrate gradually based on effect to side-effects

Electroconvulsive therapy
- Remarkably effective for depressive illness
- Subcortical disease increases risk of adverse events—weigh accordingly and refer to specialist.
Treatment of cognition

- Overall, remarkably disappointing options;
- Anticholinesterase inhibitors
  - Approved for DAT, not for VaD.
  - Limited benefit in DAT, but generally safe.
  - In VaD, mild-moderate evidence of benefit.
- Memantine—supported by systematic reviews.
- Nimodipine—mixed and VaD.

Agitation

- Agitation and behavioral disturbances present in up to 90% of patients with dementia across the course of their disease;
- Increased risk of nursing home placement;
- Increased risk of hospitalization;
- Inability to maintain a least restrictive environment for their well-being and care.
Agitation

- Interpersonal, social, and environmental interventions can be useful in mild to moderate agitation;
- Severe agitation that threatens the integrity of patients and staff requires pharmacological treatment AFTER diagnosis;
- Differential includes constipation, urinary retention, pain, delirium, sensory deprivation, depression, etc.
  - Antidepressants--may be useful with impulsivity. Very effective with regards to depression and pseudobulbar affect.
  - Antipsychotics have the best data for treatment of non-specific agitation--they also enjoy black box warnings.

Meta-analysis (Schneider et al, 2006)

- Efficacy noted for risperidone and aripiprazole
- Smaller effects for less severe dementia, outpatients, and patients selected for psychosis
- Cognitive test scores worsened with drugs
- No evidence for increased injury, falls, or syncope;
- Significant risk for cerebrovascular events, especially with risperidone.
Agitation

Meta-analysis (Ballard & Waite, Cochrane Review, 2006):

- Risperidone & olanzapine significantly improved aggression compared to placebo;
- Risperidone significantly improved psychosis;
- Risperidone and olanzapine both showed significantly higher incidence of serious adverse cerebrovascular events (including stroke), extra-pyramidal side effects and other adverse outcomes;
- Risperidone and olanzapine had increased numbers of dropouts in trial;
- Data were insufficient to examine impact upon cognitive function.

Risk of death/AE meta-analysis (Schneider et al., JAMA, 2005)

- Death occurred more often among patients randomized to drugs (118 [3.5%] vs 40 [2.3%]).
- The OR by meta-analysis was 1.54; 95% confidence interval [CI], 1.06-2.23; P = .02
- Sensitivity analyses did not show evidence for differential risks for individual drugs, severity, sample selection, or diagnosis.
Agitation—conclusions

- Efficacy data exist for atypicals in control of aggression in dementia patients—HOWEVER
  - Significant risk of stroke and serious adverse events exist—especially in patients with history of vascular disease;
  - Use should be individualized and based upon severe aggression or aggression that limits patient's ability to remain in the least restrictive environment after other agents tried;
- Document rationale!

Conclusions & Directions for the Future

- Poor prognosis
- Primary intervention is best—prevention is key to limiting progression of disease;
- Anticoagulation may have role—weigh in relation to risk of falls and AE’s;
- Few data exist regarding role of pharmacology in significantly improving cognition and VaD;
- May be at special risk for stroke/AE’s with use of neuroleptics;
- Transition to palliative care model focusing on quality of life rather than longevity.