Vascular Dementia: An update for primary care practitioners

Harold W. Goforth, M.D.
Duke University Medical Center
Durham VAMC--GRECC

- 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 dipyrridamole/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 redution--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 conjuction 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

- Depression, continued
  - 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.

- Agitation
  - 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.

- Agitation
  - 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.