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Introduction

- Burden of cognitive impairment becomes increasingly important as people live longer.
- While Alzheimer’s disease (AD) is the most commonly diagnosed dementia cause, cognitive impairment due to cerebrovascular factors are also important, independent contributors to cognitive dysfunction.
- Overall dementia prevalence in affluent countries
  - 05–10% in individuals age 65 and >
- AD prevalence
  - Doubles every 4.3 y
- Vascular dementia (VaD) prevalence
  - Doubles every 5.3 y
- Age-adjusted dementia incidence rates (per 1000 person years)
  - AD  = 19.2
  - VaD  = 14.6
Most older studies use VaD (or Multi-Infarct Dementia, MID) when estimating prevalence and incidence. The construct of Vascular Cognitive Impairment (VCI) refers to the entire spectrum of vascular-related cognitive impairment, from mild to severe. VCI prevalence and incidence rates are therefore higher than VaD or MID rates.
VCI includes

- Prodrome conditions such as Vascular Mild Cognitive Impairment (Vascular MCI)
- "Pure" Vascular Dementia (VaD)
- "Mixed Disease": concomitant vascular and other pathology, such as pathology associated with AD
Criteria set up by Hachinski et al for MID yield a relatively large number of cases.

NINDS-AIREN criteria are relatively conservative and yield more modest rates.

Criteria that include neuroimaging data may significantly influence frequency figures.

Inclusion of “mixed disease” will yield higher numbers, as mixed pathologies may be the most common explanation of cognitive impairment in aging.

DSM V may introduce new terms (e.g., Major Neurocognitive Disorder) which may also impact prevalence and incidence rates.
The role of vascular lesion type on the extent of cognitive impairment

- Do large cortical infarcts, lacunar infarcts, subcortical white matter disease, strategically placed subcortical infarcts and a combination of these lesion types have differing cognitive footprints?
- Do vascular lesions lower the threshold for the clinical manifestation of AD?
- Is there cholinergic compromise in both AD and VCI?
Defining AD and VCI

- There has been a significant evolution in terminology of cognitive deficits associated with CVD
- MID
  - Used to identify patients who developed dementia after multiple strokes
- VaD
  - Severe cognitive and functional impairment regardless of CVD etiology
- VCI
  - Encompasses all cognitive disorders associated with CVD, from mild deficits to frank dementia
- VCI Definition
  - “A syndrome where there is evidence of clinical stroke or subclinical vascular brain injury and cognitive impairment affecting at least one cognitive domain”
- **VCI**
  - An overarching condition that includes both VaD and vaMCI
  - Criteria based on two factors
    - A demonstration of the presence of a cognitive disorder by neuropsychological testing
    - A history of clinical stroke or presence of CVD by neuroimaging that suggests a link between the cognitive disorder and the vascular disease
    - Is to be used with all etiologies of CVD, including cardioembolic, atherosclerotic, ischemic, hemorrhagic or genetically-related CVD
- Neuroimaging of cortical infarcts, subcortical infarcts and other stroke lesions is critical when associating stroke with VCI.
- Understanding the source of cardiac or vascular pathology that underlies CVD may provide more specific clinico-pathologic relationships.
- While cognitive deficits may appear soon after clinical stroke, the deficits may appear more than 3 months after the stroke.
VCI may co-exist with multiple cerebral and systemic disorders that can affect cognition in the elderly, especially AD.

- It is often difficult to determine whether cognitive deterioration is solely a consequence of vascular factors or to underlying AD.
- Determining the presence and effect of AD on dementia associated with CVD is the most difficult aspect of a VCI diagnosis.
Mild Vascular Cognitive Impairment

- Current MCI criteria include
  - “Amnestic MCI”
  - MCI associated with other cognitive impairment
    - Amnestic MCI + other cognitive deficit
    - Non-amnestic, single domain MCI
    - Non-amnestic, multiple domain MCI
- vaMCI was first thought to require deficits in executive function, however, clinical studies have shown that vaMCI subjects may present with a broader array of cognitive impairment
- Reversibility of vaMCI
  - Persons with MCI have been shown to return to normal cognition
  - Individuals with vaMCI may revert to normal cognition without specific treatment because of the presence of depression, heart failure or an autoimmune disorder
  - In addition, post-stroke recovery may result in cognitive improvement, thus moving an individual from vaMCI to normal cognitive function
Neuropsychological differentiation of AD and VCI

- Differentiation of AD and VCI by neuropsychological assessment alone has met with mixed success.
- Executive dysfunction may not specifically point to CVD.
- This line of research is complicated by difficulty in clinically differentiating AD or VCI from mixed (AD + CVD).
- The heterogeneity of CVD works against a single, unifying neurocognitive pattern of VCI deficits.
VCI Diagnostic Criteria

1. The term VCI characterizes all forms of cognitive deficits from VaD to MCI of vascular etiology

2. These criteria cannot be used in subjects who have an active diagnosis of drug or alcohol abuse/dependence--Subjects must be free of any type of substance for at least 3 months

3. These criteria cannot be used in subjects with delirium
VCI Diagnostic Criteria: Dementia

1. The diagnosis of dementia should be based on a decline in cognitive function from a prior baseline and a deficit in performance in two or more cognitive domains that are of sufficient severity to affect the subjects’ ADLs.

2. The diagnosis of dementia must be based on cognitive testing, and a minimum of 4 cognitive domains should be assessed—executive/attention, memory, language, and visuospatial functions.

3. The deficits in activities of daily living are independent of the motor/sensory sequelae of the vascular event.
VCI is a syndrome that includes a broad range of cognitive impairment severity.

Executive dysfunction is often, but not always included in the VCI cognitive impairment pattern.

The most severe form of VCI is VaD.

vaMCI includes individuals with cognitive impairment who do not meet dementia criteria.

Keys to defining VCI are neuropsychological testing, bedside or office clinical examination and neuroimaging.
Neuropathologic Aspects

- Defining the pathology underlying VCI has remained elusive
  - Infarcts vary in size, number and location, and occur commonly in the elderly, with and without dementia
  - Infarcts are typically accompanied by AD and other pathologies
  - Progress has been made by studying persons in community samples close to the time of death, then again using quantitative measurements of vascular and AD pathology at autopsy
Cerebral infarctions are the most important cerebrovascular pathology that contributes to cognitive impairment

- Cerebral infarcts are discreet regions of tissue loss, observed both macro- and microscopically
- Chronic macroscopic infarcts occur in 1/3 to ½ of older persons, far more frequently than clinical stroke
- In some community-based studies, microscopic infarcts are more common than macroscopic infarcts
In clinical-pathologic studies, larger infarct volume and increased number of macroscopic infarcts are associated with an increased likelihood of dementia.

There is yet no reliable cut-point for infarct volume and dementia.

Infarct location is important. Thalamus, angular gyrus and basal ganglia may be more likely than other regions to result in cognitive impairment.
Still, regional factors have not been clearly defined and many other regions have been related to dementia.

Microscopic infarcts have been related to dementia, even after accounting for macroscopic infarcts.

Cognitive reserve and other co-existing pathologies may be additional factors when relating cerebral infarctions to cognitive impairment and dementia.
Most persons with dementia and almost half of those with clinically probable AD have mixed (AD + CVD) pathology.

- Infarcts appear additive with AD pathology in lowering cognitive function, increasing the odds of dementia, and increasing the odds of clinical AD.
- The public health importance of infarcts and their role in dementia is likely underestimated.
- Prevention and therapies that decrease cerebral infarcts are likely to lower the prevalence of dementia.
- AD has been found to be the most common pathology associated with MCI, though mixed pathologies are also common.
WMH and CMBs are both common in the brains of older persons, and may reflect direct tissue damage.

- A role for cognitive impairment associated with WMH is suggested by neuroimaging studies, but it is currently unclear whether white matter lesions represent separate pathologic substrates of VCI.

- Some studies have not shown clear associations between neuropathologic measurements of white matter lesions and cognitive function, unless they were part of a combined vascular score that also included infarcts.
## CAA and Hereditary Small-Vessel Syndromes

<table>
<thead>
<tr>
<th>Gene/Protein</th>
<th>Condition</th>
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<tbody>
<tr>
<td>APPb - amyloid precursor protein</td>
<td>Familial CAA</td>
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<tr>
<td>Exonuclease - TREX1</td>
<td>Autosomal dominant retinal vasculopathy with cerebral leukodystrophy</td>
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<tr>
<td>TGF-b1 repressor - HTRA-1</td>
<td>Cerebral autosomal recessive arteriopathy with subcortical infarcts and</td>
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<tr>
<td></td>
<td>leukoencephalopathy</td>
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<tr>
<td>Type-IV a1 collagen subunit - COL4A1</td>
<td>Poroencephaly, ICH, and leukoencephalopathy</td>
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</table>
CAA and Hereditary SV Syndromes Recommendations

1. MRI with T2* sequences can be used to assess patients with suspected CAA (Class IIa; LOE B)
2. Notch-3 genetic testing can be used in patients with suspected CADASIL (Class IIa; LOC A)
3. Notch-3 genetic testing can be used in sporadic cases with suspected CADASIL (Class IIa; LOC A)
4. Skin on muscle biopsy looking for granular osmiophilic deposits may be considered an alternative or complementary procedure in suspected cases of CADASIL when notch-3 testing is unavailable or inconclusive (Class IIb; LOC B)
5. Treatment of cardiovascular risk factors is reasonable in suspected cases of CAA and CADASIL (Class IIa; LOE C)
6. Patients with subacute cognitive decline and suspected CAA should be treated with a course of immunosuppressive therapy (Class I, LOE B)
Neurovascular Pathologic Aspects

- IMT increases in:
  - Normal Aging
  - Blood pressure pulsality causes fragmentation and depletion of elastin and increases collagen
  - Pathological conditions
    - Medial thickening increases in response to HBP
    - Intima thickening is seen in atherosclerosis
  - IMT as associated with cognitive function
    - The thicker the artery, the lower the cognitive performance
Linking IMT to VCI

- Carotid IMT and atherosclerosis are associated with similar cardiovascular risk factors
- Atherosclerosis may cause VCI via
  - Large vessel occlusive disease with chronic hypoperfusion
  - Artery-to-artery embolism
  - Increased parenchymal oxidative stress
  - Blood pressure dysregulation affecting BBB integrity
- Systemic age-related vascular process
  - Small vessel narrowing
    - Thickening of basal membrane of capillaries
    - Perivascular collagen deposition
  - Arteriolar dysfunction
  - Endothelial leakage
- Accelerated by vascular risk factors
- Associated with arterial stiffening
- Not well studied in VCI
Neuroimaging

- VCI as a definable syndrome
  - Stroke or subclinical vascular brain injury based on clinical presentation or neuroimaging
  - Impairment of at least 1 cognitive domain
- VCI’s classic presentation
  - Stepwise progression in association with clinical stroke(s)
  - Relatively uncommon considering that asymptomatic brain infarction is more common than clinical stroke
Prevalence of silent cerebral infarction

- 05.8-17.7% based on MRI findings in the general population

**Framingham study**

- **Age related process**
  - 5\textsuperscript{th} and 7\textsuperscript{th} decade: 10%
  - 8\textsuperscript{th} decade: 17%
  - 9\textsuperscript{th} decade: 30%

- **Lesion location**
  - Basal ganglia: 52%
  - Other subcortical areas: 35%
  - Cortical areas: 11%
Progressive leukoaraiosis or silent brain ischemia correlate with persistent cognitive impairment, especially executive function.

- Stroke
  - Doubles the risk of dementia
  - Dementia post stroke is associated with 2- to 6-fold increase in long-term mortality
  - The prevalence of dementia post stroke is 30%
Radiological predictors of VCI
- Silent cerebral infarcts, WMH, and global atrophy, and medial temporal lobe atrophy
- Location of the stroke
  - Left hemisphere, anterior and posterior cerebral artery distribution, and multiple infarcts
  - “Strategic location” of the infarct
    - Left angular gyrus, inferomesial temporal, mesial frontal, anterior and dorsomedial thalamus, left capsular genu, and caudate nuclei
- 19-61% of VCI patients may have concomitant AD
Role of Neuroimaging in VCI

- Role of brain MRI in VCI is not well defined
  - High sensitivity--Can detect asymptomatic vascular abnormalities such as LA and CMBs
  - Limited accuracy
    - WM changes may be not vascular in origin
    - Not all vascular lesions can be detected by current state-of-the-art MRI
    - Confounded by coincident AD or vascular depression
- Recommendation: Use of brain MRI or head CT may be reasonable in making the diagnosis of VCI (Class IIb; LOE B)
Risk Factors

- Included studies addressing the range of VCI
- Studies generally included tests that conform to the NINDS-CSVCI harmonization standards, reported at the minimum one non-memory cognitive test of a function typically affected in VCI, or a diagnosis of VCI or VaD
Like most neuro-cognitive disorders of late life, VCI is likely to be more common as age increases.

- There is no apparent association of APO E ε4 and VCI.
- More genetic candidates are expected to emerge as additional studies on endophenotypes of VCI are studied.
- These traits include specific cognitive domains such as speed of processing, vascular (macrovascular and microvascular) lesions.
The following lifestyle interventions in persons at risk for VCI are suggested:

- Smoking cessation (Class IIa, LOE A)
- Moderation of alcohol intake (Class IIb, LOE B)
- Weight Control (Class IIb, LOE B)
- Physical Activity (Class IIb, LOE B)
- The use of antioxidants and B vitamins in persons at risk for VCI are not useful based on current evidence (Class III, LOE A)
The following **physiologic risk factors** in persons at risk for VCI should be considered:

- Midlife systolic and diastolic BP, history of HBP, and total cholesterol level predict VCI
- DM and hyperglycemia are associated with VCI
- CRP, a marker of inflammation, is associated with VaD
Treatment of the following **physiologic factors** in persons at risk for VCI should be considered:

- Hypertension (Class I, LOE A)
- Hyperglycemia (Class IIb, LOE C)
- Hypercholesterolemia (Class IIb, LOE A)
- It is uncertain if treatment of inflammation will reduce the risk of VCI in persons at risk of VCI (Class IIb, LOE C)
Concomitant Vascular Disease

- Preventable chronic vascular conditions have been linked to dementia
  - CAD
  - Chronic Kidney Disease
  - Stroke
  - AFIB
  - PAD
  - CHF, low CO
- Some of them may cause VCI directly, by brain damage (stroke), or indirectly
- **CAD**
  - Independent risk factor for VCI
  - CABG is associated with poorer cognitive function and higher late-life dementia

- **Chronic Kidney Disease (CKD)**
  - Patients with CKD have increased prevalence of cognitive impairment
  - The association between CKD and cognitive impairment may be confounded by shared vascular risk factors for stroke
Stroke

- Dementia is common after stroke
  - 10% of new and 30% of those with recurrent stroke may develop new-onset dementia
- Variables that may affect these observations
  - Location, clinical severity, volume of brain tissue affected, early post-stroke complications (e.g., seizures, hypotension, hypoxia, and delirium)
  - Pre-stroke cognitive impairment, DM, low level of education, AFIB
  - Previous stroke is one of the strongest predictors of post-stroke dementia
AFIB
- Increases the risk of stroke
- Proposed as an independent risk factor for VCI, though a few studies have not observed a direct association

PAD and low CO
- Both have been associated with VCI
- Low CO may affect cerebral perfusion leading to progression of WMH and cognitive decline
## Treatment Options: VCI

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<tr>
<th>Treatment</th>
<th>Recommendation, Class/Level of Evidence</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Donepezil</td>
<td>Level A, Class IIa for “pure” VaD</td>
<td>Study 307, 308 (N=1219): modest benefit for cognitive &amp; global, less robust for function; Study 319 (N=974): only cognitive benefit</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Level A, Class IIa for mixed AD-CVD; Class IIb for “pure” VaD</td>
<td>Pure and mixed VaD Gal-Int-6 (N=592): benefit in all primary outcomes overall; “Pure” VaD (Gal-Int-26 – N=788): modest benefit in cognitive/executive measures</td>
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<tr>
<td>Rivastigmine Memantine</td>
<td>Level C, Class IIb</td>
<td>VCIND study (N=50): modest benefit in some executive functions (N=900): modest cognitive benefit only</td>
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</table>
**Donepezil**

- There is pathological and clinical evidence for cholinergic compromise in VCI, as in AD
- In donepezil trials, cognitive benefit was found, but global and functional efficacy was less consistent
- Donepezil side effect profile is similar to AD-donepezil trials
- A recent trial with CADASIL patients was neutral; post-hoc analyses showed a beneficial effect in executive function measures
Galantamine

- Showed benefit in a mixed (AD + CVD) sample, but not in an under-powered “pure” VCI group
- A second, larger study showed cognitive benefit, a trend for global benefit ($p = .06$), but no ADL benefit
Rivastigmine and Memantine

- Rivastigmine has been less well studied, with promising preliminary beneficial effects seen in two small samples
- Memantine, an NMDA antagonist, has shown cognitive, but not global or functional benefit
Cochrane Review and Meta-analysis
Conclusion of VaD Trials

- Donepezil studies have provided the best evidence for a beneficial effect for VaD
- Galantamine studies have provided best available evidence for a beneficial effect for mixed dementia (AD + CVD)
- Memantine and rivastigmine benefit is not yet proven
- A meta-analysis comments that the cognitive benefits of cholinergic agents and memantine are of uncertain significance in VaD
Future Directions

- More clinical trial evidence would be helpful, including pharmaco-economic evaluations.
- Future studies should use updated case selection and outcome criteria, including more sensitive executive function measures.
- Use of advanced neuroimaging biomarkers that better define atrophy and vascular brain injury is recommended.
- Amyloid labeling and/or cerebrospinal fluid markers might be considered to detect concomitant AD pathology.
Pharmacologic Treatment of VCI: Recommendations

1. Donepezil can be useful for cognitive enhancement in patients with VCI (Class IIa, LOE A)
2. Administration of galantamine can be beneficial for patients with mixed AD/VCI (Class IIa, LOE A)
3. The benefits of rivastigmine and memantine are not well established (Class IIb, LOE A)
- Few non-pharmacologic therapies have been tested and found to be beneficial in the VCI population
- Cognitive rehabilitation/cognitive stimulation have not proven effective, though there are few randomized controlled trials and many methodological limitations in this area
- Acupuncture in human VaD was inconclusive
- No formal recommendations are offered for non-pharmacologic treatments, as evidence is limited
Prevention of VCI and AD by Risk Factor Control

- Even a modest delay in the appearance or worsening of cognitive deterioration could translate into a relatively large reduction of the incidence of disease.
- Midlife vascular and metabolic risk factors should be regarded as potential major targets for dementia prevention.
- Safeguarding normal cognitive development during childhood and adolescence (e.g., through proper nutrition) may also be an important preventative factor of later cognitive decline and impairment.
Blood Pressure Lowering and Cognition

- Observational studies point to some benefit of anti-hypertensive treatment on risk of AD
- Few large blood pressure lowering trials have incorporated cognitive assessment or dementia diagnosis
- Meta-analyses neither prove nor disprove the efficacy of anti-hypertensive treatment on dementia risk
BP Recommendations

1. In patients with stroke, lowering blood pressure is effective for reducing the risk of post-stroke dementia (Class I, LOE B)

2. There is reasonable evidence that, in middle-aged and young-elderly, lowering blood pressure can be useful for the prevention of late-life dementia (Class IIa, LOE B)

3. The usefulness of lowering blood pressure in individuals age 80+ is not well-established (Class IIb, LOE B)
Persons with diabetes of long duration are at risk for cognitive decline and dementia.

Both hyperglycemia and hyperinsulinemia are associated with cognitive dysfunction and stroke dementia.

Hyperglycemia treatment has been associated with prevention of both microvascular and macrovascular events.

No studies have specifically investigated possible protective effects of hyperglycemia control on VCI.

There is no convincing evidence relating type or intensity of diabetic treatment to the prevention or management of cognitive impairment in type 2 diabetes.
The effectiveness of treating DM/hyperglycemia for the prevention of dementia is not well established (Class IIb, LOE C)
Lipids

- Treatment with statin therapy has been documented to protect from stroke
- However, statin therapies do not prevent cognitive decline in the elderly
- There is need for additional studies on the role of hyperlipidemia in cognitive impairment
Lipids Recommendation

- The usefulness of hyperlipidemia for prevention of dementia is uncertain (Class IIb, LOE C)
Aspirin

- The few observational studies that have examined the effect of aspirin on cognition have shown inconsistent results.
- In both the AAA and PRoFESS trials, aspirin therapy was not found to affect cognitive outcomes.
Other Interventions on Vascular Factors: Lifestyle

- There is a relationship between adherence to a Mediterranean diet and better cognition and lower dementia risk.

- Increased physical activity has been associated with better cognitive function and in cognitive improvement in one small intervention study.

- There are no intervention studies relating smoking cessation to better cognitive outcomes.
Folic acid study results are mixed

- No cognitive benefits were shown to be associated with folic acid supplementation in a study with older healthy women or in a separate study with patients with mild to moderate cognitive decline and different forms of dementia.

- However, a third study found improved cognitive function in domains that tend to decline with age in subjects who took 800 mg daily oral folic acid compared to placebo.
Recommendation

- A Mediterranean-type dietary pattern has been associated with less cognitive decline in several studies (Class IIb, LOE B)

- Vitamin supplementation is not proven to improve cognitive function, even if homocysteine levels have been positively influenced, and its usefulness is not well established (Class IIb, LOE B)
Physical activity might be considered for the prevention of cognitive impairment (Class IIb, LOE B), but the usefulness of other lifestyle or vitamin interventions are uncertain (Class IIb, LOE B)

Effectiveness of antiaggregant therapy for VCI is not well established (Class IIb, LOE B)
Summary and Course of Action

- In developed countries, we anticipate a rapid increase in the aged population; an estimated 2 billion persons aged 60 or over by 2050
- Dementia affects an estimated 30% of persons over 80 years of age
Identification of persons at risk for cognitive impairment and dementia hold promise for prevention or postponement of dementia, resulting in increased functional independence of older persons and for public health cost savings.

Cognitive function and its relationship to CVD and stroke risks should be screened for in clinical practice and these risk factors should be treated.
- It is now accepted that many traditional risk factors for stroke are also risk markers for AD and VCI.
- There may be a convergence of pathogenic mechanisms in vascular and neurodegenerative processes which cause cognitive impairment (e.g., an angiogenesis hypothesis for AD).
- Epidemiologic studies also point to linkages between traditional CV risk factors and AD risk.
More “upstream targets,” such as shared vascular risk markers, extrinsic (e.g., somatic and mitochondrial mutations) and intrinsic (e.g., telomere shortening) mechanistic pathways which may influence prevention outcomes
We might consider that AD is actually a group of disorders that could be driven by different pathophysiological mechanisms, some of which include vascular risk factors such as HBP, DM and dyslipidemia.
Consider efforts to better understand “covert” brain injury, such as “silent” strokes and white matter lesions, as they may be associated with neuropsychological deficits and eventual stroke sequelae.