Vascular cognitive impairment

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DISCLOSURE

Relevant Financial Relationship(s)
None

Off Label Usage
Acetylcholinesterase inhibitors

Outline

• Background
• Review Epidemiology
• To recognize the heterogeneity of presentation
• Discuss how advances in neuroimaging have improved our understanding of vascular cognitive impairment
  • Amyloid PET
  • Functional imaging
  • Microinfarcts
• Review clinical cases
• Review treatment of vascular cognitive impairment
What is vascular dementia (VaD)?

History

Our understanding of this disease process has evolved over time.

Diagnostic Criteria

- The heterogeneity of vascular diseases makes a unifying criteria difficult.
- For many years, the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN) criteria were used.

Probable vascular dementia

1. Dementia
2. Evidence of cerebral vascular disease
   A. Focal examination findings consistent with stroke but history of stroke not necessary
   B. CT or MRI evidence of infarcts, including multiple large-vessel infarcts, single strategically placed infarct, or multiple basal ganglia or white matter lacunes
3. Onset of dementia within 3 months after stroke or abrupt, step-wise course, or abrupt cognitive decline

Based on NINDS-AIREN criteria (Roman, Tatemichi et al. 1993)

Diagnostic Criteria

- Shown to be specific, but not sensitive
- Overlooked infarcts that were clinically silent
- In fact, the clinical diagnosis of "probable VaD" compared to subsequent pathologic confirmation was 20%

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The term VCI characterizes all forms of cognitive deficits from VaD to MCI of vascular origin

AHA/ASA Scientific Statement

Vascular Contributions to Cognitive Impairment and Dementia

A Statement for Healthcare Professionals From the American Heart Association and the American Stroke Association

The American Heart Association affirms the value of this question as an educational tool for practitioners.

The Alzheimer's Association participated in the development of this statement to enhance knowledge and understanding of the course of dementia and the factors that contribute to its progression.
Epidemiology

- Rotterdam study: Conservative NINDS-AIREN criteria
  - Ages 60-64 years: 0.1 per 1000 person years
  - Ages 90-94 years: 7.0 per 1000 person years (men > women)

- Rochester, MN study: Dementia cases at autopsy
  - 13% pure vascular dementia
  - 12% had significant vascular and AD pathology


Rush Memory and Aging Project: Vascular disease played an important role in 54.1% of dementia cases
  - 38.0%: AD and infarcts
  - 30.0%: Pure AD
  - 12%: Infarcts alone
  - 4.1% AD with infarctions and LBD

Schneider, J. et al. 2007 Neurology

Dementia risk after stroke
  - 9 times greater than expected
  - Risk 2x control even if:
    - There was no dementia the first year after stroke
    - Silent infarct

Secondary Prevention of Small Subcortical Strokes trial
  - 47% had mild cognitive impairment even in the absence of physical disabilities related to the stroke

Steenkens, S et al. 2003. The Netherlands Journal of Medicine, 60, 725-32
Clinical Presentation

- No typical clinical presentation; wide variety of features

<table>
<thead>
<tr>
<th>Condition</th>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large territory stroke</td>
<td>Focal signs on exam</td>
</tr>
<tr>
<td>Cerebral small vessel disease</td>
<td>Gait disturbance, cognitive slowing, and parkinsonism</td>
</tr>
<tr>
<td>Mixed AD and VaD</td>
<td>Amnestic syndrome indistinguishable from typical AD</td>
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</tbody>
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Neuropsychology

- No single neuropsychologic profile
  - A pattern emerges when studying groups of VCI patients
  - Executive > Memory
  - More difficulty with tasks of cognitive speed


Amyloid PET in Vascular Cognitive Impairment
Myth: VaD does not exist without AD

- Six cases of pure VaD found among 1,929 autopsied patients from 10 university medical centers
- Multi-infarct dementia unaccompanied by neuropathologic evidence of AD is rare

Myth: VaD does not exist without AD

- Amyloid PET was used in 45 patients with subcortical vascular dementia
- Two-thirds of cases were negative for amyloid deposition
  - Pure VaD phenotype can be appreciated antemortem

Amyloid imaging: Cerebral Amyloid Angiopathy

- Amyloid PET detects cerebrovascular beta-amyloid
- Amyloid PET signal increased at microbleed sites
- CAA-related bleeds occur at sites of increased amyloid deposition
- Amyloid burden in CAA but not AD dementia correlates with WMH volume
Amyloid imaging: Cerebral Amyloid Angiopathy

- Compared amyloid PET in ICH related to probable CAA (Boston Criteria, n = 10) and HTN-ICH (n = 9) without dementia
- Mean global cortical amyloid uptake was higher in CAA than HTN-ICH (SUVR: 1.41 vs 1.15 p = 0.001)
- Mean occipital SUVR (1.44 vs 1.17 p < 0.001)
- Visual read positive for 10/10 patients with CAA vs 1/9 HTN-ICH

Illustrative cases

White matter hyperintensity

- Initially thought to be of indeterminate significance but is increasingly recognized as detrimental
  - Lower cognitive and lower extremity function
  - Impaired executive function and episodic memory
  - Decline in gait, progression to disability, decreased cognitive speed and incident depression
Mixed Pathology

- Probably the most important subgroup of VCI
  - Coexistence of vascular pathology modifies clinical expression of dementia
  - Requires a lower AD pathology burden to develop dementia

- Baltimore Longitudinal Study of Aging
  - OR for dementia was significantly increased by the presence of an infarct (4.0; [CI], 2.1–7.8)
  - Independent of whether the infarct was symptomatic

<table>
<thead>
<tr>
<th>AD and non-AD Pathologies when Probable AD Dementia is Clinical Diagnosis</th>
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<tbody>
<tr>
<td>Community Cohort</td>
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<tr>
<td>------------------</td>
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<tr>
<td>NIA Reagan High AD</td>
</tr>
<tr>
<td>NIA Reagan Intermed AD</td>
</tr>
<tr>
<td>Infarcts (any)</td>
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<tr>
<td>Lewy Bodies (any)</td>
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<tr>
<td>One pathology only</td>
</tr>
<tr>
<td>Mixed pathologies</td>
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<tr>
<td>FTLD or other atypical pathology</td>
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</table>
Microinfarcts

- Contribute to dementia as much as macroscopic infarcts
- They are defined pathologically as infarcts that are not visible on gross tissue, but are found microscopically
- The population attributable risk of dementia for microinfarcts was 33%


Microinfarcts

- Macroinfarcts, WMH, and hemorrhages correlate with presence of microinfarcts
- 1 microinfarct on 9 routine pathologic specimens indicates the presence of 100s more
- Increase rate of atrophy independent of AD pathology in a watershed distribution


Microinfarcts

- Possible cerebral microinfarcts identified on 7 and 3T MRI in vivo
- Ex vivo 7T MRI with histopathologic confirmation of microinfarct
- Prevalence 30% to 40% of population in vivo at 7T MRI
- Subset seen on 3T MRI

Microinfarcts

- Evaluated CMIs on 3 Tesla MRI
- Nondemented elderly (72–80 years) with hypertension
- Lesion <5 mm in diameter, and restricted to the cortex
- Identified CMIs on 3T MRI in 6%

Van Dalen et al. Stroke 2015

Microinfarcts

- The definition of microinfarct size varies greatly
  - Smallest criteria at 50-400μm to the largest criteria at ≤5mm
- Imaging studies have investigated imaging large cortical microinfarcts (1-3mm) on MRI
- These studies aimed to detect microinfarcts in vivo since microinfarcts impact cognition
- Pathologically, microinfarcts have a mean diameter of ~0.2mm.
- The large (>1mm) lesions that these studies capture represent a small fraction of pathology identified microinfarcts
- Therefore, we are still only able to see a small fraction of the overall burden with clinical MRI

van Dalen, J.W., et al. 2015 Stroke

Treatment

- Should focus on identifying and managing hypertension, diabetes mellitus, atrial fibrillation and hyperlipidemia
- Aggressive treatment seems logical but few prospective trials exist
In the active treatment group at two years, blood pressure was decreased by 8.3 mmHg on average and the incidence of dementia was reduced from 7.7 to 3.8 cases per 1000 patient-years.

**Systolic Hypertension in Europe trial**
- Double-blind placebo-controlled
- Non-demented subjects
- > 50 years old
- Baseline systolic blood pressure over 160 mmHg

**Aggressive blood pressure management**
- n=1238

**Placebo**
- n=1180


**Treatment**

• **Perindopril Protection Against Recurrent Stroke Study**
  - Randomized, double-blind, placebo-controlled trial
  - Investigated anti-hypertensive treatment in patients with prior stroke or TIA
  - Cognitive decline occurred in 9.1% of patients on treatment and in 11.0% on placebo

**TZOURIO, C., et al. 2003.** Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Archives of internal medicine, 163, 1069-75.

**Treatment**

- **Acetylcholinesterase inhibitors**
  - Improve cognitive function to a small degree in patients with VCI

- **SSRIs**
  - Can improve neuropsychiatric symptoms such as depression and pseudobulbar affect

- **Dextromethorphan/quinidine**
  - Recently been approved by the FDA for treatment of pseudobulbar affect
Treatment

• PREDIMED Study
  • Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events (HR = 0.70)
  • Mediterranean diet supplemented with olive oil or nuts is associated with improved cognitive function

Conclusions

• Our understanding of Vascular dementia has evolved
• Heterogenous types of vascular cognitive impairment exist
• Following stroke patients for cognitive decline is important
• Advances in neuroimaging will allow for better diagnosis, prognosis
• Treating vascular risk factors is logical but more data is needed

Questions & Discussion