Overview

1. Historical background
2. Diagnostic criteria
3. Difficulties with VaD
4. Epidemiology
5. Aetiology
6. Assessment
7. Management
Historical background (I)

- 600 – Term dementia (Latin “de mens” without mind (Isadore) coined)
- 1642 - Dementia “post apoplexy (stroke)” described (Willis)
- Up to 1960s dementia seen as consequence of ageing, due to ‘vascular’ disease
- 1889- A Alzheimer Senile Dementia (“hardening of arteries”)
Historical background (II)

- 1907 Alzheimer described first case AD in 51 y.o. female ("presenile dementia")
- ‘Alzheimer’s disease’ (characteristic pathology) originally thought to be ‘presenile dementia’
- 1968, AD recognised as main cause dementia in late life (Blessed, Tomlinson and Roth)
Historical background (III)

- 1974 – Multi-infarct dementia (MID) coined (Hachinski). ICD and DSM based on this
- 1980’s/90’s – MID just one of many causes of Vascular dementia (e.g. subcortical disease)
- 2003 – Broader term Vascular Cognitive Impairment preferred to dementia (the “memory” issue), includes all subtypes, e.g. “vascular MCI” and VaD
DSM-IV Criteria for VaD

1. Multiple Cognitive Deficits including amnesia
2. Significant impairment in social or occupational functioning which is a change
3. Presence of focal neurological signs and symptoms or laboratory evidence (=neuroimaging) of cerebrovascular disease judged to be aetiologically related to dementia (stepwise decline dropped)
4. Deficits not only during a delirium
ICD-10 Criteria for VaD

1. Dementia (multiple cognitive deficits including amnesia, clear consciousness, impaired functioning, change)
2. Uneven distribution of cognitive deficits
3. Abrupt onset or stepwise deterioration
4. Presence of focal neurological signs and symptoms of cerebrovascular disease judged to be aetiologically related to dementia

NB: No neuroimaging criteria
NINDS-AIREN Criteria
(Roman et al, 1993)

- Dementia (memory and 2 or more domains)
- Cerebrovascular disease (focal neurology and CVD on brain imaging)
- Link between the 2 (3 months or abrupt/fluctuating clinical course)
- **Possible** VaD if brain imaging negative or relationship (3/12) not clear
Difficulties with these diagnostic criteria

1. Problems with criteria
2. Inherent in VaD
Problems with criteria

1. Biased towards AD
2. Not validated and unreliable
Biased towards Alzheimer’s disease

- Standard dementia criteria make amnesia mandatory
- Executive dysfunction is characteristic of CVD
- Attentional deficits also more prominent in VaD
- Cognitively and functionally impaired may not meet dementia criteria
Comparability and interrater reliability of clinical criteria for VaD (Chui et al 2000)

‘Sample’: 25 case vignettes of varying types of cognitive impairment

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Int rater</th>
<th>DSM IV</th>
<th>HIS</th>
<th>ADDTC</th>
<th>NINDS-AIREN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>26%</td>
<td>25%</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.6</td>
<td>0.6</td>
<td>0.4</td>
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</tbody>
</table>
# Sensitivity and Specificity of NINDS-AIREN Criteria (Gold et al 2002)

<table>
<thead>
<tr>
<th>Diagnostic criteria (neuropathology)</th>
<th>VaD (20)</th>
<th>AD (46)</th>
<th>Mixed (23)</th>
<th>Sens</th>
<th>Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDS/AIREN probable</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>.20</td>
<td>.93</td>
</tr>
<tr>
<td>NINDS/AIREN Possible</td>
<td>11</td>
<td>4</td>
<td>7</td>
<td>.55</td>
<td>.84</td>
</tr>
<tr>
<td>DSM-IV</td>
<td>10</td>
<td>5</td>
<td>6</td>
<td>.5</td>
<td>.84</td>
</tr>
<tr>
<td>ICD-10</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>.2</td>
<td>.94</td>
</tr>
</tbody>
</table>

Gold et al 2002
Inherent difficulties with VaD

1. Variety of vascular diseases and anatomical locations for diseases
2. Mixed pathology (AD/DLB/VaD) is common and increasingly so with increasing age
3. But pure VaD is not common
TWO MAJOR FORMS OF CVD

Large-vessel disease
Cardiac embolic events

Large cortical and subcortical infarcts

Small-vessel disease

Small subcortical infarcts
Diffuse white matter lesions
Different types of cerebrovascular disease (1)

- Ischaemic infarct
- White matter ischaemia
- SIVD - lacunar state
Different types of cerebrovascular disease (2)

Multi-infarct dementia (MID)

SIVD - WMLs CADASIL

Thalamic infarcts
Pure Vascular Dementia is not common
Neuropathology from NIH dementia series

- AD (+DLB): 40%
- Mix- Lge VLs: 10%
- Mix- Small VLs: 2%
- pure VaD: 8%
- other: 10%
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>VaD (%)</th>
<th>Pure VaD (%)</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galasko et al. (1994)</td>
<td>170</td>
<td>9</td>
<td>2</td>
<td>AD Research Centres</td>
</tr>
<tr>
<td>Drach et al. (1997)</td>
<td>59</td>
<td>27</td>
<td>12</td>
<td>Nursing home</td>
</tr>
<tr>
<td>Hulette et al. (1997)</td>
<td>1,929</td>
<td>0.6</td>
<td>0.3</td>
<td>CERAD study</td>
</tr>
<tr>
<td>Bowler et al. (1998)</td>
<td>122</td>
<td>6</td>
<td>3</td>
<td>Memory disorders clinic</td>
</tr>
<tr>
<td>Holmes et al. (1999)</td>
<td>80</td>
<td>29</td>
<td>9</td>
<td>Dementia register</td>
</tr>
<tr>
<td>Lim et al. (1999)</td>
<td>134</td>
<td>34</td>
<td>3</td>
<td>AD patient registry</td>
</tr>
<tr>
<td>Duara et al. (2000)</td>
<td>307</td>
<td>16</td>
<td>4</td>
<td>Dementia brain bank</td>
</tr>
<tr>
<td>Barker et al. (2002)</td>
<td>384</td>
<td>18</td>
<td>3</td>
<td>Memory clinics, GP</td>
</tr>
</tbody>
</table>
White Matter Hyperintensities in the Forties: Their Prevalence and Topography in an Epidemiological Sample Aged 44–48

Lesson: Presence of WMH should NOT be used to diagnose VaD
‘Mixed dementia’ is common

- CVD, AD and LBD are all common and age related pathologies
- In the ‘old-old’ (80s & 90s) two or more such pathologies are frequently found at autopsy
- Clinically, an AD-type presentation with stroke before or after is regularly seen
Snowdon et al, JAMA, 1997, Nun Study

Open circle = no infarcts
Solid circle = 1 or more infarcts
Epidemiology

- Second most common cause of dementia (AD 60%, VaD 20%, DLB 15%)
- Rates rise with age (double 5.3y) as for AD (double 4.5y) (Jorm et al, 1987; 2003)
- Prevalence higher in Asia (38%) (Fratiglioni et al, 1999)
- Males > females, but females “catch up” at older ages (Jorm and Jolley, 1998)
- Dementia 3/12 after stroke in 15-30%. A further 20-25% develop delayed dementia.
Aetiology of VaD

- Stroke (but no clear link with location)
- Hypertension (in mid-life)
- Hypotension (in late-life)
- Hyperlipidaemia (in some studies)
- Diabetes (& ‘metabolic syndrome’)
- Smoking (and probably other vrf’s)
- Genetic causes (rare)
- But age is strongest ‘risk factor’
# Inheritance of Cerebrovascular disease

<table>
<thead>
<tr>
<th>Group</th>
<th>Specific types</th>
<th>Genetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke(s)</td>
<td>CADASIL, CARASIL, RVCL (HERNS, CRV,HVE)</td>
<td>Notch 3, other genes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TREX1 gene</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>Familial Binswanger’s/</td>
<td>unknown</td>
</tr>
<tr>
<td>angiopathies</td>
<td>Leukoencephalopathies</td>
<td></td>
</tr>
<tr>
<td>Amyloid</td>
<td>Icelandic, Dutch, Flemish, Prion, Finnish, Hungarian, British, Danish, Others</td>
<td>Cystatin C, AβPP, PrP, Gelsolin, TTR, BRI</td>
</tr>
<tr>
<td>angiopathies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other angiopathies</td>
<td>Moyamoya disease</td>
<td>Gene unknown/ Chr 3</td>
</tr>
<tr>
<td>Aneurysms</td>
<td>Sacular (berry), large aneurysms</td>
<td>Genes unknown (also congenital forms)</td>
</tr>
<tr>
<td>Vascular malformations</td>
<td>Cavernous angiomas</td>
<td>KRI1 &amp; other genes on Chr 7 and 3 loci</td>
</tr>
<tr>
<td></td>
<td>Cavernous malformations</td>
<td></td>
</tr>
</tbody>
</table>
Assessment of Vascular Dementia
Clinical features of Vascular dementia

• Course: variable, classically abrupt onset of CI, stepwise deterioration but commonly gradual
• Symptoms and signs- focal signs, motor/sensory deficits, bulbar, gait; depression, anxiety
• Neuropsychometric findings- Executive dysfunction (vs memory and language function); attentional deficits
• Depression relatively common; emotional lability common
• History of vascular disease: CHD, AF, TIA, PAD etc
• Imaging- CT/MRI- focal infarcts (70-90%); WMLs (70-100%)
• SPECT or PET- decreased CBF; patchy
• EEG- compared to AD usually normal
• Laboratory- changed cardiovascular disease markers
1. Establish presence of dementia
2. Careful history and physical assessment for evidence of CVD (stroke; falls; paresis etc)
3. Physical investigations: high BP or cholesterol; infarct(s) on neuroimaging
4. Determine (as far as possible) relationship between CVD and dementia (by pattern of onset)
5. Prominent executive dysfunction, attentional deficits, slowed information processing suggest VaD more likely
6. Mood changes, emotional lability and disinhibited behaviour are also more characteristic of VaD
# Cache County Study

Lyketsos et al, 2000 (n=5092)

<table>
<thead>
<tr>
<th>Neuropsychiatric Inventory Item</th>
<th>Participants With Alzheimer's Disease (N=214)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Participants With Vascular Dementia (N=62)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Item Absent</td>
<td>Item Present</td>
</tr>
<tr>
<td>Domain</td>
<td>N     %</td>
<td>N     %</td>
</tr>
<tr>
<td>Delusions&lt;sup&gt;b&lt;/sup&gt;</td>
<td>161  75.2</td>
<td>48  22.4</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>180  84.1</td>
<td>28  13.1</td>
</tr>
<tr>
<td>Depression&lt;sup&gt;c&lt;/sup&gt;</td>
<td>17   7.9</td>
<td>43  20.1</td>
</tr>
<tr>
<td>Anxiety</td>
<td>175  81.8</td>
<td>31  14.8</td>
</tr>
<tr>
<td>Apathy</td>
<td>150  70.1</td>
<td>61  28.5</td>
</tr>
<tr>
<td>Irritability</td>
<td>168  78.5</td>
<td>43  20.1</td>
</tr>
<tr>
<td>Elation</td>
<td>213  99.5</td>
<td>1    0.5</td>
</tr>
<tr>
<td>Agitation/aggression</td>
<td>163  76.2</td>
<td>48  22.4</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>194  90.7</td>
<td>17  7.9</td>
</tr>
<tr>
<td>Aberrant motor behavior</td>
<td>173  80.8</td>
<td>36  16.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>79   36.9</td>
<td>114  53.3</td>
</tr>
</tbody>
</table>

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<sup>a</sup> Numbers across columns do not add up to total N and percents do not add up to 100% in some cases because of missing data.

<sup>b</sup> Participants with Alzheimer’s disease were more likely to have delusions (odds ratio=3.15, 95% confidence interval [CI]=0.19–0.52, \( \chi^2 = 5.36, \) df=1, p=0.02).

<sup>c</sup> Participants with vascular dementia were more likely to have depression (odds ratio=1.93, 95% CI=1.01–3.67, Wald \( \chi^2 = 4.17, \) df=1, p=0.04).
Prevalence of neuropsychiatric Features after stroke  
(Angelelli et al, 2004)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Healthy Controls (n=61)</th>
<th>Post-stroke patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2 months (n=45)</td>
</tr>
<tr>
<td>Delusion</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Hallucination</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Agitation</td>
<td>0.2</td>
<td>1.5**</td>
</tr>
<tr>
<td>Depression</td>
<td>0.3</td>
<td>2.9***</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.3</td>
<td>1.6***</td>
</tr>
<tr>
<td>Euphoria</td>
<td>0.0</td>
<td>0.6**‡</td>
</tr>
<tr>
<td>Apathy</td>
<td>0.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>0.0</td>
<td>0.6</td>
</tr>
<tr>
<td>Irritability</td>
<td>0.3</td>
<td>2.0**</td>
</tr>
<tr>
<td>Aberrant motor behaviour</td>
<td>0.0</td>
<td>0.8***§</td>
</tr>
</tbody>
</table>

NB: Mood lability
Structural imaging should be used to exclude other cerebral pathologies and to help establish the subtype diagnosis. MRI is preferred modality to assist with early diagnosis and detect subcortical vascular changes, though CT can be used.

HMPAO SPECT should be used to help differentiate between AD, VaD and FTD if the diagnosis is in doubt.

CSF measurement should not be used as routine investigations.
Management of Vascular Dementia
Chui and Gonthier (1999)

- Review of 13 papers ($n = 470$)
  - significantly shorter survival in multi-infarct dementia than compared to AD

- Review of 9 studies ($n = 175$)
  - no consistent differences in rate of decline of cognitive progression between AD and VaD
1. Preventative Studies (Secondary prevention)

2. Treatment Studies (Tertiary Prevention)
Preventative Studies

- In theory, modifying vrfs/vascular diseases should reduce VCI/VaD

- However, findings overall from studies directly assessing this are disappointing

- Frailty and co-morbidity in patients may mean extrapolation from studies in stroke and CHD are not appropriate
Aspirin in VaD
(Meyer et al, 1989)

- 70 with MID randomised to 325mg aspirin (n=37) or no treatment (n=33)
- Followed annually for 3 years
- Aspirin treated patients had significantly higher cognitive performances c/w no treatment
- Criticisms: low numbers, high dropout (61%), no placebo
Statins in VaD

- Small trial of atorvastatin, beneficial at 6/12 but equivocal at 12/12 (Sparks et al 2005)
- But three large RCTs have found no effect of statins on cognitive decline (Santanello et al 1997; Heart Protection Study 2002; Shepherd et al 2002)
- However, atorvastatin has different lipid solubility
Hypertension in VaD

- Only one study has shown treatment of HTn to reduce dementia incidence (Fourette et al 1998)
- >4 RCTs have shown no such benefits on dementia incidence or cognitive decline
- May relate to stage at which treatment is given (over-zealous treatment may cause hypotensive damage)
Nimodipine in subcortical VaD  (Pantoni et al, Stroke 2005)

- 242 subjects, subcortical VaD on ICD-10 and CT evidence; Nimodipine 90mg or PBO
- Primary outcome measure NS (Sandoz Clinical Assessment Geriatric scale)
- Some improvements on secondary measures (GDS, lexical memory)
- CV adverse events more frequent in placebo group (RR 2.26 (CI 1.11-4.6))
1. Preventative Studies (Secondary prevention)

2. Treatment Studies (Tertiary Prevention)
Memantine in VaD: Two published 6 month studies

- Orgogozo et al, Stroke, 2002. 321 probable VaD. ADAS-Cog improved 0.6 pts in treated group, declined 1.6 pts in placebo
- No effect on global outcome (CIBIC+)
- Wilcock et al, ICP, 2002. 579 probable VaD. Drug treated patients 1.75 pts higher on ADAS-Cog than placebo at 6 months
- No effect on global outcome (CGI-C)
Cochrane review of memantine (McShane et al 2006)

Published data from two 6 month RCTs suggest a small beneficial effect of memantine on cognition and behaviour at six months in those with mild to moderate vascular dementia, this effect was not clinically detectable.
Absence of cholinergic deficits in “pure” VaD (Perry et al 2005)

<table>
<thead>
<tr>
<th>Condition</th>
<th>ChAT activity (BA 36), nmol/h/mg of protein</th>
<th>Duration of dementia, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>VaD, n = 9</td>
<td>2.1 ± 1.0</td>
<td>3.1 ± 2.2</td>
</tr>
<tr>
<td>AD with VaD, n = 12</td>
<td>0.76 ± 0.63</td>
<td>3.2 ± 1.8</td>
</tr>
<tr>
<td>AD, n = 10</td>
<td>1.1 ± 0.77</td>
<td>3.1 ± 2.0</td>
</tr>
<tr>
<td>Control, n = 12</td>
<td>2.3 ± 0.68</td>
<td>—</td>
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</tbody>
</table>

Table: Cholinergic function in vascular dementia and Alzheimer disease
# RCTs of CHEI in Vascular dementia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cognition</th>
<th>Global</th>
<th>ADL</th>
<th>Behaviour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galantamine (Gal-INT-06) (n=121) Erkinjuntti et al, 2001</td>
<td>No (p=0.06)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Galantamine (Gal-INT-26) (n=788) Aucher et al, 2007</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Donepezil (307) (n=603) Black et al, 2003</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>Donepezil (308) (n=616) Wilkinson et al, 2003</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>Donepezil (319) (n=974) Unpublished (press release 16.3.06*)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>Rivastigmine (VantageE) (n=710) Unpublished (<a href="http://www.novartisclinicaltrials.com">www.novartisclinicaltrials.com</a>)</td>
<td>Yes (p=0.028)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Mood Disturbance in VaD

• There is little evidence demonstrating benefit from antidepressants for depression in dementia in general, including VaD

• Cochrane review concludes insufficient evidence

• Emotional lability: small case-control studies report benefits from low dose TCA and from SSRIs (typically within two weeks)
Psychosis/Aggression in VaD

- RCTs report only modest benefits from APD in dementia; best evidence is for risperidone
- All APD are associated with cognitive decline & poorer quality of life, as well as EPSE etc
- APD are associated with a small increased risk of stroke and death in dementia
- Regulatory authorities caution against their use, especially in the presence of stroke disease
- APD should only be used in severe cases after other interventions have failed
For people with vascular dementia, cholinesterase inhibitors and memantine should not be used for the treatment of cognitive decline, except as part of properly constructed clinical studies.

People with vascular dementia who develop non-cognitive symptoms or behaviour that challenges should not be prescribed cholinesterase inhibitors, except as part of properly constructed clinical studies.

Mixed dementia should be managed according to the condition that is thought to be the predominant cause of the dementia.