Vascular Cognitive Impairment and Frontal-Subcortical Dementias

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Learning Objectives

• Subcortical dementia refers to a clinical constellation of findings that result when there is damage to areas in the thalamus, basal ganglia or brain stem nuclei with resulting impairment in frontal-subcortical circuits.

• The differential diagnosis for this clinical presentation is broad but can often be narrowed down by associated clinical findings.

• The term “Vascular Cognitive Impairment” describes a spectrum of impairment ranging from VCI-ND to VCI-dementia to VCI-mixed and may present with a frontal-subcortical clinical picture.
History

- Early reports described a similar cognitive/emotional state
  - Huntington’s Disease (caudate)
  - Wilson’s Disease (putamen + globus pallidus)
  - Encephalitis Lethargica (basal ganglia)
  - Binswanger’s Disease

Turner, 2002
History

Progressive Supranuclear Palsy
– Alpert et al, 1974: case series and literature review

- Gait and eye movement disturbance
- Forgetfulness
- Slowness of thought
- Impairment in manipulating acquired knowledge
- Personality/mood changes

Huntington’s Disease
McHugh PR and Folstein, 1975
- Lack of aphasia, agnosia, amnesia
Subcortical Dementia: an emerging concept

Cummings, 1984

Pathologic changes involve:
- thalamus
- basal ganglia
- brain-stem nuclei

with sparing of the cortex
Subsequent debate re: usefulness of the term

“evidence to date suggests that intellectual dysfunction in DAT, HD, and PD may relate to a combination of cortical as well as subcortical degeneration.” Annals of Neurology, 1983

“Subcortical dementia is a CLINICAL not an ANATOMICAL concept”
## Table 2
Etiologies that cause frontal-subcortical circuit dysfunction at cortical and subcortical levels

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Cortical level</th>
<th>Subcortical level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurodegenerative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Corticobasal degeneration</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>−</td>
<td>+</td>
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<tr>
<td>Multiple system atrophy</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binswanger disease</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Stroke</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Cummings, 2002
Cortical Dementia

Aphasia
Apraxia
Agnosia
Amnesia (learning rather than retrieval deficit)
Visuospatial fxn
Frontal Cortex

http://www.indiana.edu/~p1013447/dictionary/assn_cor.htm
Subcortical Dementia

- Slowness of thought
- Poor Retrieval of memories
- Executive function deficits
- Mood abnormalities/apathy
- Motor Disturbance
Frontal Subcortical Circuits

Alexander, 1984
Frontal Subcortical Circuits: three behavioral syndromes

Tekin and Cummings, 2002

Apathy
Psychomotor retardation
akinetiic mutism

Executive
dysfunction

Impulsivity
Poor judgment
emotional lability
irritability
sexual remarks

Anterior Cingulate Cortex

Caudate

Substantia nigra

Thalamus (VA)

Dorsolateral Prefrontal Cortex

Caudate (dorsolateral)

Globus Pallidus (Lateral Dorsomedial)

Thalamus (VA and MD)

Lateral Orbitofrontal Cortex

Globus Pallidus (Medial Dorsomedial)

Thalamus (VA and MD)
Anterior cingulate syndrome in FTLD

Anterior cingulate mediates motivated behavior
Bilateral lesions can cause akinetic mutism
Abulia /apathy
loss of initiative
Impersistence, slowness, bradyphrenia
Loss of curiosity, tastes and preferences
Often mistaken for depression
May be normal on cognitive testing
Orbitofrontal Syndrome in FTLD

Personality Change

Behavioral disinhibition
  inappropriate jocularity
  hypersexuality
  impulsivity

Emotional lability
  irritability
  explosive outbursts

Poor judgement
Poor self care

Massimo, 2009
Dorsolateral Prefrontal Syndrome

- Loss of planning and internal goal-directed behavior
- Loss of behavioral plasticity
- Stimulus-boundedness; utilization behavior and other purposeless behaviors
- Paucity of thought
- Poor performance on specific cognitive testing
Figure Legend:
Basal Ganglia Disease With Neurobehavioral Symptoms [A]: executive cognitive functioning (dark gray shading); [B]: personality (medium gray shading); [C]: motivation (light gray shading).
<table>
<thead>
<tr>
<th>Frontal-Subcortical Dementia</th>
<th>Cortical Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Language</strong></td>
<td></td>
</tr>
<tr>
<td>No aphasia (anemia and comprehension deficit when dementia syndrome is severe)</td>
<td>Aphasia early</td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td></td>
</tr>
<tr>
<td>Recall impaired; recognition normal or better preserved than recall</td>
<td>Recall and recognition impaired</td>
</tr>
<tr>
<td><strong>Visuospatial skills</strong></td>
<td></td>
</tr>
<tr>
<td>Impaired</td>
<td>Impaired</td>
</tr>
<tr>
<td><strong>Calculation</strong></td>
<td></td>
</tr>
<tr>
<td>Preserved until late</td>
<td>Involved early</td>
</tr>
<tr>
<td><strong>Frontal systems abilities</strong></td>
<td></td>
</tr>
<tr>
<td>Disproportionately affected compared with other neuropsychological abilities</td>
<td>Impaired to a degree consistent with involvement of other abilities</td>
</tr>
<tr>
<td><strong>Speed of cognitive processing</strong></td>
<td></td>
</tr>
<tr>
<td>Slowed early</td>
<td>Normal until late in disease course</td>
</tr>
<tr>
<td><strong>Personality</strong></td>
<td></td>
</tr>
<tr>
<td>Apathetic, inert</td>
<td>Unconcerned</td>
</tr>
<tr>
<td><strong>Mood</strong></td>
<td></td>
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<tr>
<td>Depressed</td>
<td>Euthymic</td>
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<tr>
<td><strong>Speech</strong></td>
<td></td>
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<tr>
<td>Dysarthric</td>
<td>Normal articulation until late</td>
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<tr>
<td><strong>Posture</strong></td>
<td></td>
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<tr>
<td>Bowed or extended</td>
<td>Upright</td>
</tr>
<tr>
<td><strong>Coordination</strong></td>
<td></td>
</tr>
<tr>
<td>Impaired</td>
<td>Normal until late</td>
</tr>
<tr>
<td><strong>Adventitious movements</strong></td>
<td></td>
</tr>
<tr>
<td>Present: chorea, tremor, tics, dystonia</td>
<td>Absent (myoclonus occurs in some cases of AD)</td>
</tr>
<tr>
<td><strong>Motor speed</strong></td>
<td></td>
</tr>
<tr>
<td>Slowed</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Bonelli 2008
Bedside Testing of Executive Functioning

MMSE is not very helpful!! Supplement with
Clock Drawing
Trails
Go-no go test: green don’t tap, red tap once
Luria’s motor programs
Luria’s recursive figures
FIGURE 4 Abnormal clock drawings in VCI patients with normal Mini Mental State Exam (MMSE) scores who were asked to draw a clock and set the hands at 10 past 11.

A: 81-year-old man with 23 years of education and MMSE score of 27/30, diagnosed with mixed Alzheimer’s dementia (AD) and cerebrovascular disease (CVD).

B: 78-year-old woman with 12 years of education with an MMSE score of 25/30, diagnosed with mixed AD and CVD.

C: 75-year-old woman with 16 years of education scoring 26/30 on the MMSE, diagnosed with probable vascular dementia.

Black, 2011
Diseases Presenting with the Frontal-Subcortical Dementia Syndrome

- **Degenerative**
  - HD, PSP, PD, CBD, MSA

- **Vascular disorders**
  - Thalamic infarction
  - Subcortical Ischemic Vascular Disease

- **Metabolic disorders**
  - Wilson’s Disease

- **Demyelinating**
  - Multiple Sclerosis
  - AIDS dementia Complex

- **Misc.**
  - Normal Pressure Hydrocephalus
  - Dementia syndrome of Depression
  - Dementia Pugilistica
  - Alcoholic dementia
Vascular Dementia

< 1950’s Dementia was commonly thought to be related to vascular causes “hardening of the arteries”

1960’s-70’s: AD was thought to be the primary pathology

Now there is a greater appreciation for the intertwining of the two pathologies
Vascular Cognitive Impairment is a spectrum concept with deficits ranging from VCI-ND to mixed AD-VaD.
Cerebral infarcts increase likelihood of dementia expression in patients with AD pathology

Schneider, 2004
Risk Factors VaD

Demographic
- Age
- Male
- Lower educational level

Atherosclerotic
- HTN, Lipids, DM
- Cigarettes, MI

Genetic
- CADASIL
- apo E4

Stroke Related
- Volume of tissue loss
- Bilateral
- Strategic
- White matter disease

Shared risk factors with AD

Gorelick, 2004
Clinical Forms of Vascular Cognitive Impairment

- **Acute (poststroke)**
  - MID
  - Strategic
    - PCA
    - Basal Forebrain
    - Thalamic
    - Inferior Genu
    - Caudate

- **Subacute (subcortical)**
  - Lacunar State
  - Binswanger’s
  - CADASIL
  - CAA

(Roman, 2005)
Multi-Infarct Dementia

- Replaced older term cerebral arteriosclerosis
- VaD was thought to be the result of multiple small or large cerebral infarcts
- It was thought that a certain amount of brain tissue had to be destroyed (50-100ml)
- Now recognized as just one form of VaD

O’ Brian, 2003
Strategic

- Basal forebrain
- Caudate nucleus
- Globus Pallidus
- Angular gyrus
- Thalamus

Black, 2005
Subcortical Ischemic Vascular Disease (SIVD)

**Lacunar State**

**Binswanger’s**

Clinically homogenous $\rightarrow$ subcortical syndrome
Responsible for 36-67% of VD
Insidious onset

O’ Brian, 2003
Hypertension → Arteriolosclerosis

- Occlusion → Complete infarct → Lacune → Lacunar state
- Hypoperfusion → Incomplete infarct → White matter signal hyperintensities → Binswanger’s disease

Risk factor:
- Resultant cerebrovascular disease
- Cause of ischaemia
- Type of brain injury

Lesion on MRI:
- Clinical syndrome

Roman et al, Lancet Neurology 2002
Diagnosis: DSM IV vs 5

Dementia (DSM IV) =

Cognitive decline

Involving multiple spheres

Functional Impairment

Memory +

Executive Functioning

Language/Aphasia

Sensory/Agnosia

Motor/ Apraxia

Functional impairment = MCI or Cognitive d/o NOS (VA)
Major Neurocognitive Disorder (DSM-5)

Cognitive decline
Involving one or multiple spheres

Functional Impairment

Mild: deficits in instrumental ADL
Moderate: deficits in basic ADL
Severe: completely dependent

Learning and Memory
Executive Functioning
Language/Aphasia
Perceptual/ Motor
Complex Attention
Social Cognition

Functional impairment = Mild NCD
Behavior clearly out of acceptable social range; shows insensitivity to social standards of modesty in dress or of political, religious, or sexual topics of conversation. Makes decisions without regard to safety.
Major or Mild Vascular Neurocognitive Disorder

A. Criteria are met for major or mild NC disorder
B. The clinical features are c/w a vascular etiology
   - Either the onset of cog. deficits is temporally related to one or more vascular events or
   - Evidence for decline is prominent in complex attention and frontal-executive function
C. There is evidence of CVD from history, physical or neuroimaging considered sufficient to account for deficits
Major or Mild Vascular Neurocognitive Disorder

• Probable Vascular NCD needs one of the following
  – Clinical criteria are supported by **neuroimaging evidence** of significant parenchymal injury attributed to CVD
  – The neurocognitive syndrome is **temporally related** to one or more documented cerebrovascular events
  – Both clinical and genetic evidence of CVD is present (CADASIL)
Evaluation for vascular contribution to dementia

- History
- Physical Exam (gait, balance, extensor plantar response, pseudobulbar palsy, exaggerated DTR’s, palmar grasp)
- Blood pressure measurement
- Laboratory evaluation
  - Lipid panel/fasting glucose
- MRI
- Cognitive Evaluation
  - Tests of executive functioning/attention
Suggestive Motor Sx.

- Mild UMN signs (drift, reflex asymmetry, incoordination)
- Gait disorder (slower, small steps)
- Imbalance and falls
- Urinary frequency and incontinence
- Dysarthria
- Dysphagia
- EPS
Treatment of VaD

• Primary prevention
  – Minimize cerebrovascular and heart disease
  – Modify risk factors

• Secondary Prevention
  – Stroke management

• Disease management
  – Cognitive
  – Behavioral
  – Caregiver Support
Risk Factor Modification

- Risk Factors:
  - CAD, CHF, afib
  - HTN, orthostatic hypotension
  - CVA, TIA
  - DM, OSA, smoking
  - Hyperhomocysteinemia (not modifiable)
Psychopharmacological Intervention

• Cholinesterase Inhibitors
  – Boost acetylcholine and can have a variable effect on cognition
  – May have a similar effect in VaD compared with AD but evidence is not as strong
  – Side effects: bradycardia, nausea, GI, abnormal dreams
Cholinergic hypothesis of VaD

- Penetrating arteries most affected by HTN
- Deep nuclei, nucleus basalis of Meynert
Cholinergic hypothesis of VaD

Selden, 1998; Schwartz 2003
### Table 3. Pharmacological Treatments for VCI

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Recommendation (Class/Level of Evidence)</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Donepezil</td>
<td>Class IIa, Level A, for “pure” VaD Study 307, 308 (n=1219): modest benefit for cognitive and global, less robust for function; Study 319 (n=974): only cognitive benefit</td>
<td>“it is reasonable”</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Class IIa, Level A, for mixed Alzheimer disease—cerebrovascular disease; Class IIb for “pure” VaD Gal-Int-6 (n=592): benefit in all primary outcomes overall; only cognitive benefit in pure disease; “Pure” VaD (Gal-Int-26; n=788): modest benefit in cognitive/executive measures</td>
<td>“may be considered”</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Class IIb, Level C VCI ND study (n=50): modest benefit in some executive functions</td>
<td></td>
</tr>
<tr>
<td>Memantine</td>
<td>Class IIb, Level A n=900: Modest cognitive benefits only</td>
<td></td>
</tr>
</tbody>
</table>

Gorelick, 2011 Stroke
References


References

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