Dementia and Behavior
Neurology

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Differential Diagnosis: Top Ten
(easy mnemonic device: AVDEMENTIA)

1. Alzheimer Disease
2. Vascular Dementia
3. Drugs, Depression, Delirium
4. Ethanol
5. Medical / Metabolic Systems
6. Endocrine (thyroid, diabetes), Ears, Eyes, Environ.
7. Neurologic (other primary degenerations, fronto-temporal, consider dementia with Lewy body, Parkinson component)
8. Tumor, Toxin, Trauma
9. Infection, Immunologic
10. Autoimmune, Apnea, AAMI
Dementia etiology

- Vascular: MID
- Inflammatory: MS
- Infectious: HSE, CJD
- Tumor: frontal tumor
- Traumatic: head injury
- Idiopathic: NPH
- Metabolic: thyroid disease, B1, B12 deficiency,
- Degenerative: AD

Gold standard for degenerative etiology is Neuropathology!
Dementia clinical syndrome

- Cognitive impairment
- Memory loss
- Behavior disturbance
- Mood, personality change
- Functional impairment
- IADL, ADL dependent

D/D syndrome: delirium; psychiatric disorder; mental retard
Degenerative dementia-subtype

- Memory
- Executive
- Visuospatial

Initial stage

- PPA SD
- FTD
- PCA
- AD
Degenerative dementia-subtype

Language

PPA SD

Memory

AD

Advance stage

FTD

Executive

PCA

Visuospatial
Criteria for other degenerative dementia

• Fronto-temporal dementia:

• Dementia with Lewy body:

• Progressive aphasia syndrome:

• Posterior cortical atrophy:
Accuracy of four clinical diagnostic criteria for the diagnosis of neurodegenerative dementias

- The mean sensitivity for AD was 95%, for PSP 75%, for FTD 97%, and for DLB 34%.
- The mean specificity for AD was 79%, for PSP 98.5%, for FTD 97%, and for DLB 94%
- The generalized K for AD was 0.73, for PSP 0.82, for FTD 0.75, and for DLB 0.37
AD
Criteria for degenerative dementia

- Alzheimer’s disease: NINDS-ADRDA criteria:

Panel 2: Diagnostic criteria for AD

Probable AD: A plus one or more supportive features B, C, D, or E

Core diagnostic criteria
A. Presence of an early and significant episodic memory impairment that includes the following features:
   1. Gradual and progressive change in memory function reported by patients or informants over more than 6 months
   2. Objective evidence of significantly impaired episodic memory on testing; this generally consists of recall deficit that does not improve significantly or does not normalise with cueing or recognition testing and after effective encoding of information has been previously controlled
   3. The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances

Supportive features
B. Presence of medial temporal lobe atrophy
   - Volume loss of hippocampi, entorhinal cortex, amygdala evidenced on MRI with qualitative ratings using visual scoring (referenced to well characterised population with age norms) or quantitative volumetry of regions of interest (referenced to well characterised population with age norms)
   - Abnormal cerebrospinal fluid biomarker
     - Low amyloid β_{42} concentrations, increased total tau concentrations, or increased phospho-tau concentrations, or combinations of the three
     - Other well validated markers to be discovered in the future
C. Specific pattern on functional neuroimaging with PET
   - Reduced glucose metabolism in bilateral temporal parietal regions
   - Other well validated ligands, including those that foreseeably will emerge such as Pittsburg compound B or FDDNP
D. Proven AD autosomal dominant mutation within the immediate family

Lancet Neurology 2007;16:734-746
Revised NINCDS-ADRDA criteria (2007)
International Working Group for New Research Criteria for the Diagnosis of AD

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Supportive features

C. Abnormal cerebrospinal fluid biomarker

- Low amyloid $\beta$ 1–42 concentrations, increased total tau concentrations, or increased phospho-tau concentrations, or combinations of the three
- Other well validated markers to be discovered in the future
CSF in Alzheimer’s Disease, both MCI and Dementia patients: Low Aβ and High Tau

Revised NINCDS-ADRDA criteria (2007)

**Supportive features**

D. Specific pattern on functional neuroimaging with PET

- Reduced glucose metabolism in bilateral temporal parietal regions
- Other well validated ligands, including those that foreseeably will emerge such as Pittsburg compound B or FDDNP
18-F Fluordeoxyglucose Positron Emission Tomography (FDG-PET)

- Short-lived positron-labeled form of sugar that follows the early steps of glucose, but gets trapped in the cell
  - Fluorine-18: 120 minutes
- Under normal conditions the brain uses glucose as its sole source of energy
- Glucose metabolism primarily reflects synaptic activity
- Hypometabolism may not correspond to areas with greatest changes in routine neuropathy
- Routine neuropathology is better at detecting loss of neuronal cell bodies than synapses
Revised NINCDS-ADRDA criteria (2007)

**Supportive features**

E. Proven AD autosomal dominant mutation within the immediate family
Diagnostic Criteria for Dementia of the Alzheimer Type

A. Multiple Cognitive Deficits
   1. Memory Impairment
      Especially new learning, a prominent early symptom
   2. Other Cognitive Impairment:
      Aphasia, apraxia, agnosia, or executive dysfunction

B. Deficits sufficiently severe to impair Social/Occupational functioning

C. Course Shows Gradual Onset And Decline
   Must represent a decline from a previous level of functioning

D. Deficits Are Not Due to:
   1. Other CNS Conditions
   2. Substance Induced Conditions

E. Do Not Occur Exclusively during Delirium

F. Not Due to Another Psychiatric Disorder
Major Neurocognitive Disorder
(DSM-V, May 2013)

A. Evidence of significant cognitive decline from a previous level of performance in one or more of the domains outlined above based on:
   1. Concerns of the patient, a knowledgeable informant or the clinician that there has been a significant decline in cognitive function
   AND
   2. Clear decline in neurocognitive performance, typically 2 or more standard deviations below appropriate norms (i.e., below the 3rd percentile) on formal testing, or equivalent clinical evaluation.

B. The cognitive deficits are sufficient to interfere with independence (i.e., requiring assistance at a minimum with instrumental Activities of Daily Living [more complex tasks such as paying bills or managing medications]).

C. The cognitive deficits do not occur exclusively in the context of a delirium.

D. The cognitive deficits are not wholly or primarily attributable to another Axis I disorder (e.g., Major Depressive Disorder, Schizophrenia)
Genetic Causes of AD

- Down syndrome (trisomy 21)
- β-secretase
- γ-secretase
- APP mutations
- PS1, PS2 mutations
- Inflammation
- Oxidative stress
- Excitotoxicity
- Direct toxicity
- Neuron death
Behavioral and Psychological symptoms of dementia

• **Behavioral symptoms: based on observation**
  – Wondering, screaming, agitation, aggression, repetitive acts, repetitive questioning, sexual disinhibition, cursing, catastrophic reaction, hyperphagia, insomnia, sundowning

• **Psychological symptoms: based on an interview with patients and relatives**
  – Depression, anxiety
  – Apathy
  – Psychotic symptoms
NPI profile in normal elderly & AD

Normal elderly

- Mood: mean depression score: 0.25 (0-6)
- Irritability: mean score: 0.05 (0-2)
- Behavior: dis-inhibition: 0.13 (0-4)

Alzheimer’s disease

- Only 12% of AD had no evidence of neuropsychiatry symptom
- Mild AD: apathy (47%), agitation (47%) and disinhibition, irritability (35%) [mmse 30-21]
- Moderate AD: apathy (80%), anxiety (65%) agitation (55%) [mmse 20-11]
- Severe AD: apathy (92%), agitation (85%) aberrant motor behavior (84%) [mmse 10-0]
An integrated model for development of BPSD

Individual past history and learning

Genetic constitution

Dementia disorder

Neurotransmitter change
- Acetylcholine, Dopamine, Norepinephrine, Serotonin, Glutamate
- HPA axis overactivity
- disturbed diurnal change

Neuropathology

Environmental influence

Neuropsychiatric symptoms
Application of NPI

• Biological correlation of NPI
  – Apathy: correlate with prefrontal and anterior temporal perfusion of blood flow by SPECT

• Differential diagnostic properties of the NPI
  – FTD: more apathy, dis-inhibition, euphoria and aberrant motor behavior than AD
  – PSP: more apathy and less agitation than AD
MRI in different degenerative dementia-FTD
MRI in different degenerative dementia

Semantic dementia

Posterior cortical atrophy
Frontal-Subcortical Circuits

- Dorsolateral circuit $\rightarrow$ executive function
- Orbitofrontal circuit $\rightarrow$ socially appropriate behavior
- Anterior cingulate circuit $\rightarrow$ motivated behavior
# Dementia with frontal features

## Table. Organic Dementias with Frontal Features of Differential Diagnostic Interest

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS with dementia</td>
<td>Creutzfeldt-Jakob disease with frontal emphasis</td>
</tr>
<tr>
<td>Progressive aphasic disorders</td>
<td>Alzheimer’s disease with frontal emphasis</td>
</tr>
<tr>
<td>Pick’s disease</td>
<td>Binswanger’s disease</td>
</tr>
<tr>
<td>Dementia lacking distinctive histology</td>
<td>Selective incomplete white matter infarction</td>
</tr>
<tr>
<td>Rare familiar forms (Kim)</td>
<td>Strategic infarct dementia</td>
</tr>
<tr>
<td>Chromosome 17 linked disorders</td>
<td>Huntington’s disease</td>
</tr>
<tr>
<td>Corticobasal degeneration</td>
<td>Progressive supranuclear paralysis</td>
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<tr>
<td>Progressive subcortical gliosis</td>
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</tbody>
</table>

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*The Human frontal lobes frontotemporal dementia*  
Clinical and pathological aspects of Arne Burn 1999 p. 353
Frontotemporal Dementia

• a clinically, genetically and pathologically heterogeneous group of neurodegenerative dementia
• frontal and/or temporal lobes are relatively affected, even into later stages of the disease
• associated with subcortical pathology

Epidemiology of Frontotemporal Dementia

- the second commonest cause of degenerative dementia in persons younger than 65 years
- equal incidence in males and females
- occur primarily between the age of 35 and 75 years
- disease duration: 5-10 years
- 20-40% of patients have a strong family history of dementia
Criteria of frontotemporal dementia

• 1. Criteria proposed by The Lund and Manchester Groups (1994)
• 2. Consensus criteria for frontotemporal dementia (Neary, et al., 1998)
• 3. Clinical Criteria for FTD (Mckhann et al 2001)

By Work Group on Frontotemporal Dementia and Pick’s Disease
Clinical Criteria for FTD (2001)
By Work Group on Frontotemporal Dementia and Pick’s Disease

• 1. The development of behavioral or cognitive deficits manifested by either
   (a) early and progressive change in personality, characterized by difficulty in modulating behavior, often resulting in inappropriate responses or activities, or
   (b) early and progressive change in language, characterized by problems with expression of language or severe naming difficulty and problems with word meaning.

• 2. The deficits outlined in 1a or 1b cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
Clinical Criteria for FTD (2001)
By Work Group on Frontotemporal Dementia and Pick’s Disease

• 3. The course is characterized by a gradual onset and continuing decline in function.
• 4. The deficits outlined in 1a or 1b are not due to other nervous system conditions (eg, cerebrovascular disease), systemic conditions (eg, hypothyroidism), or substance-induced conditions.
• 5. The deficits do not occur exclusively during a delirium.
• 6. The disturbance is not better accounted for by a psychiatric diagnosis (eg, depression)

Notice that the areas circled in red have less white area compared with the other areas. This indicates loss of brain tissue (atrophy).
Clinical variant of frontotemporal dementia

- frontal or behavioral variant (fvFTD)
- aphasic variant
  - progressive nonfluent aphasia (PNFA) (perisylvian),
  - progressive fluent aphasia; semantic dementia (temporal) (tv-FTD)
- motor variant: FTD-MND, CBD

John R. Hodges, Clinicopathological Correlates in Frontotemporal Dementia Ann Neurol 2004;56:399–406
Behavioural disorder in FTD

- Insidious onset and slow progression
- Early loss of personal awareness (neglect of personal hygiene and grooming)
- Early loss of social awareness (lack of social tact, misdemeanours such as shoplifting)
- Early signs of disinhibition (such as unrestrained sexuality, violent behaviour, inappropriate jocularity, restless pacing)
- Mental rigidity and inflexibility
- Hyperorality (oral/dietary changes, overeating, food fads, excessive smoking and alcohol consumption, oral exploration of objects)

Behavioural disorder in FTD (continued)

- Stereotyped and perseverative behaviour (wandering, mannerisms such as clapping, singing, dancing, ritualistic preoccupation such as hoarding, toileting, and dressing)
- Utilisation behaviour (unrestrained exploration of objects in the environment)
- Distractibility, impulsivity, and impersistence
- Early loss of insight into the fact that the altered condition is due to a pathological change of own mental state.

Asymmetric variants of FTD

- FTD-rv (right hemisphere predominant FTD)
  - prominent perseveration and personality changes
  - preserved speech and language function

- FTD-lv (left hemisphere predominant FTD)
  - early speech and language difficulty
  - normal behavioral status

Edwards-Lee et al, 1997
Frontotemporal demenita with motor neuron disease (FTD-MND)

• ranging from mild cognitive impairment (ALSci) to a more fulminant progressive dementia of the frontotemporal type (FTD) with a small subset with an aphasic pattern
• The most common pattern of cognitive decline in MND is a progressive dementia of the frontal lobe type.
• Individuals with bulbar-onset disease appear to be at greater risk for the development of cognitive impairment
• reduced frontal and temporal cortical blood flow in ALSci
• ubiquitinated inclusions

Dementia and aphasia in motor neuron disease: an underrecognised association? Wojtek P Rakowicz, John R Hodges
J Neurol Neurosurg Psychiatry 1998;65:881–889
Differences Between FTD and AD

- **FTD**
  - cerebral atrophy in the frontal and anterior temporal lobes
  - not classically amnesic
  - prominent behavior problems early
  - presevered visuospatial ability

- **Alzheimer’s disease**
  - affects the hippocampal, posterior temporal and parietal regions
  - amensia with preserved social skills
  - impaired visuospatial ability
Vit B12
Neurological Manifestations in VitB12 deficiency

- Dementia, encephalopathy
- myelopathy
- peripheral neuropathy
- optic neuropathy
Vitamin B12 for cognition.

• Low serum vitamin B12 concentrations are found in more than 10% of older people.

• A high prevalence of low serum vitamin B12 levels, and other indicators of vitamin B12 deficiency have been reported among people with Alzheimer's disease.

• Evidence of any efficacy of vitamin B12 in improving the cognitive function of people with dementia and low serum B12 levels is insufficient.

Cochrane Database of Systematic Reviews. (3):CD004326, 2003
Young-onset dementia
Terminology

• presenile dementia: used widely in the published literature until about 10 years ago.
• “young-onset dementia”, “younger-onset dementia”, and “younger people with dementia” are now commonly used.
Prevalence rates of EOD and relative contribution from presumed etiological mechanisms
Epidemiology-young onset dementia

Only a few studies have addressed these issues.

- In two London boroughs in the UK, the prevalence of dementia with onset between the ages of 30 and 65 years was 0.054% and 0.098% between the ages of 45 and 65 years.
  ~ J Neurol Neurosurg Psychiatr 2003;74:1206–09~
- 0.042% in the Ibaraki prefecture in Japan between the ages of 18–65 years.
  ~ Stroke 2009;40:2709–14~
Neuropsychological signatures of young-onset dementia
~Lancet Neurol. 2010 August ; 9: 793–806~
Parkinson’s Disease Dementia (PDD)
Clinical profile of PDD

*Signs and symptoms*

- Dementia develops in the context of established PD
- The features below can occur to a different extent in individual patients

<table>
<thead>
<tr>
<th>Functional impairments</th>
<th>Behavioral symptoms</th>
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<tbody>
<tr>
<td>• Attention</td>
<td>• Affective changes</td>
</tr>
<tr>
<td>• Memory</td>
<td>• Mood disturbances</td>
</tr>
<tr>
<td>• Executive function</td>
<td>• Hallucinations</td>
</tr>
<tr>
<td>• Visuo-spatial function</td>
<td>• Delusions</td>
</tr>
<tr>
<td>• Language</td>
<td>• Apathy</td>
</tr>
<tr>
<td></td>
<td>• Excessive daytime sleepiness</td>
</tr>
</tbody>
</table>

Clinical profile of PDD

Incidence and prevalence of dementia in PD

**Incidence rate of dementia in PD**
- 4 to 6 times higher than in the general age-matched (non-PD) population
- 10% of PD population per year

**Point prevalence of dementia in PD**
- Close to 30%

**Cumulative prevalence of dementia in PD**
- In separate studies:
  - 78% of PD population develop dementia after 8 years of follow-up
  - 48% of PD population develop dementia after 15 years of follow-up

Clinical profile of PDD

Risk factors for developing PDD

- Many demographic and clinical features have been assessed as potential risk factors for developing dementia in PD, including:
  - Rigidity
  - Postural
  - Instability
  - Gait disturbance

Diagnosing PDD

Diagnostic steps

Confirmation of idiopathic PD before development of dementia symptoms is the essential first step in the diagnosis of PDD

I. Core features
Diagnosis of PD +
Dementia syndrome

II. Associated clinical features
Impairment of at least two
of four cognitive domains
(May be supported by behavioural symptoms)

PDD diagnosis

III. Presence of features which make diagnosis uncertain
- Co-existence of any abnormality that could itself cause cognitive impairment, but not cause dementia
- Unknown time interval between onset of motor and cognitive symptoms

IV. Presence of features which make diagnosis impossible
Cognitive and behavioural symptoms presenting as a result of other conditions, for example:
- Acute confusion due to systemic diseases/ abnormalities or drug intoxication
- Major depression according to DSM IV
- Features of ‘probable vascular dementia’ according to NINDS-AIREN

Probable
Possible
Impossible

AIREN, Association Internationale pour la Recherche et l’Enseignement en Neurosciences; DSM, Diagnostic and Statistical Manual of Mental Disorders; NINDS, National Institute of Neurological Disorders and Stroke.

Differentiating PDD and DLB

Symptoms – Early movement disorder in PDD vs. DLB

PDD

Movement disorder appear first; cognitive symptoms begin > 1 year after

More frequent:
- PIGD phenotype
- REM sleep behavior disorder

DLB

Clinical and neuropathological symptoms, including visual and auditory hallucinations (PDD, 45-65%; DLB, 60-80%)

Multiple patterns of symptoms presentation

PIGD, postural instability gait difficulty; REM, rapid eye movement.

Differentiating PDD and DLB

Neuroimaging – Greater amyloid burden in DLB vs. PDD

Aβ ligand binding may be increased in PDD, not PD

PDD

Brain amyloid deposition contributes to cognitive impairment

Cortical Aβ ligand binding generally normal or increased

Aβ may interact synergistically with other pathological processes

DLB

Brain amyloid deposition more marked vs. PDD

Aβ ligand binding greater than PDD

PIGD, postural instability gait difficulty; REM, rapid eye movement.

Thank you for your attention

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