Young onset and atypical dementia

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Young and atypical dementia

- Definition of dementia
- Delirium vs dementia
- Subcortical vs cortical dementia
- Causes and differential diagnosis of dementia
- The dementias...
What is dementia?

• A disorder of two or more domains of cognition:
  – memory
  – language
  – visuoperceptual ability
  – praxis
  – abstract thinking and judgement
  – personality
  – social conduct

• Substantially impacting everyday life
<table>
<thead>
<tr>
<th>FEATURE</th>
<th>DELIRIUM</th>
<th>DEMENTIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>abrupt/sub-acute</td>
<td>insidious</td>
</tr>
<tr>
<td>Course</td>
<td>fluctuating</td>
<td>slow progression</td>
</tr>
<tr>
<td>Duration</td>
<td>hours-weeks</td>
<td>months-years</td>
</tr>
<tr>
<td>Alertness</td>
<td>abnorm high or low</td>
<td>typically normal</td>
</tr>
<tr>
<td>Sleep-wake</td>
<td>disrupted</td>
<td>relatively normal</td>
</tr>
<tr>
<td>Attention</td>
<td>impaired</td>
<td>intact in early dement.</td>
</tr>
<tr>
<td>Orientation</td>
<td>impaired</td>
<td>intact in early dement.</td>
</tr>
<tr>
<td>Working mem</td>
<td>impaired</td>
<td>impaired</td>
</tr>
<tr>
<td>Episodic mem</td>
<td>impaired</td>
<td>impoverished</td>
</tr>
<tr>
<td>Thought</td>
<td>disorganised, delus.</td>
<td>word-finding difficulty</td>
</tr>
<tr>
<td>Speech</td>
<td>slow/rapid, incoh.</td>
<td>us. intact in early dem.</td>
</tr>
<tr>
<td>Perception</td>
<td>illusn/halln common</td>
<td>varies: oft. intact early</td>
</tr>
<tr>
<td>Behaviour</td>
<td>withdrawn/agitated</td>
<td></td>
</tr>
<tr>
<td>FUNCTION</td>
<td>CORTICAL</td>
<td>SUBCORTICAL</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Alertness</td>
<td>normal</td>
<td>‘slowed up’</td>
</tr>
<tr>
<td>Attention</td>
<td>normal early</td>
<td>impaired</td>
</tr>
<tr>
<td>Executive ftn</td>
<td>amnesia</td>
<td>forgetfulness</td>
</tr>
<tr>
<td>Episodic mem</td>
<td>aphasic</td>
<td>reduced output</td>
</tr>
<tr>
<td>language</td>
<td>impaired</td>
<td>relatively normal</td>
</tr>
<tr>
<td>Praxis</td>
<td>apraxia</td>
<td>impaired</td>
</tr>
<tr>
<td>Perception + vis/sp</td>
<td>preserved (unless</td>
<td>apathetic, inert</td>
</tr>
<tr>
<td>Personality</td>
<td>frontal type)</td>
<td></td>
</tr>
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</table>
Causes of ‘dementia’

- Inherited: HD, Wilson’s, leucodystrophies
- Primary degenerative: Alzheimer’s, Cortical Lewy Body disease, Fronto-temporal dementia
- Vascular: multi-infarct, subcortical, strategic infarction
- Infective: HIV, TSE, HSE, Whipple’s, SSPE
- Inflammatory: MS, vasculitis, Hashimoto’s, limbic encephalitis
- Neoplastic: 1°/2° CNS tumours, limbic encephalitis
- Traumatic: Post head injury
- Structural: hydrocephalus, chronic subdurals
- Physiological: Epileptic amnesia (EAS, TEA)
- Metabol/endocrine: hypothyroidism
- Deficiency: B12/folate
- Sleep-related: OSA
- Substances/drugs: alcohol, anticholinergics, hypnotics etc
- Psychiatric: depression (pseudo-dementia)
History

General examination
Systemic Function

Neurological examination
Neurological Function

Cognitive examination
Cognitive Function

Neuropsychiatric examination

Thought Mood Personality Behaviour
Alzheimer’s disease

- Episodic memory impairment -> widespread cognitive decline
- Apathy, disinhibition, agitation; psychosis; mood disturbance
- Slowly progressive: circa 3 point MMSE decline/year
- Pyramidal, extrapyramidal signs; primitive reflexes; epilepsy
- Neuritic plaques: Abeta amyloid derived from APP
- Neurofibrillary tangles: hyperphosphorylated tau
- Cholinergic deficit
- <5% autosomal dominant: presenilin 1(14), 2(1), APP (21)
- Apolipoprotein E alleles 2, 3 and 4; Down’s syndrome; vascular risk factors
- CT, MRI, SPECT, PET, amyloid imaging
- CSF biomarkers
- Central Achase inhibitors; memantine
Atypical presentations of AD

• <10% AD

• Posterior cortical atrophy (PCA)
  – Almost always due to AD

• Slowly progressive aphasia
  – More varied pathology
  – Usually non-fluent, occasionally fluent in AD

• Slowly progressive apraxia

• Dysexecutive or ‘behavioural’ presentation
MEMORY
Amnesia

EXECUTIVE FUNCTION
‘Frontal lobe syndrome’

PRAXIS
Apraxia

AROUSAL

PERCEPTUO-SPATIAL FUNCTION
Agnosia
Spatial disorientation

LANGUAGE
Aphasia
Alexia
Agraphia
Acalculia
Posterior cortical atrophy - PCA

• Circa 5% AD cases have ‘visual presentation’
• Early onset, typically mid 50s-early 60s
• Mild female predominance
• Most common features are
  – Alexia and agraphia
  – Simultanagnosia
  – Optic ataxia
• ‘dorsal stream’ symptoms and signs predominate but both ventral and dorsal streams affected
• Relative preservation of memory, insight, language, executive function
ASSESSING CELL LOSS IN DIFFERENT PARTS OF THE BRAIN

Typical Alzheimer’s disease

Posterior Cortical Atrophy
ASSESSING CELL LOSS IN DIFFERENT PARTS OF THE BRAIN

Typical Alzheimer’s disease

Posterior Cortical Atrophy
THINNING OF THE CORTEX

Left side of the brain

FRONT

-20%

AD thinner than PCA

-10%

0%

10%

20%

BACK

PCA thinner than AD
Vascular dementia

• subcortical ischaemic dementia: cognitive slowing, attentional and executive impairment, gait disturbance

• multi-infarct dementia: mixed cortical/subcortical features, fluctuating cognition, pseudobulbar palsy/affect, gait/bladder disturbance

• strategic infarction eg thalamus, basal forebrain, left angular gyrus

• vascular risk factors including thrombophilia, vasculitis, CADASIL

• Imaging - MRI

• manage vascular risk factors
CADASIL
Dementia with Lewy bodies

- Cognitive decline + Parkinsonism, visual hallucinations, fluctuations (two features -> probable DLB, one feature possible DLB)
- Neuropsychology: impaired psychomotor speed, attention, executive function, visuospatial ability
- REM sleep behaviour disorder
- More rapidly progressive than pure AD
- Lewy body: eosinophilic intraneuronal inclusion bodies, mainly aggregated filaments of alpha-synuclein
- DLB and Lewy body variant of AD
- Neurochemical pathology
- The therapeutic dilemma
- Achase inhibitors
Atypical dementia

• Features atypical of a common cause!
  – Age
  – family history
  – systemic features (apart from vascular disease)
  – rapidity
  – syndromes eg:
    • cognitive decline, epilepsy, chorea, oral self-mutilation
    • frontal lobe dementia with bulbar and pseudo-bulbar palsy
    • apraxia, limb myoclonus, alien limb
    • falls, axial rigidity, supranuclear gaze palsy, subcortical dementia
Frontotemporal dementia

- 10-15% dementia < 65 years, 25-50% familial
- Frontal lobe (behavioural) variant
  - personality and behavioural change with loss of insight
- Temporal lobe variant
  - L: semantic dementia
  - R: recognition + knowledge of people
- Progressive non-fluent aphasia
- FTD with MND
- NB relative preservation of episodic memory
- Pathologies – see Appendix!
- Imaging: focal atrophy
Frontotemporal dementia

- FH in 25-50% cases
- Autosomal dominant FTD
- Microtubule associated protein gene (MAPT)
- Progranulin
- Valosin-containing protein
- Charged multi-vesicular body protein 2B
- C9ORF72
  - ~35% familial ALS, 25% familial FTD
  - NB association with psychosis
## Recommended nomenclature for FTLD
(Neumann et al, 2009)

<table>
<thead>
<tr>
<th>Previous terminology</th>
<th>Recommended terminology</th>
<th>Major pathological subtypes</th>
<th>Associated gene</th>
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<tbody>
<tr>
<td>Tau +ve FTLD</td>
<td>FTLD-U, TDP-43 +ve</td>
<td>PiD, CBD, PSP</td>
<td>MAPT</td>
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<tr>
<td></td>
<td>FTLD-U, TDP-43 –ve</td>
<td>AgD, MSTD, FTDP-17</td>
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<tr>
<td></td>
<td>NIFID, DLDH Other (BIBD)</td>
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<tr>
<td>Tau –ve FTLD</td>
<td>FTLD-TDP</td>
<td>Type 1 (SD)</td>
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<td></td>
<td>FTLD-UPS</td>
<td>Type 2 (FTD +/- MND)</td>
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<td>FTLD-IF</td>
<td>Type 3 (FTD/PNFA)</td>
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<td></td>
<td>FTLD-ni</td>
<td>Type 4 (IBMPFD)</td>
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<tr>
<td></td>
<td>BIBD</td>
<td>aFTLD-U</td>
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<td>FTD-3</td>
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<td></td>
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<td>GRN</td>
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<td>VCP</td>
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<td></td>
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<td>CHMP2B</td>
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PSP + CBD

• **PSP**
  - supranuclear gaze palsy
  - truncal rigidity, instability, akinesia, falls
  - bulbar features
  - subcortical dementia
  - mood, personality, behaviour
  - neurofibrillary tangles (tau) in basal ganglia and brain stem
  - MRI: midbrain atrophy

• **CBD**
  - asymmetric limb apraxia
  - alien limb phenomena
  - limb myoclonus
  - Parkinsonism
  - cognitive impairment
  - neurofibrillary tangles (tau) in frontal and parietal cortex and basal ganglia
  - MRI: frontoparietal atrophy
A: Syndrome-specific regional atrophy patterns: patients vs. controls

B: Intrinsic functional connectivity networks: healthy controls

C: Structural covariance networks: healthy controls
Huntington’s disease

- autosomal dominant, variable age of onset, anticipation
- chorea -> other extrapyramidal + features; Westphal variant; epilepsy; subcortical dementia; depression, apathy, aggressivity common, psychosis, obsessional behaviour, suicide in a minority: progression to immobility and dementia over 15-20 years
- loss of small striatal neurons + cortical neurons
- anticipation especially with paternal transmission
Prion dementia

- spCJD - rapid dementia, ataxia, visual syndromes, multifocal signs, myoclonus: usually 55-70 yrs, median duration circa 4 months
- vCJD - psychiatric prodrome, dysaesthesiae, cognitive impairment, multifocal signs, myoclonus: 2nd - 4th decades, med durn 14 m.
- iatrogenic and familial CJD; GSS; FFI; kuru
- Pathology
- The prion gene (chromosome 20) and the prion hypothesis
- Investigations: EEG in spCJD; CSF 14-3-3 in spCJD, tau in vCJD; MRI; tonsillar and brain biopsy
Sporadic CJD
HIV-1 associated dementia

- 20-30% AIDS patients present with or develop:
  - Insidious, subcortical: poor concentration, slowing, forgetfulness, apathy, social withdrawal; pyramidal and cerebellar signs.
  - Tends to occur with CD4 count < 200 x 10^6.
  - Early entry of HIV-1 to CNS -> persistence in macrophages and microglia -> multinucleated giant cells; white matter affected focally (MGCs) or diffusely; cortical neuronal loss.
  - MRI, CSF.
  - Differential diagnosis: depression, drugs, substance abuse, systemic illness, CNS tumours, opportunistic infection (toxoplasmosis, TB, cryptococcus, CMV, syphilis, PML).
Hydrocephalus

- large head
- headache
- hydrocephalic attacks + death
- visual failure
- gait disturbance
- incontinence
- subcortical dementia
- communicating, obstructive, compensated, normal pressure
- Imaging, lumbar puncture, CSF pressure studies
- Shunting
Wilson’s disease

- rare, treatable, autosomal recessive
- usually presents in childhood or adolescence but up to 5th decade
- psychiatry: personality change, psychosis, dementia
- neurology: extrapyramidal features (tremor, dysarthria, drooling, rigidity, bradykinesia, dystonia)
- KF rings
- liver failure
- copper transporting ATP-ase on chromosome 13 -> copper deposition especially in GP and putamen
- copper chelation: penicillamine, trientine, zinc: controversial
Obstructive Sleep Apnoea

• Common in middle age
• Clues
  – snoring history
  – Daytime sleepiness – see ESS
  – Morning headache
  – Befuddlement
• Sleep study
• CPAP
Daytime sleepiness: Epworth Sleepiness Scale

- Sitting and reading
- Watching TV
- Sitting inactive in a public place eg theatre, meeting
- Passenger in a car for an hour
- Lying down to rest in the afternoon
- Sitting and talking to someone
- Sitting quietly after lunch
- In a car while stopped in traffic

- 0 = would never dose
- 1 = slight chance of dosing
- 2 = moderate chance
- 3 = high chance
Transient Epileptic Amnesia
(Butler et al Ann Neurol 2007)

- Onset in later life
- Male predominance
- Attacks 30-60 minutes
- Attacks on waking common
- Amnesia can be sole feature
- +/- olfactory hallucinations, automatisms, brief unresponsiveness
- Partial recall common
- Excellent treatment response
- Diagnosis usually delayed
- Interictal memory complaints usual
  - 2/3 Autobiographical amnesia
  - 1/2 Accelerated forgetting
  - 1/3 Topographical amnesia
**Peri-ictal MRI**

1.5T MRC25445
Ex: 1
cor oblique flair
Se: 7/1
Im: 17/30
Cor: A15.2 (CC)

1962 Mar 08  M  T 16925
Acc: 4912783
2006 Mar 10
Acq: 42:15:109980

266 x 224

**One month later**

**Peri-ictal FDG-PET**

![Peri-ictal FDG-PET images]
Young and atypical dementia

- Wide differential diagnosis
- Broad assessment required
- Degenerative dementia as a network disease
- Some treatable conditions present as dementia

Rossor et al Lancet Neurol 2010; 9: 793–806